Psychiatry Research 319 (2023) 114989

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Caffeine levels and dietary intake in smokers with schizophrenia and bipolar disorder

Rachel L. Rosen [a], Rahul S. Ramasubramani [b], Neal L. Benowitz [c], Kunal K. Gandhi [d], Jill M. Williams [b,*]

[a] Rutgers, The State University of New Jersey, Department of Psychology, 152 Frelinghuysen Road, Piscataway, NJ 08854, United States
[b] Rutgers Robert Wood Johnson Medical School, Department of Psychiatry, 317 George Street, Suite 105, New Brunswick, NJ 08901, United States
[c] University of California San Francisco, School of Medicine, Zuckerberg San Francisco General Hospital, 1001 Potrero Ave, San Francisco, CA 94110, United States
[d] Novartis, Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936, United States

ARTICLE INFO

Keywords:
Caffeine
Nicotine
Cigarette
Serious mental illness
Smoke

ABSTRACT

Caffeine is one of the most widely used psychoactive drugs in the United States. High rates of caffeine use have been observed in adult smokers as well as those with serious mental illness. The current secondary analysis aimed to extend previous findings demonstrating high caffeine intake in schizophrenia by examining dietary intake of caffeine and serum caffeine levels in outpatient smokers with schizophrenia (SCZ), bipolar disorder (BP) and control smokers with no psychiatric diagnoses (CON). Two hundred forty-eight adult smokers (SCZ=80; BP=80; CON=88) were included in the current study. Adult smokers with schizophrenia, bipolar disorder, and no psychiatric diagnoses were 40.85 (SD = 11.90) years old on average and all participants were current smokers (~20 cigarettes per day). Twenty-four hour self-reported caffeine intake (in mg) was highest among individuals with bipolar disorder (median=195.3), followed by adults with schizophrenia (median=155.0) and controls (median=131.7). Participants with bipolar disorder also had the highest serum caffeine levels (in ng/ml; median=1725), followed by those with schizophrenia (median=1194) and controls (median=613.2). These results provide additional evidence of high caffeine intake among adults with schizophrenia and extend findings by identifying even higher rates of caffeine use in those with bipolar disorder. The current study suggests that caffeine intake is higher among subgroups of patients with serious mental illness.

1. Introduction

Caffeine is a widely used psychoactive drug, with more than 89% of adults in the United States reporting daily use (Fulgoni et al., 2015). More than 98% of caffeine intake among US adults comes from beverages, including coffee, tea, and soda (Mitchell et al., 2014). Evidence suggests that it is safe for most healthy adults to consume up to 400 mg of caffeine per day, which is the equivalent of about 4 cups of coffee (Nawrot et al., 2003). While studies have demonstrated that most adults in the United States consume an average of 186 mg of caffeine per day (Fulgoni et al., 2015), heavier use has been observed in subpopulations, including among smokers (Swanson et al., 1994) and adults with serious mental illness (Gandhi et al., 2010; Strassnig et al., 2006).

Caffeine dose, and not merely use, is an important consideration because although adults in the United States consume 3 mg/kg of caffeine on average controlling for body weight, there are subsets of adults who take in much higher amounts (over 5 mg/kg) (Institute of Medicine (US) Committee on Military Nutrition Research, 2001). Effects of very high caffeine use are not well understood. Doses over 600 mg are generally not recommended and symptoms of caffeine toxicity can include negative side effects, including psychological (anxiety, restlessness, insomnia) and physical (tachycardia, excess stomach acid, heartburn) symptoms. High doses of caffeine may also negatively impact mood although this may be less notable in individuals with caffeine tolerance (Institute of Medicine (US) Committee on Military Nutrition Research, 2001). There is also evidence that age and sex can affect responses to caffeine dose (Institute of Medicine (US) Committee on Military Nutrition Research, 2001) and medications, such as "inducers of the liver enzyme CYP1A2" as opposed to "global hepatic inducers" and oral contraceptives, can also impact serum caffeine levels.

The main effect of caffeine is cognitive performance enhancement via increased alertness, attention, and vigilance. The effects of caffeine

* Corresponding author at: 317 George St, Suite 105, New Brunswick, NJ 08901, United States.
E-mail address: jill.williams@rutgers.edu (J.M. Williams).

https://doi.org/10.1016/j.psychres.2022.114989
Received 16 February 2022; Received in revised form 23 November 2022; Accepted 27 November 2022
Available online 28 November 2022

are U-shaped, such that higher levels of caffeine intake contribute to higher levels of arousal (up to about 300 mg) followed by poorer functioning at even higher rates (McLellan et al., 2016). Caffeine is readily absorbed within 45 min of ingestion and blood levels peak within about two hours (Institute of Medicine (US) Committee on Military Nutrition Research, 2001). The half-life of caffeine is approximately five hours although it can range to as much as 9 h in some individuals. Caffeine is metabolized in the liver, mainly by the CYP1A2 cytochrome enzyme (Institute of Medicine (US) Committee on Military Nutrition Research, 2001). Caffeine increases alertness, attention, and vigilance through inhibition of adenosine receptors in the body. Adenosine is as an endogenous inhibitory neurotransmitter that has sedative effects; however, when blocked by caffeine, it leads to stimulation (Lara et al., 2006). Antagonizing the adenosine receptor may also have a neuroprotective role, slowing cognitive and memory decline, but effects are complex as adenosine also has numerous neuromodulatory effects on other neurotransmitters. Less is known about its role in impacting executive functions, such as reasoning and decision making, and many studies of the cognitive effects of caffeine have been done with healthy adults without mental illness.

There are several hypotheses that seek to explain the relationship between caffeine intake and mental illnesses like schizophrenia. One explanation is the well-established association between caffeine and smoking. Specifically, the tars in cigarette smoke increase the metabolism of caffeine via induction of the CYP1A2 hepatic enzyme which lowers serum caffeine levels (Zevin and Benowitz, 1999). Thus, in order to maintain the same stimulating effects of caffeine (e.g., alertness), one might compensate by increasing their caffeine intake (i.e., consuming more caffeinated beverages). Individuals with mental illnesses smoke at rates 2–3 times higher than the general population, and thus it is necessary to control for smoking in studies of caffeine use in those with mental illness to account for the pharmacokinetic effects of smoking on caffeine. Studies of dietary intake in schizophrenia find almost twice as much caffeine consumption compared to controls, although these were in mixed samples that included both smokers and non-smokers (Henderson et al., 2006; Strassnig et al., 2006). Behavioral research also provides support for the co-use of caffeine and cigarettes, highlighting that in addition to metabolic influences, caffeine use may influence smoking motivations, such as urge to smoke or palatability of cigarettes (Treloar et al., 2014). Less is known about additional factors that may explain the relationship between caffeine use and serious mental illness; however, self-medication of psychiatric symptoms, compensation for the sedative effects of medications, coping with sleep deprivation, and pharmacokinetic interactions with other medications are viable explanations.

Another theory links high caffeine intake to adenosine receptors and supports a possible self-medication effect. Adenosine dysfunction may contribute to the inhibitory deficits of cholinergic and dopaminergic systems observed in schizophrenia. Adenosine is considered an endogenous anticonvulsant and neuroprotective agent and A1 receptor agonists have antipsychotic properties. A2A receptors are co-localized with dopamine D2 receptors, and have antipsychotic properties. It is theorized that individuals with schizophrenia have decreased adenosinergic activity, perhaps due to lower expression of the A1 receptor (Lara et al., 2006). Moderate caffeine doses could help to make the system more functional. There is one study showing evidence of a neurocognitive (i.e., processing speed, working memory) benefit from caffeine in schizophrenia, though this was only seen in males (Núñez, 2015).

Despite the potential to enhance cognition at low to moderate caffeine doses, the effects of caffeine are complex and possibly harmful at high doses, especially among adults with serious mental illness who are on many medications and who frequently smoke. A recent review of caffeine use in adults with bipolar disorder suggested that changes in caffeine intake were associated with mood states and interacted with sleep and medication levels (Frigerio et al., 2021). Far less is known about how high caffeine intake may impact psychiatric symptoms (e.g., depressive symptoms, cognitive functioning) in adults with serious mental illness who smoke. These complex associations warrant further study. The current study aimed to replicate and build on previous findings that demonstrated high levels of caffeine use in adults with schizophrenia compared to nonpsychiatric control participants. Further, the current study aimed to expand on these findings by examining rates of caffeine intake in adults with bipolar disorder, a self-report dietary intake questionnaire, *and* serum caffeine levels in adult smokers with and without serious mental illness.

2. Method

2.1. Participants

The current study is a secondary analysis of data from a larger study (Williams et al., 2011) examining nicotine intake and smoking behavior. The current study examined caffeine intake and serum caffeine levels in outpatient smokers with schizophrenia (SCZ), bipolar disorder (BPD) and control smokers who did not have mental illness (CON). In the parent study (conducted from 2006 to 2009), participants were

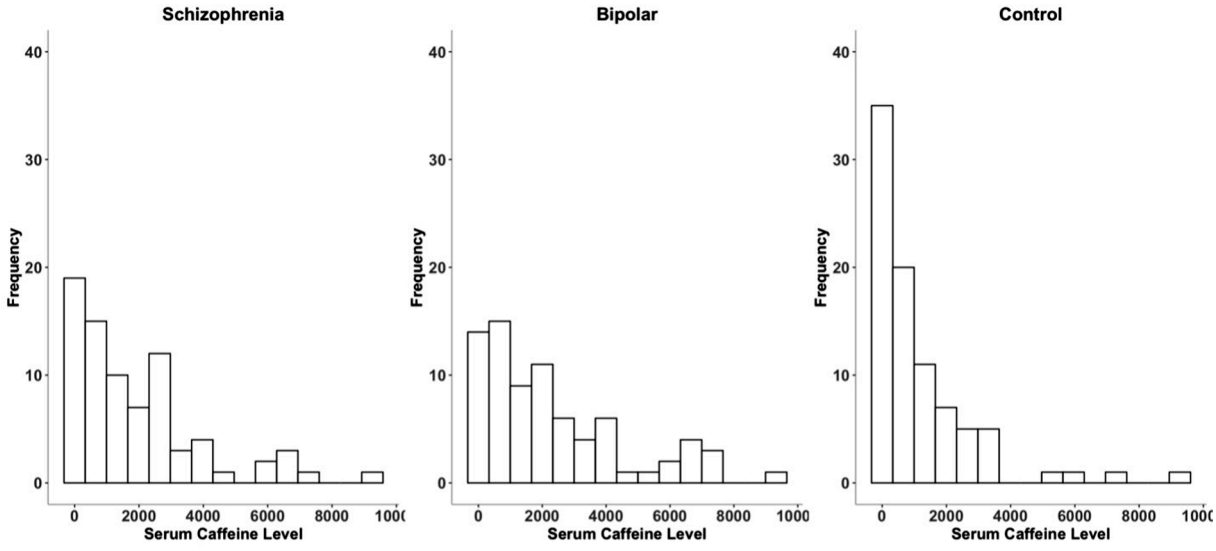

Fig. 1. Serum Caffeine Levels (ng/ml) by Diagnosis Group.

recruited through outpatient behavioral health care agencies and community advertisements. Two hundred seventy-six adults participated in the original study. All subjects with schizophrenia or bipolar disorder were enrolled in mental health treatment and had their diagnosis confirmed with the Structured Clinical Interview for DSM-IV (SCID; First and Gibbon, 2004). Individuals with schizoaffective disorder were excluded from the study. Adults in the control condition had to be without any mental illness within the last year (SCID confirmed) and could not be taking an antidepressant, mood stabilizer or anxiolytic for any reason within the previous 6 months. More detailed descriptions of study design and data collection have been published elsewhere (Williams et al., 2011, 2012). This study was approved by the Rutgers-Robert Wood Johnson Medical School Institutional Review Board.

All subjects were ≥18 years of age, smoked 10 or more cigarettes per day (CPD), and had a baseline expired carbon monoxide (CO) level greater than 8 parts per million (ppm). Subjects were not seeking smoking cessation treatment and were excluded if they were receiving any form of nicotine replacement, clonidine, bupropion, or nortriptyline. Subjects who were using tobacco products other than cigarettes, those who were pregnant, or who had an current substance use problem (as defined by the Drug Abuse Screening Test; (Gavin et al., 1989) or Alcohol Use Disorders Identification Test; (Babor and Grant, 1989), were also excluded.

Two hundred forty-eight adult smokers (SCZ=80; BPD=80; CON=88) were eligible for this secondary analysis. Additional exclusion criteria included missing the afternoon blood draw (which was used to examine serum caffeine levels) and missing the self-report dietary questionnaire.

2.2. Procedure

After signing a consent form, participants completed a baseline assessment, which included basic demographic questions, smoking history, physical health indicators, and psychiatric symptom measures. Assessment protocols are described in detail elsewhere (Williams et al., 2011, 2012). No one was abstinent from smoking during the study procedures, during which usual smoking behavior was assessed.

Following completion of the baseline assessment, subjects provided a blood sample. Blood was drawn at 3pm under standardized conditions. Ten mL (2 to 3 teaspoons) of blood was collected in a serum tube, centrifuged for 15 min and frozen at –20 °C for later analysis. Specimens were sent to the Clinical Pharmacology Laboratory at the University of California San Francisco for analysis of nicotine, cotinine, caffeine and 3-hydroxycotinine (3HC), which were quantified using liquid chromatography-mass spectrometry (Jacob et al., 1981). Nicotine, cotinine and 3HC results have been previously reported (Williams et al., 2011, 2012). Consistent with procedures used elsewhere (Gandhi et al., 2010), subjects with a serum caffeine level lower than 1.0 ng/ml were excluded from most analyses, given a high likelihood that they did not regularly consume caffeine. We calculated 3-hydroxycotinine to cotinine ratio (commonly referred to as the nicotine metabolite ratio, NMR), a biomarker of the rate of nicotine metabolism.

2.3. Measures

Participant characteristics: Participants provided basic demographic information, including age, race, ethnicity, sex, education, and employment.

Smoking history. Participants provided information about their current and past smoking behavior. The baseline assessment also included biochemical verification of smoking (via expired breath CO). To assess cigarette dependence, we used the Fagerström Test for Cigarette Dependence (FTCD; Fagerström, 2011; Heatherton et al., 1991) and urges to smoke were assessed via the Questionnaire of Smoking Urges Brief Form (QSU; Cox et al., 2001).

Caffeine use: Participants completed the Caffeine Consumption Questionnaire (Shohet and Landrum, 2001), on which they reported their consumption of various caffeinated substances including energy drinks and caffeine containing medication. Participants were asked to specify how many servings of each substance they consumed in the prior 48 h, as well as the time of day each was consumed. Patients were asked to recall caffeine intake using a standardized instrument, which included a broad list of commonly used caffeinated products and is also broken down by time of day. We used visual prompts of actual cup sizes during the interview to more accurately capture quantities of caffeinated beverages consumed.

Physical Health: We assessed current medication use and additional physical health indicators, including measures of weight, body mass index (BMI), and vital signs. Antipsychotic medication dose was converted to chlorpromazine equivalents (CPZ) to standardize dose across different medications (Woods, 2003). We also coded the following medications as global hepatic inducers which are known to affect CYP1A2: Carbamazepine, Oxcarbazepine, Phenytoin, Phenobarbital.

Psychological Symptoms: Participants with schizophrenia or bipolar disorder were assessed for current psychological symptoms using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989) and the

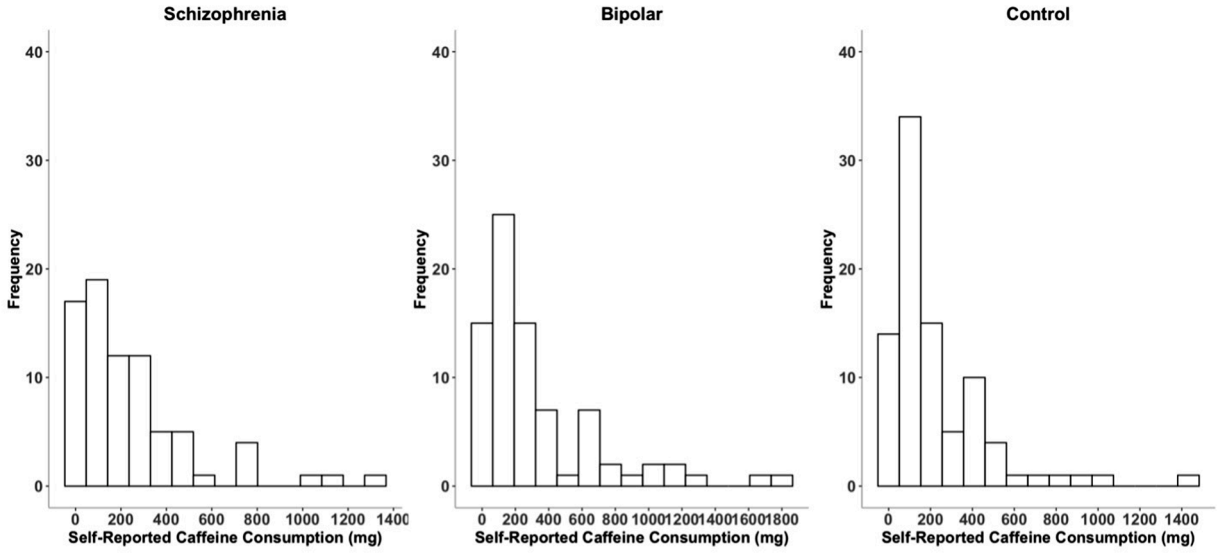

Fig. 2. Self-Reported Caffeine Intake (mg) in past 24 hours by Diagnosis Group.

Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979). All participants completed the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988).

2.4. Data analytic plan

Independent sample t-tests (for continuous variables) and chi-square analyses (for categorical variables) were used to examine baseline differences in socio-demographic variables, substance use variables, physical health indicators, and psychological symptom scores across groups. Serum caffeine values as well as the dietary caffeine intake were analyzed using the nonparametric Kruskal Wallis Test.

Separate multivariate gamma regression with a log link were conducted to identify predictors of serum caffeine and dietary caffeine intake. The following theoretically relevant variables were included in analyses: diagnosis group (control, schizophrenia, bipolar disorder), age, sex (male, female), race/ethnicity (White, Black, Hispanic/Latino, not listed), cigarettes per day, 3HC/cotinine ratio, taking a global hepatic inducer (yes/no). P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS v28.0.

3. Results

3.1. Participant characteristics

One-way ANOVA (for continuous variables) and chi-square analyses (for categorical variables) were used to identify associations between diagnosis group and basic demographic characteristics in the current sample. Adults smokers with schizophrenia ($n = 80$), bipolar disorder ($n = 80$), and no psychiatric diagnoses ($n = 88$) were 40.85 (SD = 11.90) years old on average. Participants with schizophrenia were older, on average, than individuals with bipolar disorder and individuals with no psychiatric diagnoses [SZC: $M = 45.5$ (10.7), BP: $M = 38.8$ (11.5), Control: $M = 38.5$ (12.2); F(2, 245)=9.826, $p<.001$].

More than half of the participants (58.5%) were male, and White (55.6%). The remaining participants were Black (30.6%), Hispanic/Latino (9.7%) or identified as a different race (4%). There was a significant association between diagnosis group and race [$x^2(2)=6.725$, $p=.035$]. A greater proportion of participants in the schizophrenia condition were male (70%) compared to the control group (51.1%). We also identified a significant association between race/ethnicity and diagnosis group [$x^2(6)=21.1$, $p=.002$]. A greater proportion of individuals with bipolar disorder were White (70%) compared to those in the Schizophrenia condition (45%). A greater proportion of participants with schizophrenia were Black (46.3%) compared to those with bipolar disorder (16.3%). There were no significant differences in the proportion of individuals identifying as Hispanic/Latino or another race across diagnosis groups. There was a significant difference in BMI across groups ($p = .043$). Post-hoc comparisons suggest that control participants had lower BMIs than each other group (all $p < 0.05$).

Few participants completed any college (35.5%) and the majority of participants were unemployed (75%). There was a significant association between diagnosis group and employment status [$x^2(2)=23.576$, $p<.001$]. A greater proportion of individuals in the control condition were currently employed (43.2%) compared to individuals with bipolar disorder (18.8%) and schizophrenia (12.5%). Additional sample characteristics and group comparisons are described in Table 1.

Affect and depression scores and differences across groups are reported in Table 1. MADRS scores were in the mild depression range and not different between SCZ and BPD. The PANSS positive, negative and total scores were significantly higher in adults with SCZ. There was a significant difference in PANAS negative and PANAS positive scores across groups (all $p < 05$). Post-hoc comparisons revealed that adults with bipolar disorder had significantly higher negative affect compared to each of the other groups (all $p < .05$) and the control group had significantly higher positive affect than each of the other two groups (all $p < 0.05$). Participants with schizophrenia were taking significantly higher doses of CPZ than participants with bipolar disorder. Almost half of the participants with bipolar disorder reported a history of psychosis (48.1%) and approximately three quarters (73.4%) were taking antipsychotic medication. All but one adult with schizophrenia reported

Table 1
Participant characteristics and group comparisons.

	Schizophrenia Group ($n = 80$) Mean (SD)	Bipolar Group ($n = 80$) Mean (SD)	Control Group ($n = 88$) Mean (SD)	X^2 or F	p
Age	45.5 (10.7)	38.8 (11.5)	38.5 (12.2)	9.83	<0.001
Sex				6.73	0.035
Male	56	44	45		
Female	24	36	43		
Race/ Ethnicity				21.10	0.002
White	36	56	46		
Black	37	13	26		
Hispanic	4	7	13		
Not listed	3	4	3		
Education				6.67	0.154
Less than high school	24	17	15		
High School or Equivalent	33	29	42		
At least some College	23	34	31		
Employment Status				23.58	<0.001
Currently working	10	15	38		
Currently unemployed	70	65	50		

Table 2
Smoking, caffeine consumption and associated health variables.

	Schizophrenia Group ($n = 80$) Mean (SD)	Bipolar Group ($n = 80$) Mean (SD)	Control Group ($n = 88$) Mean (SD)	X^2 or F	p
Cigarettes Smoked per Day	22.1 (11.2)	19.8 (7.8)	20.0 (7.3)	1.73	0.179
BMI (kg/mˆ2)	32.3 (8.2)	32.4 (6.7)	29.6 (9.3)	3.18	0.043
Pulse (beats/ min)	81.0 (14.2)	80.9 (14.9)	77.8 (12.1)	1.49	0.228
	Median (25th P, 75th P)	*Median (25th P, 75th P)*	*Median (25th P, 75th P)*	*Test Statistic*	*p*
CCQ Self-Reported Caffeine Consumed Last 24 Hrs (mg)	155.0 (56.0, 326.3)	195.3 (81.3 414.3)	131.7 (69.94, 330.0)	2.38	.304
Serum Caffeine 3 PM (ng/ml)	1194.1 (370.8, 2811.8)	1725.2 (468.0, 3368.8)	613.2 (197.3, 1560.6)	14.16	.001
CCQ Self-Reported Caffeine Consumed Last 24 Hrs by weight (mg/kg)	1.63 (0.52, 3.90)	1.82 (0.88, 4.62)	1.62 (0.80, 3.77)	1.98	.372

taking antipsychotic medication. Additional information is presented in Table 2.

3.2. Smoking and caffeine use

All participants were current cigarette smokers. On average, participants smoked 20.62 (SD=8.93) cigarettes per day and had an expired breath carbon monoxide level of 20.25 (SD= 10.33) parts per million. Participants did not differ in terms of cigarettes smoked per day.

Caffeine intake data (self-reported caffeine intake (mg) within the past 24 h and serum caffeine levels (ng/ml)) are right skewed (Figs. 1 and 2). Individuals with bipolar disorder had the highest self-reported caffeine intake (median=195.3), followed by adults with schizophrenia (median=155.0) and controls (median=131.7). Participants with bipolar disorder also had the highest serum caffeine levels (median=1725 ng/ml), followed by those with schizophrenia (median=1194 ng/ml) and controls (median=613.2 ng/ml). A Kruskal-Wallis Test revealed no significant difference in self-report caffeine intake (p=.304); however, there was a significant difference in serum caffeine levels across groups (p=.001). Specifically, the control group differed significantly from each other diagnosis group (i.e., schizophrenia, bipolar disorder). Further, a Kruskal-Wallis Test revealed no significant difference in self-reported caffeine consumption by weight (mg/kg) across the three diagnosis groups (p=.372) and a chi square analysis did not reveal a significant difference in the proportion of participants who consumed more than 4 mg/kg of caffeine in the preceding 24 h (p=.528). Across all groups, approximately 18–25% of participants consumed more than 400 mg of caffeine based on self-report. Though not stasticially significant, more participants with bipolar disorder (14.3%) and schizophrenia (9%) had serum caffeine levels higher than 5000 ng/ml compared to the control participants (5.6%). Similarly, though not statistically significant, more participants with bipolar disorder (5.2%) had serum caffeine levels higher than 7000 ng/ml compared to the control participants (2.3%) and participants with schizophrenia (1.3%). Additional information is presented in Table 3.

There was a small, but significant correlation between self-reported caffeine intake over the previous 24 h and serum caffeine levels (r = 0.174, p=.007). Four individuals who self-reported no caffeine intake in the past 24 h had concordant serum caffeine levels (0 ng/ml). Two hundred one individuals who reported caffeine intake during the past 24 h had concordant serum caffeine levels (>0 ng/ml). However, for 36 individuals, there was disagreement in self-report and serum caffeine levels. Twelve individuals denied caffeine intake during the past 24 h but had a non-zero serum caffeine level. The median detected serum caffeine level among these 12 participants was 412.10 ng/ml. Twenty-four individuals reported consuming caffeine in the past 48 h but had a serum caffeine level of 0 ng/ml. Given that the dietary report assessed caffeine use over the past 48 h, it is possible that some individuals consumed caffeine in the past 48 h but not recently enough to be detected in the serum. Seven participants had missing serum levels or self-report caffeine information. Follow-up correlation analysis including only participants with concordant serum caffeine levels and self-reported caffeine intake (i.e., both > 0) was not significant (r = 0.093, p=.188).

Gamma regression models with a log link were used to examine predictors of caffeine use in adults with and without serious mental illness. Participants were only included in the analysis if they had valid serum levels or self-report caffeine levels greater than 0. In the first analysis, we found an association between race, diagnosis group, and age on serum caffeine levels. In the second analysis, we found an association between age and diagnosis group on self-report caffeine intake. Detailed results can be found in Table 4.

Table 4
Predictors of caffeine intake in adult smokers with and without serious mental illness, using multivariate gamma regression with log link.

	B	SE	Wald Chi-Square	p	Effect Size[a]
Adults with schizophrenia, bipolar disorder, and healthy controls, analysis of serum caffeine (n = 213)					
Age	**.014**	**.006**	**5.385**	**.020**	**1.410**
Race/Ethnicity					
White	Ref	–	–	–	
Black	**−0.637**	**.166**	**14.762**	**<0.001**	
Hispanic/Latino	−0.320	.211	3.300	.129	
Not Listed	−0.481	.335	2.060	.151	
Sex					
Male	Ref	–	–	–	
Female	.154	.137	1.26	.262	
Diagnosis Group					
No Psych Dignoses	Ref	–	–	–	
Schizophrenia	**.500**	**.173**	**3.381**	**.004**	**64.872**
Bipolar Disorder	**.502**	**.156**	**10.306**	**.001**	**65.202**
Cigarettes per day	.009	.008	5.384	.238	
Global Hepatic Inducer Use					
No	Ref	–	–	–	
Yes	.700	.439	2.542	.111	
3HC Ratio	−0.309	.189	2.678	.102	
Adults with schizophrenia, bipolar disorder, and healthy controls, analysis of self-report caffeine intake (n = 228)					
Age	**.015**	**.006**	**7.293**	**.007**	**1.511**
Race/Ethnicity					
White	Ref	–	–	–	
Black	−0.233	.147	2.527	.112	
Hispanic/Latino	.029	.216	.018	.893	
Not Listed	−0.300	.319	.888	.346	
Sex					
Male	Ref	–	–	–	
Female	−0.024	.130	.033	.856	
Diagnosis Group					
No Psych Dignoses	Ref	–	–	–	
Schizophrenia	.050	.161	.095	.758	
Bipolar Disorder	**.359**	**.154**	**5.440**	**.020**	**43.190**
Cigarettes per day	.013	.008	2.548	.110	
Global Hepatic Inducer Use					
No	Ref	–	–	–	
Yes	.057	.448	.016	.899	
3HC Ratio	.018	.202	.008	.929	

The effect size is derived using the following formula: (exp(B)−1) x 100 and is intepretted as the percent change in the outcome for every one unit change in the predictor, or in the case of categorical variables, the percent change in outcome compared to the reference group.

Table 3
Mental health characteristics.

	Schizophrenia Group (n = 80) Mean (SD)	Bipolar Group (n = 80) Mean (SD)	Control Group (n = 88) Mean (SD)	t or F	p
CPZ	514.4 (491.2)	281.9 (387.6)	–	3.18	.002
MADRS Total	10.4 (8.1)	10.7 (7.9)	–	−0.25	0.804
PANSS Positive	18.3 (6.0)	13.0 (4.7)	–	6.18	<0.001
PANSS Negative	18.4 (6.1)	13.0 (5.7)	–	5.60	<0.001
PANAS Positive	22.1 (9.5)	22.3 (9.2)	26.7 (7.7)	7.50	.001
PANAS Negative	7.7 (7.7)	12.0 (9.7)	5.1 (6.9)	15.24	<0.001

4. Discussion

These results replicate our prior study which shows higher serum caffeine levels in smokers with schizophrenia compared to controls who smoke the same amount of cigarettes per day. This study builds on prior work by finding even higher rates of caffeine use in adults with bipolar disorder compared to controls. Further, this study adds to the literature by identifying predictors of caffeine use when measured via serum caffeine levels and self-report caffeine intake. Although not presented here, the overwhelming route of ingestion of caffeine from questionnaire data was coffee and soda. Use of energy drinks or caffeine supplements was negligible in this sample (collected 2006–2009).

Adults with schizophrenia and bipolar disorder had higher serum caffeine levels than control participants who smoked the same amount. However, values were highest in the bipolar group. Consistent with our prior work, this relationship does not seem to be merely an effect of taking antipsychotic medications, having a higher antipsychotic dose, or merely a history of psychosis. Only half of the participants with bipolar disorder reported a history of psychosis and about three quarters were taking antipsychotic medication. It also seems unlikely that the higher caffeine levels are due to interactions at the CYP1A2 enzyme since we did not find an association with taking these antipsychotic medications.

Additional predictors of serum caffeine were consistent with prior findings and included age (Arrojo-Romero et al., 2015) and race (Black vs White; Rehm et al., 2020). In this study we did not find an effect of taking a hepatic inducer or sex on caffeine levels despite such findings in other studies (Arrojo-Romero et al., 2015; Rasmussen et al., 2002).

We did not find significant differences in caffeine intake between groups based on questionnaire data. Further, self reported caffeine intake data and serum levels were only slightly correlated. Others have similarly found that questionnaire data are unreliable and may have limited validity (Banko et al., 2010), providing more support for the use of blood levels as the preferred measurement approach. The lack of association between caffeine meaures and symptom scores could be due tolerance to caffeine's effects.

Although we had a sizeable portion of the sample (18–25%) that reported heavy caffeine intake (more than 4 mg/kg), this also did not vary between the different diagnosis groups. The overall heavy intake of caffeine in the total sample likely reflects the considerable daily smoking also observed. The clinical implications of high caffeine levels are not well understood, particularly in terms of how it may impact serious mental illnesses. The current study demonstrated large group differences in negative and positive mood, measured by the PANAS positive and negative scores. We previously reported on the effect of positive and negative affect on measurements of smoking intensity (Williams et al., 2011, 2012). Individuals with serious mental illness may use substances like nicotine and caffeine more intensely (more frequently and in higher doses) in response to having less ability to tolerate negative affect related to their illness or because they are more sensitive to the effects of substance withdrawal. Future work should examine relationships between caffeine intake and psychiatric symptoms, including positive and negative affect, depression, psychosis, and mania.

Strengths of the current study include study procedures which standardized the timing of assesssments and blood draws. Additionally, the current study included non-psychiatric control participants who smoked the same amount of cigarettes per day and were matched in several measures of SES to the participants with bipolar disorder and schizophrenia. Control participants were also not taking any psychiatric medications. There are several limitations worth noting. First, the current study was a secondary analysis designed to examine differences in caffeine use among adults with and without serious mental illness. However, the original study was not designed with these study aims in mind. Thus, we cannot rule out possible metabolic and genetic differences that might result in different caffeine levels and inclusion of caffeine metabolites should be included in any future analyses. Second, due to extremely low endorsement of oral contraceptive use in the current sample, we are unable to determine possible influences of these medications on caffeine levels. Similarly, although caffeine has the potential to increase renal clearance of lithium (Frigerio et al., 2021), we were not able to determine any potential interactions due to small sample size (i.e., only 13 people in the study reporting lithium use). Finally the impact of sleep duration and quality was not measured. This is particularly relevant and warrants attention in future studies given evidence that sleep disruption, in terms of duration and quality, are observed in patients with bipolar disorder (e.g., Keskin et al., 2018). Thus, caffeine intake may be used to compensate for poorer sleep and account for higher intake, as observed in the current study. Future studies should consider additional assessment techniques, including take home or web-based diaries to ensure less recall bias and greater accuracy in reporting caffeine intake. New sources of caffeinated beverages and products as well differences in product preparation (i.e. cold brew) add to the complexity of measuring caffeine, and would need to be considered in future studies.

The current study suggests that caffeine intake is high in subgroups of patients with serious mental illness yet numerous questions remain about its impact on health and mental health. The impact of caffeine on cognition, as well as affective, anxiety and psychotic symptoms is still poorly understood. Adults with mental illness who smoke may be at the highest risk of negative health consequences because they are consuming more caffeine to overcome the hepatic induction associated with smoking cigarettes. In the context of quitting smoking, caffeine levels would be expected to be higher, as was demonstrated in one study by Benowitz et al. (1989), inducing possible caffeine intoxication. This could undermine efforts to quit smoking and cause considerable distress, including feelings of anxiety. As the US adult population trends indicate increases in coffee and energy drink consumption, more studies of high caffeine intake, especially among vulnerable populations, are warranted.

CRediT authorship contribution statement

All authors reviewed and approved the final manuscript.

Declaration of Competing Interest

KG is a full-time employee of Novartis owning company shares. NB has been a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications, and has been an expert witness in litigation against tobacco companies.

Acknowledgments

This work was funded in part by a grant to JMW (R01-MH076672-01A1) from the National Institute on Mental Health, and an analytical chemistry resource grant to NLB (P30 DA012393) from the National Institute on Drug Abuse.

References

Arrojo-Romero, M., Armas Barbazán, C., López-Moriñigo, J.D., Ramos-Ríos, R., Gurpegui, M., Martínez-Ortega, J.M., Jurado, D., Diaz, F.J., de Leon, J., 2015. Caffeine consumption in a long-term psychiatric hospital: tobacco smoking may explain in large part the apparent association between schizophrenia and caffeine use. Schizophr. Res. 164 (1–3), 234–241. https://doi.org/10.1016/j.schres.2015.01.042.

Babor, T.F., Grant, M., 1989. From clinical research to secondary prevention: international collaboration in the development of the Alcohol Disorders Identification Test (AUDIT). Alcohol Health Res. World 13, 371–374.

Banko, L.T., Haq, S.A., Rainaldi, D.A., Klem, I., Siegler, J., Fogel, J., Sacchi, T.J., Heitner, J.F., 2010. Incidence of caffeine in serum of patients undergoing dipyridamole myocardial perfusion stress test by an intensive versus routine caffeine history screening. Am. J. Cardiol. 105 (10), 1474–1479.

Benowitz, N.L., Hall, S.M., Modin, G., 1989. Persistent increase in caffeine concentrations in people who stop smoking. BMJ Br. Med. J. 298 (6680), 1075. https://doi.org/10.1136/bmj.298.6680.1075.

Cox, L.S., Tiffany, S.T., Christen, A.G., 2001. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco 3 (1), 7–16. https://doi.org/10.1080/14622200020032051.

Fagerström, K., 2011. Determinants of tobacco use and renaming the FTND to the Fagerström Test for Cigarette Dependence. Nicotine & Tobacco Research 14 (1), 75–78.

First, M.B., Gibbon, M., 2004. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis. II Disorders (SCID-II).

Frigerio, S., Strawbridge, R., Young, A.H., 2021. The impact of caffeine consumption on clinical symptoms in patients with bipolar disorder: a systematic review. Bipolar Disord. 23 (3), 241–251. https://doi.org/10.1111/bdi.12990.

Fulgoni III, V.L., Keast, D.R., Lieberman, H.R, 2015. Trends in intake and sources of caffeine in the diets of US adults: 2001–2010. Am. J. Clin. Nutr. 101 (5), 1081–1087. https://doi.org/10.3945/ajcn.113.080077.

Gandhi, K.K., Williams, J.M., Menza, M., Galazyn, M., Benowitz, N.L., 2010. Higher serum caffeine in smokers with schizophrenia compared to smoking controls. Drug Alcohol Depend. 110 (1–2), 151–155. https://doi.org/10.1016/j.drugalcdep.2010.01.021.

Gavin, D., Ross, H., Skinner, H., 1989. Diagnostic Validity of the Drug Abuse Screening Test in the Assessment of DSM-III Drug Disorders. Br. J. Addict. 84, 301–307. https://doi.org/10.1111/j.1360-0443.1989.tb03463.x.

Heatherton, T.F., Kozlowski, L.T., Frecker, R.C., Fagerstrom, K.-O., 1991. The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br. J. Addict. 86 (9), 1119–1127.

Henderson, D.C., Borba, C.P., Daley, T.B., Boxill, R., Nguyen, D.D., Culhane, M.A., Louie, P., Cather, C., Evins, A.E., Freudenreich, O., Taber, S.M., Goff, D.C., 2006. Dietary Intake Profile of Patients with Schizophrenia. Ann. Clin. Psychiatry 18 (2), 99–105. https://doi.org/10.1080/10401230600614538.

Institute of Medicine (US) Committee on Military Nutrition Research, 2001. Caffeine For the Sustainment of Mental Task Performance: Formulations for Military Operations. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK223802/.

Jacob III, P., Wilson, M., Benowitz, N.L, 1981. Improved gas chromatographic method for the determination of nicotine and cotinine in biologic fluids. J. Chromat. B Biomed. Sci. Appl. 222 (1), 61–70.

Kay, S.R., Opler, L.A., Lindenmayer, J.P., 1989. The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. Br. J. Psychiatry Suppl. 7, 59–67.

Keskin, N., Tamam, L., Ozpoyraz, N., 2018. Assessment of sleep quality in bipolar euthymic patients. Compr. Psychiatry 80, 116–125. https://doi.org/10.1016/j.comppsych.2017.09.012.

Lara, D.R., Dall'Igna, O.P., Ghisolfi, E.S., Brunstein, M.G, 2006. Involvement of adenosine in the neurobiology of schizophrenia and its therapeutic implications. Prog. Neuropsychopharmacol. Biol. Psychiatry 30 (4), 617–629. https://doi.org/10.1016/j.pnpbp.2006.02.002.

McLellan, T.M., Caldwell, J.A., Lieberman, H.R., 2016. A review of caffeine's effects on cognitive, physical and occupational performance. Neurosci. Biobehav. Rev. 71, 294–312. https://doi.org/10.1016/j.neubiorev.2016.09.001.

Mitchell, D.C., Knight, C.A., Hockenberry, J., Teplansky, R., Hartman, T.J., 2014. Beverage caffeine intakes in the U.S. Food Chem. Toxicol. 63, 136–142. https://doi.org/10.1016/j.fct.2013.10.042.

Montgomery, S.A., Åsberg, M., 1979. A New Depression Scale Designed to be Sensitive to Change. Br. J. Psychiatry 134 (4), 382–389. https://doi.org/10.1192/bjp.134.4.382.

Nawrot, P., Jordan, S., Eastwood, J., Rotstein, J., Hugenholtz, A., Feeley, M., 2003. Effects of caffeine on human health. Food Addit. Contam. 20 (1), 1–30. https://doi.org/10.1080/0265203021000007840.

Núñez, C., 2015. Effects of caffeine intake and smoking on neurocognition in schizophrenia. Psychiatry Res. 8.

Rasmussen, B.B., Brix, T.H., Kyvik, K.O., Brøsen, K., 2002. The interindividual differences in the 3-demthylation of caffeine alias CYP1A2 is determined by both genetic and environmental factors. Pharmacogenet. Genomics 12 (6), 473–478.

Rehm, C.D., Ratliff, J.C., Riedt, C.S., Drewnowski, A., 2020. Coffee Consumption among Adults in the United States by Demographic Variables and Purchase Location: analyses of NHANES 2011-2016 Data. Nutrients 12 (8), E2463. https://doi.org/10.3390/nu12082463.

Shohet, K.L., Landrum, R.E., 2001. Caffeine Consumption Questionnaire: a standardized measure for caffeine consumption in undergraduate students. Psychol. Rep. 89 (3), 521–526. https://doi.org/10.2466/PR0.89.7.521-526.

Strassnig, M., Brar, J.S., Ganguli, R., 2006. Increased caffeine and nicotine consumption in community-dwelling patients with schizophrenia. Schizophr. Res. 86 (1), 269–275. https://doi.org/10.1016/j.schres.2006.05.013.

Swanson, J.A., Lee, J.W., Hopp, J.W., 1994. Caffeine and nicotine: a review of their joint use and possible interactive effects in tobacco withdrawal. Addict. Behav. 19 (3), 229–256. https://doi.org/10.1016/0306-4603(94)90027-2.

Treloar, H.R., Piasecki, T.M., McCarthy, D.E., Baker, T.B., 2014. Relations Among Caffeine Consumption, Smoking, Smoking Urge, and Subjective Smoking Reinforcement in Daily Life. J. Caffeine Res. 4 (3), 93–99. https://doi.org/10.1089/jcr.2014.0007.

Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. J. Pers. Soc. Psychol. 54 (6), 1063–1070. https://doi.org/10.1037/0022-3514.54.6.1063.

Williams, J.M., Gandhi, K.K., Lu, S.-E., Kumar, S., Steinberg, M.L., Cottler, B., Benowitz, N.L., 2011. Shorter interpuff interval is associated with higher nicotine intake in smokers with schizophrenia. Drug Alcohol Depend. 118 (0), 313–319. https://doi.org/10.1016/j.drugalcdep.2011.04.009.

Williams, J.M., Gandhi, K.K., Lu, S.-E., Steinberg, M.L., Benowitz, N.L., 2012. Nicotine intake and smoking topography in smokers with bipolar disorder. Bipolar Disord. 14 (6), 618–627. https://doi.org/10.1111/j.1399-5618.2012.01047.x.

Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatry 64 (6), 663–667. https://doi.org/10.4088/jcp.v64n0607.

Zevin, S., Benowitz, N.L., 1999. Drug interactions with tobacco smoking. An update. Clin. Pharmacokinet. 36 (6), 425–438. https://doi.org/10.2165/00003088-199936060-00004.