Treatment with stimulants and the risk of COVID-19 complications in adults with ADHD

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ABSTRACT

Adults with attention deficit hyperactivity disorder (ADHD) have shown higher infection rates and worse outcomes from COVID-19. Stimulant medications are prescribed as the first-line treatment for ADHD in adults and mitigate risk of negative ADHD-related health outcomes, but little is known about the association between stimulant medications and COVID-19 outcomes. The objective of this study was to assess the risks of severe COVID-19 outcomes among people with ADHD who were prescribed stimulant medications versus those who were not. This retrospective cohort study used electronic health records in the TriNetX research database. We assessed records of adults with ADHD diagnosed with COVID-19 between January 1, 2020 and June 30, 2021. The stimulant cohort consisted of 28,011 people with at least one stimulant prescription; the unmedicated cohort comprised 42,258 people without prescribed stimulants within 12 months prior to their COVID infection. Multiple logistic regression modeling was utilized to assess the presence of critical care services or death within 30 days after the onset of COVID diagnoses, controlling for patient demographics, and comorbid medical and mental health conditions. The stimulant cohort was less likely to utilize emergency department, hospital, and intensive care services than the unmedicated cohort, and had significantly lower 30-day mortality. Further research, including prospective studies, is needed to confirm and refine these findings.

1. Background

The Coronavirus pandemic (COVID-19) has created persistent public health challenges, particularly for adults experiencing mental health problems (Ceban et al., 2021). Recent research showed higher COVID-19 infection and mortality rates among individuals with mental health conditions, including those with attention deficit hyperactivity disorder (ADHD) (Wang et al., 2021a). Individuals with ADHD have more severe symptoms and more frequent hospitalizations due to COVID-19 (Merzon et al., 2021). Furthermore, the extent to which treatment with stimulant medications, an evidence-based treatment pharmacotherapy for ADHD, could impact COVID-19 outcomes has not been studied.

ADHD is a mental health disorder with origins in a spectrum of genetic, neurobiological, and socioeconomic factors, (Volkow and Swanson, 2013; Cénat et al., 2021) and is characterized by inattention and/or hyperactivity and impulsivity. These symptoms often emerge in childhood, then follow a chronic course into adulthood, (Katzman et al., 2017) affecting 4–6% of the U.S. adults in the past decade (Kessler et al., 2006). Neuroscience research has found disruption in brain dopamine neurotransmission as well as lower norepinephrine level among people with ADHD (Volkow and Swanson, 2013; Volkow et al., 2009). The dysfunction of dopamine reward and norepinephrine pathways can contribute to executive function, attention, and mood dysregulation.

Limited evidence suggests higher infection rates and worse outcomes of COVID-19 among people with ADHD. Researchers have speculated this may be related to ADHD symptoms; poor concentration, emotional and interpersonal problems, and learning difficulties may affect the ability to access, understand, and adopt critical safety information about COVID-19, (Shinn and Viron, 2020) delay seeking testing or medical attention that, in turn, may result in care delays and worse health outcomes (Wang et al., 2021a).

Additionally, compared to the general population, adults with ADHD are more likely to have concomitant mental health conditions, including

depression, anxiety, and bipolar disorders, (Katzman et al., 2017) which are risk factors for more severe COVID-19 infection (Wang et al., 2021a). ADHD has also been linked to the increased risk of substance use disorders (SUD) including nicotine, alcohol, opioid, cannabis, cocaine, or stimulant use disorders, (Nigg, 2013; van Emmerik-van Oortmerssen et al., 2012; Capusan et al., 2019) which have also been identified as a risk factor for worse COVID-19-related outcomes (Wang et al., 2021b). People with SUD account for over 15% of the population infected with SARS-CoV-2 virus, and are more likely to be hospitalized and die due to COVID-19 than those without SUD (Wang et al., 2021b).

Adults with ADHD also have been shown at increased risk of obesity, diabetes, and cardiovascular conditions (Nigg, 2013). Those medical problems can negatively influence immune and respiratory system, increasing vulnerability to the SARS-CoV-2 virus infection (Geng et al., 2021) and its complications (Yek et al., 2022; Centers for Disease Control and Prevention, 2020). Additional research is required to examine associations between ADHD and worse COVID-19 outcomes, controlled for co-occurring physical health problems.

Stimulant medications, the first-line pharmacotherapy for treating ADHD in adulthood, (Cortese et al., 2018) stimulate brain receptors associated with dopamine and norepinephrine signaling to produce and release enough neurotransmitters, which contribute to increased metabolic activities in the prefrontal cortex, resulting in well-documented improvement in executive function and attention (Faraone and Glatt, 2010; Faraone et al., 2004). Several stimulant medications have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD in adults (Adler et al., 2008; Biederman et al., 2006; Spencer et al., 2007; Surman et al., 2013). Approximately 6.6% (16 million) of U.S. adults were prescribed stimulants in 2016–2017 (Compton et al., 2018). Adults on sustained stimulant medication have reduced ADHD symptoms leading to long-term improvements in quality of life (Adler et al., 2008; Chang et al., 2017). Side effects, through their activation of the adrenergic receptor agonists, including accelerated heart rate, blood vessel constriction, and increased blood pressure (Latronica et al., 2021; Olfson et al., 2013), have raised concerns about cardiovascular risk complications.

While stimulant medication as a treatment for ADHD has been shown to reduce other negative outcomes, it is unclear about whether stimulant medications are associated with less or improved COVID-19 outcomes (Nemani et al., 2022). This study aimed to address the existing knowledge gap about the potential associations between stimulant therapy for ADHD and severe COVID-19 outcomes by comparing health care utilization (emergency department (ED) visits, hospitalization, and intensive care unit (ICU) treatment) and mortality outcomes among adults with COVID-19 and ADHD who were prescribed stimulant medications versus those who were not. Understanding factors that may increase susceptibility versus resilience to severe COVID-19 complications can inform care guidelines and assist clinicians to better care for patients with ADHD and SARS-CoV-2 infection.

2. Methods

2.1. Study design and data sources

This retrospective cohort study utilized EHR data of 57 healthcare organizations from the TriNetX research network database (Cambridge, MA). TriNetX is a global health data network, which contains de-identified EHR data of more than 80 million patients from participating healthcare organizations predominately from the U.S. Data in the TriNetX database have shown referential integrity and reliability (Topaloglu and Palchuk, 2018). Their coding has undergone extensive curation and mapping to common clinical entities and terminologies to ensure high usability as well as consistency with the Reporting of studies Conducted using Observational Routinely collected Data (RECORD) guidelines (Benchimol et al., 2015). This study used deidentified datasets downloaded from TriNetX, without any protected health information; the process by which research data sets were de-identified was attested to through a formal determination as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule, and this research was determined to be exempt from the Institutional Review Board oversight by the Pennsylvania State University's Human Research Protection Program.

2.2. Cohort selection procedure

The study population consisted of adults (age≥18 years) with ADHD and COVID-19 infection. They were considered to have COVID-19 based on the presence of the ICD-10 diagnostic codes or positive laboratory test results confirming COVID-19 during the 18-month study assessment period (January 1, 2020-June 30, 2021; see Table A.1 for details) (Tuan et al., 2021). Because an individual could have experienced a COVID-19 infection more than once, the first COVID-19 infection episode during the study assessment period was considered the "index" infection. The 30-day follow-up period, during which the healthcare utilization and mortality outcomes were assessed, started at the onset of the index COVID-19 infection. A patient's ADHD diagnosis must have predated the index COVID-19 infection to be eligible for the study.

The 'stimulant cohort' consisted of people with ADHD who had at least one prescription of a stimulant medication within 12 months before the onset of their index COVID-19 infection. The 'unmedicated cohort' consisted of those who did not receive any prescriptions for stimulants within 12 months before their index COVID-19 infection. The study excluded people with ADHD treated with non-stimulant medications (atomoxetine, clonidine, guanfacine or viloxazine), with diagnoses of cancer, or a skilled nursing or palliative care status any time prior to their index COVID-19 infection. A cohort selection flowchart is provided in Fig. 1.

2.3. Stimulant medications

Stimulant medications used for the ADHD treatment were identified using normalized name and code sets for medications based on the Prescription for Electronic Drug Information Exchange (RxNorm) (Nelson et al., 2011). RxNorm has been developed by the National Library of Medicine to link and map standard clinical medication names to various drug nomenclatures and terminologies commonly used in EHR and pharmacy management systems. Stimulant medications were identified based on both generic (amphetamine, dextroamphetamine, lisdexamfetamine, methylphenidate, methamphetamine, dexmethylphenidate) and brand names (Piper et al., 2018; Quinn et al., 2017). The list of RxNorm codes is provided in Supplemental Table A.1.

2.4. Demographics and medical and mental health characteristics

Data on baseline characteristics of the study cohorts at the time of the index COVID-19 infection were extracted. The available demographic data included sex (male/female), age, ethnicity (Hispanic/non-Hispanic) and race (White/Black/Other). Data on conditions known to be associated with the COVID-19 illness severity and/or ADHD outcomes included the diagnoses of medical conditions (obesity, diabetes, chronic kidney disease, cardiovascular disorders), (Yek et al., 2022; Tuan et al., 2021) mental health disorders (depression, anxiety, bipolar), (Wang et al., 2021a) and SUDs (tobacco/nicotine, alcohol, cannabis, cocaine, stimulant, opioid) (Wang et al., 2021b). Because the 'current status' of tobacco use/smoking was unavailable in the TriNetX database, the presence of the tobacco/nicotine use disorder diagnoses was used as the proxy of smoking/tobacco use. To account for confounding effects that might influence associations between the use of stimulant medications and severe COVID-19 outcomes, these baseline characteristics were included and controlled for in the regression modeling. Detailed information on the diagnostic codes for the conditions extracted in this study is provided in Table A1.
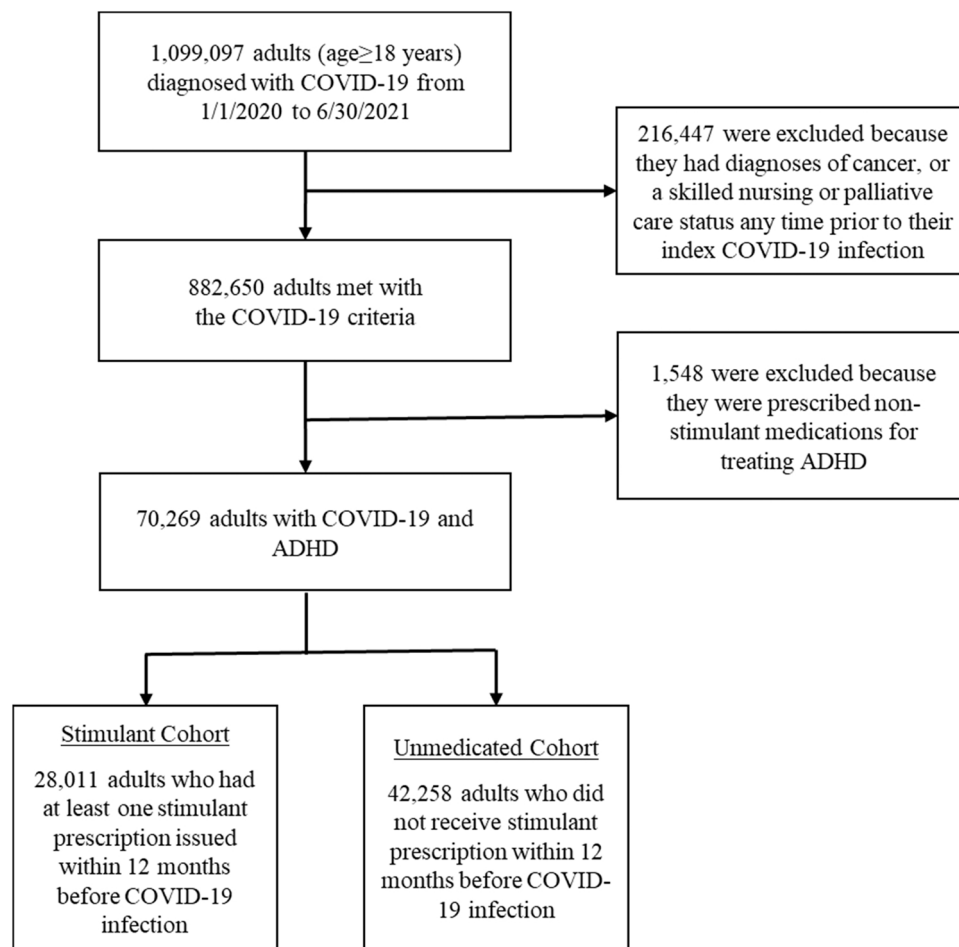
Fig. 1. Flowchart of the study cohort selection process.

2.5. COVID-19 severity related outcome measures: healthcare utilization and mortality

Outcome measures indicative of COVID-19 infection severity included dichotomous variables, with '1' assigned if a target outcome occurred at least once, and '0'assigned if a target variable did not occur within 30 days of the onset of the index COVID-19 infection. The healthcare utilization metrics corresponding to the more severe COVID-19 infection included ED visits, hospital admissions, and ICU stay within 30 days of infection. COVID-19-related mortality was defined as death within 30 days after the onset of the index COVID-19 infection.

2.6. Statistical analysis

Descriptive statistics were computed to describe sample characteristics. Differences in continuous variables between the stimulant and unmedicated cohorts were compared using the t-test for parametric or equivalent tests for non-parametric analyses. Proportion differences in categorical variables were evaluated using the Chi-square test.

Multiple logistic regression modeling was used to assess the risk of serious medical complications of COVID-19, including death (binary dependent variable, Yes/No), within 30 days of COVID-19 infection among adults in the stimulant and unmedicated cohorts, when controlled for demographic characteristics and comorbid conditions known to contribute to the COVID-19 severity risk. The regression analysis was computed using the Maximum Likelihood Estimation method, which provided regression coefficients, standard errors (SEs), Wald 95% confidence intervals (CIs) for the coefficients, and p-values for each of the model variables. The likelihood ratio test, the global test

of parameters in the regression model, was assessed first; if the model's likelihood ratio test was significant ($p < 0.05$), individual variables' coefficients and p values were then considered. The adjusted odds ratio (aOR) and 95% CI of each variable was also calculated to predict the risk of the outcome measure. The significance level was determined based on two-tailed p-value < 0.05. All statistical analyses were performed using PROC LOGISTIC procedure (Version 9.4 SAS Institute Inc., Carey, NC).

3. Results

3.1. Study population characteristics

70,269 adults met eligibility criteria between January 1, 2020 and June 30, 2021. In this sample, 28,011 were prescribed a stimulant medication (stimulant cohort) and 42,258 were not prescribed medications for ADHD (unmedicated cohort) prior to their index COVID-19 infection (Fig. 1).

Compared to the unmedicated cohort, the stimulant cohort had a greater percentage of females and White individuals, was slightly older, and had higher rates of chronic medical and mental health conditions, smoking/tobacco dependency, and alcohol/drug use disorders, known risk factors for COVID-19 complications (Table 1).

3.2. Stimulant versus unmedicated cohorts: unadjusted healthcare utilization and mortality outcomes

Compared to the unmedicated cohort, the stimulant cohort had lower rates of ED visits (19.0% vs 26.3%, $p < 0.01$), hospitalization (7.6% vs 10.1%, $p < 0.01$), ICU care (1.2% vs 2.0%, $p < 0.01$), and

Table 1
Characteristics of the study sample of adults with ADHD diagnoses and COVID-19 infection.

Characteristics	Total, N = 70,269	Stimulant cohort, N = 28,011	Unmedicated cohort, N = 42,258	p-value[a]
Female, n (%)	36,844 (55.0)	15,842 (59.3)	21,002 (52.1)	< 0.001
Age, mean (SD)	34.0 (13.0)	35.3 (12.6)	33.1 (13.1)	< 0.001
Age group, n (%)				<0.001
18–39 yrs	48,089 (71.8)	18,215 (68.1)	29,874 (74.2)	
40–64 yrs	17,088 (25.5)	7847 (29.4)	9241 (22.9)	
65 + yrs	1840 (2.7)	673 (2.5)	1167 (2.9)	
Hispanic, n (%)	4033 (6.0)	1441 (5.4)	2592 (6.4)	< 0.001
Race, n (%)				<0.001
White	54,537 (81.4)	22,826 (85.4)	31,711 (78.7)	
Black	6699 (10.0)	1566 (5.9)	5133 (12.7)	
Other	5781 (8.6)	2343 (8.8)	3438 (8.5)	
Chronic medical conditions				
Obesity, n (%)	14,987 (22.4)	5428 (20.3)	9559 (23.7)	< 0.001
Cardiovascular condition, n (%)	13,555 (20.2)	5296 (19.8)	8259 (20.5)	0.03
Chronic kidney disease, n (%)	1229 (1.9)	404 (1.6)	825 (2.1)	< 0.001
Diabetes, n (%)	923 (1.4)	304 (1.1)	619 (1.5)	< 0.001
Mental health conditions				
Depression, n (%)	29,105 (43.4)	11,430 (42.8)	17,675 (43.9)	< 0.01
Anxiety, n (%)	34,560 (51.6)	14,198 (50.5)	20,362 (53.1)	< 0.001
Bipolar, n (%)	8176 (12.2)	2295 (8.6)	5881 (14.6)	< 0.001
Tobacco/nicotine use disorder, n (%)	13,273 (19.8)	4075 (15.2)	9198 (22.8)	< 0.001
Alcohol/drug use disorder				
Alcohol use disorder, n (%)	4980 (7.4)	1565 (5.9)	3415 (8.5)	< 0.001
Opioid use disorder, n (%)	3212 (4.8)	987 (3.7)	2225 (5.5)	< 0.001
Cannabis use disorder, n (%)	3777 (5.6)	916 (3.4)	2861 (7.1)	< 0.001
Cocaine use disorder, n (%)	1553 (2.3)	341 (1.3)	1212 (3.0)	< 0.001
Stimulant use disorder, n (%)	1990 (3.0)	578 (2.2)	1412 (3.5)	< 0.001
Outcome measure				
ED visit, n (%)	15,656 (23.4)	5073 (19.0)	10,583 (26.3)	< 0.001
Hospitalization, n (%)	6096 (9.1)	2019 (7.6)	4077 (10.1)	< 0.001
ICU admission, n (%)	1121 (1.7)	333 (1.2)	788 (2.0)	< 0.001
Death, n (%)	172 (0.3)	50 (0.2)	122 (0.3)	< 0.01

ED: Emergency department; ICU: Intensive care unit
[a] T-test statistics were computed to assess differences in mean ages between the stimulant and unmedicated cohorts. Chi-square statistics were computed for the rest of characteristics to evaluate differences in proportions between the stimulant and unmedicated cohorts.

deaths (0.2% vs 0.3%, $p < 0.01$) within 30 days following their index COVID-19 infection (Table 1).

3.3. Stimulant versus unmedicated cohorts: adjusted healthcare utilization and mortality outcomes

Multiple logistic regression modeling analysis evaluated the risk for COVID-19 complications among the stimulant vs unmedicated cohort after adjusting for demographic characteristics and the prevalence of the common medical and mental health disorders, which could impact COVID-19 infection severity.

Table 2 presents the adjusted odds ratios (aORs) of critical care utilization and death within 30 days of COVID-19 infection. The likelihood ratio test was statistically significant at the 0.05 level for all the regression models, suggesting that at least one risk factor was likely to be affecting the assessed study outcomes.

After controlling for the above additional factors, the stimulant cohort, compared to the unmedicated cohort, had a reduced risk of ED visits (aOR=0.78, $p < 0.01$), hospitalization (aOR=0.88, $p < 0.01$), ICU care (aOR=0.76, $p < 0.01$), without difference in the 30-day mortality between the cohorts within 30 days of the index COVID-19 infection.

In addition to the primary goal of the analysis to assess healthcare utilization and mortality following COVID-19 infection among the stimulant versus unmedicated cohorts of adults with ADHD, the multiple regression model yielded secondary findings regarding the effects of demographics and comorbid conditions on the probability of utilizing different health care resources and death after COVID-19 infection. Among the demographic characteristics, females were at lower risk for hospitalization, ICU care, and death than their male counterparts (aOR=0.62–0.89, $p < 0.01$). Those 40 years or older had lower risk of ED visits (aOR=0.76, $p < 0.01$) and hospitalization (aOR=0.85, $p < 0.01$); however, people 65 years old or older had a higher risk of hospitalization (aOR=1.34, $p < 0.01$), ICU care (aOR=1.44, $p < 0.01$) and death (aOR=3.49, $p < 0.01$) following COVID-19. Moreover, individuals of Hispanic ethnicity experienced increased risk of ED visits (aOR=1.16, $p < 0.01$), compared to non-Hispanics. Blacks were more likely to require ICU care (aOR=1.36–2.06, $p < 0.01$) or die (aOR=1.82, $p < 0.01$) after COVID-19 infection than Whites, without differences in care utilization or mortality found between Whites and 'Other' racial category.

In general, people with chronic medical conditions were more likely (aOR=1.12–1.50, $p < 0.01$) to have ED visits after COVID-19 infection. Individuals with cardiovascular conditions, chronic kidney disease, and diabetes were also more likely to be hospitalized (aOR=1.72–2.65, $p < 0.01$), require ICU care (aOR=1.54–4.08, $p < 0.01$) or die (aOR=2.65–3.17, $p < 0.01$) within 30 days of their index COVID-19 infection.

Presence of depression, anxiety or bipolar disorder diagnoses was associated with increased risk of ED visits (aOR=1.14–1.67, $p < 0.01$) and hospitalization (aOR=1.08–1.66, $p < 0.01$), and people with depression were more likely to require ICU services (aOR=1.15, $p < 0.01$). The 30-day mortality rate was not affected by mental health diagnoses.

Presence of nicotine/tobacco use disorder was linked to a higher risk of ED visits (aOR=1.93, $p < 0.01$), hospitalization (aOR=1.82, $p < 0.01$), and ICU admission (aOR=2.07, $p < 0.01$), but did not impact the 30-day post-COVID-19 mortality. Overall, presence of alcohol or drug use disorders was related to a greater risk of ED visits (aOR=1.21–1.52, $p < 0.01$) and hospitalization (aOR=1.35–1.76, $p < 0.01$). Individuals with alcohol use disorder, opioid use disorder, and stimulant use disorder (excluding cocaine) were found more likely to require ICU care after COVID-19 infection (aOR=1.53–1.99, $p < 0.01$). Increased 30-day mortality (aOR=3.76, $p < 0.01$) was found among people with opioid use disorder.

4. Discussion

4.1. Prescription stimulants and COVID-19 severity

Our study using EHR-based data from a large TriNetX database showed that adults with ADHD who were treated with stimulants had lower rates of healthcare utilization (ED visits, hospitalization, ICU care) and mortality during 30 days following the onset of their COVID-19 infection, compared to adults who did not receive pharmacotherapy for ADHD. The adjusted analyses, controlling for baseline demographic characteristics as well as medical and mental health conditions (including SUDs) associated with ADHD and COVID-19 outcomes, also indicated lower rates of ED, hospital and ICU care among stimulant-treated adults; however, the 30-day mortality risk did not differ between the stimulant and unmedicated cohorts after controlling for the

Table 2

Healthcare utilization and mortality among adults with ADHD and COVID-19 infection: Risk of emergency department (ED), hospital, and intensive care unit (ICU) care and mortality within 30 days of COVID-19 infection (multiple logistic regression).

Characteristics	Emergency Department aOR (95% CI)	Hospitalization, aOR (95% CI)	Intensive Care Unit aOR (95% CI)	Mortality, aOR (95% CI)
Stimulant cohort (vs. unmedicated)	**0.78** (0.75,0.81)**	**0.88** (0.83,0.93)**	**0.76** (0.66,0.87)**	**0.75 (0.54,1.06)**
Female (vs. male)	0.98 (0.94,1.02)	0.89** (0.84,0.95)	0.65** (0.57,0.74)	0.62** (0.45,0.85)
Age (reference: <40 yrs)				
40–64 yrs	0.76** (0.73,0.80)	0.85** (0.79,0.91)	1.12 (0.97,1.29)	1.62** (1.13,2.33)
65 + yrs	0.88** (0.78,0.99)	1.34** (1.15,1.55)	1.44* (1.08,1.94)	3.49** (2.00,6.09)
Hispanic (vs. non-Hispanic)	1.16** (1.07,1.26)	0.88 (0.78,1.01)	0.78 (0.57,1.07)	1.46 (0.76,2.78)
Race (reference: White)				
Black	2.06** (1.94,2.18)	1.58** (1.45,1.72)	1.36** (1.13,1.63)	1.82** (1.18,2.81)
Other	0.96 (0.9,1.03)	1.06 (0.95,1.18)	1.15 (0.91,1.44)	1.12 (0.63,2.00)
Chronic medical conditions				
Obesity	1.12** (1.07,1.18)	0.97 (0.91,1.04)	0.89 (0.77,1.03)	1.21 (0.86,1.69)
Cardiovascular condition	1.31** (1.25,1.38)	1.72** (1.6,1.84)	2.62** (2.28,3.02)	2.65** (1.84,3.82)
Chronic kidney disease	1.28** (1.13,1.46)	1.89** (1.63,2.19)	1.54** (1.18,2.01)	3.17** (1.98,5.06)
Diabetes	1.50** (1.30,1.73)	2.65** (2.25,3.11)	4.08** (3.18,5.23)	3.11** (1.71,5.67)
Mental health disorders				
Depression	1.27** (1.22,1.32)	1.49** (1.40,1.59)	1.15* (1.04,1.32)	1.05 (0.75,1.47)
Anxiety	1.14** (1.10,1.19)	1.08* (1.01,1.15)	1.01 (0.88,1.16)	0.91 (0.65,1.28)
Bipolar	1.67** (1.59,1.76)	1.66** (1.54,1.78)	1.16 (0.99,1.36)	0.90 (0.59,1.37)
Tobacco/nicotine use disorder	1.93** (1.84,2.03)	1.82** (1.70,1.94)	2.07** (1.8,2.38)	1.31 (0.90,1.89)
Alcohol/drug use disorder				
Alcohol use disorder	1.30** (1.22,1.40)	1.76** (1.62,1.92)	1.99** (1.69,2.35)	1.12 (0.70,1.79)
Opioid use disorder	1.37** (1.26,1.49)	1.55** (1.40,1.72)	1.53** (1.25,1.87)	3.76** (2.41,5.86)
Cannabis use disorder	1.21** (1.12,1.31)	1.35** (1.22,1.48)	0.82 (0.66,1.02)	1.67 (0.99,2.81)
Cocaine use disorder	1.25** (1.11,1.41)	0.89 (0.77,1.02)	1.03 (0.79,1.34)	1.04 (0.54,2.01)
Stimulant use disorder[a]	1.52** (1.37,1.69)	1.71** (1.52,1.92)	1.54** (1.22,1.94)	0.69 (0.34,1.41)

* $p < 0.05$
** $p < 0.01$; aOR: adjusted odds ratio; 95% CI: 95% confidence intervals
[a] Stimulant use disorder includes amphetamine-related use disorder, excluding cocaine use disorder

above factors. This suggests that it might not be stimulant medications, per se, but the characteristics linked to prescription stimulant use (e.g., younger or better overall health status) may be associated with less severe outcomes within 30 days of COVID-19 infection.

Prescription stimulants are evidence-based treatment for ADHD (Surman et al., 2013). They are designed to stimulate the receptors of the brain chemical dopamine and norepinephrine to produce and release neurotransmitters. Consequently, more neurotransmitters will stay in the synapse long enough to bind to receptors, allowing messages or signals to be relayed across the neural network. The elevated level of neurotransmitters further increases metabolic activities in the prefrontal cortex of people with ADHD, resulting in better executive functions and attention.

Yet, stimulant medications can rouse the central nervous system in the prefrontal cortex, blocking the reuptake of norepinephrine and dopamine into the presynaptic neuron and increasing their release into the extraneuronal space (Weisler et al., 2005; Hammerness et al., 2009). A rise in circulating catecholamines activates cardiovascular beta-1 adrenoreceptors causing elevated inotropy and heart rates, while activation of alpha-adrenoreceptors can lead to vasoconstriction, elevated blood pressure, and cardiovascular complications, (Latronica et al., 2021) which are known risk factors for worse COVID-19 severity (Geng et al., 2021). ADHD has also been associated with several chronic medical and mental health conditions that often acerbate COVID-19 complications (Nigg, 2013). However, our study does not show greater risk of severe COVID-19 outcomes among patients prescribed stimulants.

Although the literature has indicated greater infection rates and worse outcomes of COVID-19 among people with ADHD, (Merzon et al., 2021) prior research did not account for the potential impact of stimulant treatment and differences between treated and untreated populations. It is possible that stimulant treatment is linked to better COVID-19 outcomes through several mechanisms, including better access to and engagement in care among stimulant-treated individuals. Because stimulant medications are associated with improvements in

executive functions, such as self-control and motivation, adults who are treated with medication for ADHD may have better ability to follow through with the recommended COVID-19 preventive practices relative to untreated adults with ADHD (Adler et al., 2008; Chang et al., 2017). Essentially, stimulant medications interact with the brain and body to change people's behavior by altering brain chemistry and their perceptions about the world around them. Additional research, using a prospective design, is needed to corroborate and better understand these findings.

4.2. Baseline characteristics and COVID-19 severity

Research has shown that adults with ADHD are at increased risk of obesity, cardiovascular disease, chronic kidney disease, and diabetes, (Nigg, 2013) which make them vulnerable to the SARS-CoV-2 virus (Geng et al., 2021). Our study showed that people with ADHD and one or more chronic conditions are more likely than those without chronic conditions to be admitted to ED, hospital, and ICU due to severe illness from COVID-19. Individuals with ADHD and co-occurring chronic medical conditions also suffered higher 30-day mortality rates after COVID-19 infection, based on multiple logistic regression models. This suggests that adults with ADHD and COVID-19 might benefit from more intensive monitoring and ADHD management, to prevent serious complications from COVID-19.

The study also showed associations between severe COVID-19 outcomes and anxiety, depression and bipolar disorders among adults with ADHD. These findings are consistent with prior research examining the relationship between the presence of mental health disorders and COVID-19 outcomes, (Shinn and Viron, 2020) and suggests that people with mental health disorders have worse health status and are more susceptible to COVID-19 infection and its complications (Wang et al., 2021a). In addition, mental health disorders can affect a person's behavior and judgment, which can inadvertently increase their vulnerability to COVID-19 infection. This suggests an urgent need to ensure patients with mental health disorders, including ADHD, have access to

mental health care, especially during the pandemic.

Individuals with SUD are more likely to contract COVID-19 and suffer severe complications from the infection (Wang et al., 2021b). This study further found adults with concomitant ADHD and SUD (excluding tobacco/nicotine use disorder) experienced higher risk of critical care need and death after COVID-19 infection, especially among individuals with opioid, stimulant or alcohol use disorders. Similarly, people with tobacco/nicotine use disorder were also likely to require critical care services after being infected by COVID-19, despite no significant effect on 30-day mortality.

The pandemic has imposed challenges in accessing and delivering necessary treatment and support services for people with SUDs; this care disruption can inhibit addiction prevention and harm reduction efforts. People with ADHD and SUD can face even greater competing needs for their medical care during the pandemic, which might especially impact those who are not treated for their ADHD; those prescribed stimulants for ADHD may be better positioned to access care for SUD because they are already engaged in health care. Since the COVID-19 outbreak, telehealth has been rapidly utilized as a way to provide care for patients with SUDs and other mental health disorders. While telehealth has made delivery of behavioral and other health services more accessible, the effectiveness of such mode of treatment delivery, particularly for pharmacotherapy related decisions, remains unclear. Additional research, with potential combinations of in-person, telehealth, and asynchronous care may facilitate the development of better clinical guidelines to optimize the quality and outcomes of health services for mental health and addiction care.

4.3. Limitations

There are several limitations in the study common to all research utilizing EHR data. First, individuals with ADHD captured in the research network could have received treatment with stimulants through outside providers, which would not be part of the EHR data submitted by a given health system to the TriNetX database; this could have led to unintentional assignment of stimulant-treated individuals to the 'unmedicated' cohort. Similarly, the COVID-19 diagnosis or testing could have been completed at facilities outside of the participating networks and therefore be uncaptured in our analysis. Second, data on several important socioeconomic factors were unavailable in the research database, such as the type of insurance, education and income levels, or rural residence, that ideally would have been included as confounders in our analysis. For instance, presence or absence, and type, of health insurance can impact access to and use of health care, particularly for mental health and addiction services. People with health insurance covering ADHD and stimulant related management might be more likely to receive other routine care, which, in turn, can lead to better overall health and lesser risk of developing severe complications after COVID-19 infection. However, the large sample size available through the TriNetX database constitutes a strength of this study; it allowed for extracting data on a wide range of medical and psychiatric comorbid conditions, enabling us to account for the impacts of these conditions, as well as a limited number of sociodemographic factors, in the multiple regression analysis and minimize the impact of potential confounders, increasing the generalizability of our results. Third, we were unable to determine the 'current' smoking/tobacco use status or whether a given SUD was active versus in remission at the time of the COVID-19 infection. In addition, although we used a separate diagnosis for 'cocaine use disorder' and 'stimulant use disorder', following the prior literature, (Wang et al., 2021a, 2021b) cocaine is a stimulant; it is possible that the 'stimulant use disorder' diagnoses also encompassed 'cocaine use disorder' diagnoses, making the distinction between the impact of these two sets of diagnoses less precise. We also were unable to account for the severity or stage of the identified comorbid conditions in relation to COVID-19 infection. For example, a well-controlled, new-onset diabetes or depression in remission could carry different health

risks than their counterpart conditions (i.e., uncontrolled, long-term diabetes, active depression with severe symptoms). Prospective research could overcome these limitations. Lastly, there may be unobserved or unknown confounders present that we did not account for in statistical analysis. For instance, individuals in the stimulant cohort might consist of people experiencing more severe ADHD or other psychiatric symptoms. Thus, those individuals were likely to receive prescription stimulants, potentially resulting in selection bias. It is also possible that people treated with stimulant medications may have fewer mental health or SUD-related concerns and therefore clinicians may be more open to prescribing stimulants to treat ADHD (Babinski et al., 2022). However, the research EHR data did not contain necessary information to measure and analyze changes in ADHD severity. Future analyses using advanced data mining techniques and advanced analytical approaches (e.g., propensity score matching), utilizing artificial intelligence or machine learning algorithms, might better elucidate currently unidentified yet important confounders.

5. Conclusion

Emerging evidence indicates that adults with ADHD are at increased risk of infection and complications from the SARS-CoV-2 virus infection. Our study of TriNetX-based EHR data showed that, among adults with ADHD and COVID-19, those treated with stimulants, compared to those not treated with pharmacotherapy, had lower healthcare utilization (ED visits, hospitalization, ICU care) and mortality rates after COVID-19 infection, suggesting the risk of COVID-19 complications can be reduced in a population of adults with stimulant-treated ADHD. Additional research is needed to understand the effects of COVID-19 on neurological mechanisms and interactions with ADHD medications. Further research, accounting for the impact of potential confounders, is needed to elucidate these findings, evaluate the relationship between stimulant treatment and COVID-19 outcomes among adults with ADHD, and help guide clinical decision-making.

Author contributions

All authors contributed to conceptualization, data curation, investigation, methodology, and writing of the original and final drafts; AEZ provided supervision.

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Declaration of Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2022.07.005.

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