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Sex differences in alcohol and tobacco use disorders among individuals with panic disorder: A cross-sectional analysis from the genomic psychiatry cohort

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Anxiety disorders and substance use frequently co-occur, yet the moderating effects of sex and ancestry on these relationships remain understudied. This investigation examined associations between presumed panic disorder (pPD) and both presumed alcohol use disorder (pAUD) and tobacco use disorder (pTUD) in 10,953 individuals from the Genomic Psychiatry Cohort screened against severe mental illness. Our sample was demographically diverse (56% female; 55% European Ancestry, 45% African Ancestry), allowing robust comparison across these groups. Individuals with pPD ($n = 342$) demonstrated significantly higher mean severity scores for both pAUD (1.26 vs. 0.33, $p < 0.05$) and pTUD (1.65 vs. 0.93, $p < 0.05$) compared with those without pPD. While female sex was associated with decreased risk for pAUD (B: −0.351, $p < 0.05$) compared with males, we observed no significant ancestry-based differences in substance use patterns among those with pPD. Two-way interaction analyses revealed that sex significantly moderated the relationship between pPD and pAUD (B: −0.97, $p < 0.001$), with the association being stronger among males than females. Additionally, comorbid presumed posttraumatic stress disorder was significantly associated with increased risk for both pAUD (B: 0.650, $p < 0.05$) and pTUD (B: 0.825, $p < 0.05$) but did not interact significantly with pPD. These findings advance our understanding of how biological sex influences the manifestation of comorbid panic and substance use disorders, offering clinical implications for assessment and treatment strategies that acknowledge sex-specific vulnerability patterns while highlighting the consistent relationship between these conditions across ancestral groups.

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Introduction

Panic disorder (PD) is a debilitating condition characterized by repeated episodes of fear that last for several minutes or longer. Physical symptoms may include heart palpitations, sweating, chills, trembling, breathing problems, weakness, dizziness, and/or feeling of being out of control or impending doom. The etiology of PD is multifactorial. Current research suggests that biological, psychological, and/or environmental factors may contribute to why some individuals develop this disorder compared with others. From a genomic perspective, within certain families, some suffer more from PD than others. According to the World Mental Health Surveys (WMHS), the prevalence of PD across various countries is estimated at approximately 1.7%. Typically, the age of onset is 32, with most cases emerging between the ages of 20 and 47 (1). PD afflicts about 4.7% of U.S. adults at some time in their lives and based on diagnostic interview data from the National Comorbidity Survey Replication, an estimated 2.7% of U.S. adults were diagnosed with PD in 2017 (2). In terms of sex differences, PD tends to afflict more women than men. The prevalence is higher in females (3.8%) than in males (1.6%) (2). Further, the National Survey of American Life (NSAL) and the National Comorbidity Study (NCS) showed that non-Hispanic White participants reported higher rates of PD than non-Hispanic Black participants (4.8% vs. 3.5%) (3). WMHS also found that 80.4% of lifetime PD cases had comorbidity with other psychiatric illnesses (1). Lifetime comorbidity with other mental disorders includes other anxiety disorders, affective, substance use disorders (SUD), and impulse-control disorders (1, 4–6). PD is also associated with physical and emotional distress, detriments in social and romantic relationships, suicide attempts, financial difficulties, and SUD (7–10). Several theories for the comorbid relationships between anxiety disorders such as PD and SUD have been posited. For example, "self-medication" or "tension-reduction" theory states that patients with anxious disorders use substances to relieve their panic symptoms temporarily, thus developing SUD (11). Physiologic and/or environmental stressors from chronic substance use create situations or circumstances in which anxiety symptoms are more likely to emerge or worsen (12). As noted, the self-medication hypothesis highlights a key mechanism by which individuals with PD may use substances like alcohol and tobacco to manage their symptoms, leading to higher rates of AUD (alcohol use disorder) and TUD (tobacco use disorder). While there is a robust relationship between PD with TUD and AUD (13, 14). there are few studies that examine sex differences in PD and SUD comorbidity (15) and even fewer reporting on ancestry/race (or ancestry-by-sex) differences in the comorbidity of PD with common SUD (AUD and TUD) in large, diverse samples. Sex and ancestry/race may influence comorbidity patterns in PD and SUD. For example, sociocultural factors may shape substance use behaviors, potentially leading to varying prevalence rates of comorbid PD and SUD across these groups.

Individuals with PD are more likely to smoke and misuse alcohol compared to individuals with any other anxiety disorders (16–20). Multiple population-based studies have demonstrated the strong association between PD with TUD and AUD, including the Epidemiologic Catchment Area (ECA) survey, NCS, and the National Epidemiological Survey of Alcohol Related Conditions (NESARC). With regard to sex differences observed in recent studies on PD comorbidity with DSM-5 AUD and TUD, data derived from the NESARC found that females with PD were 4.5 times more likely to have TUD compared with males with PD (21). Regarding comorbidity, there are three main hypotheses of the mechanism underlying the association between smoking and PD, though none compare by ancestry/race as we will. (1) Smoking may increase the risk of development of PD through impaired respiration and increased vulnerability for panic attacks (22, 23) and through the expected calming effects of nicotine (24, 25); (2) Stimulant properties of nicotine may also reduce the threshold for experiencing panic attacks, especially as nicotine is metabolized in the bloodstream, and the nicotine levels drop (23, 26–28); (3) The association may be moderated by other variables such as anxiety sensitivity, a risk factor for developing PD (11).

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Table 1. Controls with and without pPD

	Presumed panic disorder (pPD) *N* = 342 (%)	No presumed panic disorder (no pPD) *N* = 10,611 (%)	Significance (*p-value*)	Overall *N* = 10,953 (%)
Female Sex	198 (57.9)	5942 (56.0)	*0.488*	6140 (56.1)
Male Sex	144 (42.1)	4668 (44.0)	*(reference group)*	4813 (43.9)
Age (mean, SD)	43.75 (14.789)	42.22 (15.368)	*0.069*	
African Ancestry (AA)	152 (44.4)	4763 (44.9)	*0.871*	4915 (44.9)
European Ancestry (EA)	190 (55.6)	5848 (55.1)	*(reference group)*	6038 (55.1)
PTSD screen positive	103 (30.1)	556 (5.2)	*< 0.05*	659 (6.0)

Using data from the NCS, Kessler described that even though males had a higher incidence of AUD, females still had higher incidences of comorbid PD and AUD than males. Females were more likely to have a diagnosis of PD before AUD, whereas males were more likely to have a diagnosis of AUD before PD, and this may exacerbate alcohol problems in females with PD since it may be a form of self-medication (29). In another study that hypothesized there were sex differences between PD individuals, 169 patients with PD and established alcohol dependence (89 males and 80 females) in the NHIRD [Taiwan National Health Insurance Research Database] were nested with other 9480 patients with only PD, the standardized incident ratio (SIR) for AUD was significantly higher for females with PD (SIR = 6.29) as compared with males with PD (SIR = 3.36) (15).

Previous studies have consistently demonstrated that PD is more prevalent among White Americans in comparison to their African Ancestry (AA) counterparts (30–33). Surprisingly, panic disorder with comorbid AUD and TUD with a focus on ancestry/race has been sparsely researched. In a study pooling data from the NESARC, Smith *et al*. analyzed racial differences in the 12-month prevalence and co-occurrence between DSM-IV AUD and PD. In the study, AA had higher rates of comorbid AUD and PD with and without agoraphobia (OR = 4.2 and OR = 3.5, respectively) compared with EA counterparts (OR = 2.7 and 2.1, respectively) (30). This finding was consistent with Grant's previous NESARC publication (21). In a separate study, Huang *et al*. compared the prevalence and co-occurrence of DSM-IV AUD along with PD among European Caucasian Ancestry (EA) and AA in a large representative sample of the U.S. population between 2001 and 2002. Consistent with past studies, Blacks (AA) (OR = 2.5) were more likely than their white counterparts (OR = 1.9) to have co-occurring PD and AUD (34).

In this study, we examined rates of "presumed" alcohol and tobacco use disorders (pAUD, pTUD) and their association with "presumed" panic disorder (pPD) based on screening items for each disorder and the moderating influence of sex and ancestry/race. As mentioned earlier, PD has many psychiatric comorbidities, including PTSD (posttraumatic stress disorder). Berens conducted a further analysis of the NESARC study, finding that approximately 27.4% of individuals with primary PD also have lifetime PTSD (35). These findings align closely with those of other epidemiological studies, such as the NCS, which similarly reported a comorbidity rate of 27% (36). Therefore, we also examined the role of pPTSD (presumed PTSD) in the associations of pPD with pAUD and pTUD and differences by sex and ancestry/race. Thus, our research questions for this analysis of the GPC cohort, based on recent findings, are:

1. Does sex and ancestry/race have an association in the prevalence of individuals who experience comorbid pPD and pAUD and pTUD compared with those without PD (no pPD)?
2. How do sex and ancestry/race work separately and in combination with one another to influence the prevalence rates of comorbid pPD and pAUD and/or pTUD?
3. What are the effect sizes of pAUD/pTUD in pPD alone versus with comorbid pPD + pPTSD? Is there an interaction between pPD and comorbid pPTSD and/or pAUD and pTUD?

Results

Among all participants in the analytic sample ($n = 10{,}953$), 342 screened positively for pPD, and 10,611 did not (no pPD). As shown in Table 1, a higher proportion of participants were female; however, rates of pPD as compared with no pPD were similar among females (pPD: 57.9%, no pPD: 56.0%) and males (pPD: 42.1%, no pPD: 44.0%). Similarly, while there was a greater number of participants of EA than of AA, rates of pPD were not statistically significantly different (EA: 55.6%; AA: 44.4%) (Table 1).

As shown in Table 2 and Figure 2, mean alcohol problem scores were significantly higher among those who screened positive for pPD when compared with those with no pPD (pPD: M = 1.26, SD = 1.923; no pPD: M = 0.33, SD = 1.940; $p < 0.05$). Similarly, tobacco use scores were significantly higher among those who screened positive for pPD when compared with those with no pPD (pPD: M = 1.65, SD = 1.675; no pPD: M = 0.93, SD = 1.435, $p < 0.05$). Female gender was associated with a decreased risk for AUD (B: −0.351, $p < 0.05$) and TUD (B: −0.520, $p < 0.05$) as compared with males. Screening positive for pPTSD was associated with increased risk for pAUD (B: 0.650, $p < 0.05$) and pTUD (B: 0.825, $p < 0.05$) (Figure 3).

Two-way interactions (pPD x ancestry/race; pPD x sex; pPD x pPTSD), and three-way interactions (pPD x sex x ancestry/race) were also examined (Table 2). These interaction effects were included to explore whether the relationships among pPD, pAUD, and pTUD varied by demographic factors such as sex, ancestry/race, and pPTSD status. Significant interaction terms indicate that the association between pPD and substance use outcomes was modified by these factors, suggesting differences in comorbidity patterns across demographic groups. The only significant moderating influences of sex on the association of pPD and alcohol use problems were observed (B: −0.97, $p < 0.001$). That is, the influence of pPD on alcohol use problems is greater among males (see Figure 3) as compared with females (Table 2; Figure 3).

Table 2. The association of pPD with alcohol use and tobacco use disorders and interactions with sex and race

	Alcohol Use Disorder		Tobacco Use Disorder	
	Effect size (beta)	*p-value*	*Effect size (beta)*	*p-value*
Main Effects				
pPD**	**1.411**	**<0.05**	**0.556**	**<0.05**
Interactions				
pPD x female sex**	**−0.974**	**<0.05**	−0.355	0.083
pPD x AA	0.017	0.918	0.125	0.594
pPD x sex x AA	−0.202	0.339	0.347	0.257
pPD x PTSD	−0.101	0.402	−0.323	0.064

**Significance $p < 0.05$.

Screener Questions for Panic Disorder	
11. Did you ever have an experience of suddenly feeling very anxious or fearful and having panic-like physical symptoms that developed and got intense within 10 minutes? *(Examples: racing heart, chest pain, choking feelings, nausea, sweating, faint, thinking you were going crazy, or dying.)*	**Yes / No**
11a. Have you had more than one attack like this… **and** had a period lasting at least 1 month of intense worries about having another attack **or** changed your behaviors for at least 1 month because of the attacks?	**Yes / No**
Screener Questions for Alcohol Use Disorder	
12. Do you often have more than 4 drinks in one day (for women) or more than 5 drinks in one day (for men?)	**Yes / No**
13. Have you been under the influence of alcohol 3 or more times in situations where you could have caused an accident or gotten hurt? *(Examples: driving while intoxicated, operating machinery, during sports, or while using a gun.)*	**Yes / No**
14. Have you often had a lot more to drink than you intended to have **or** do you often drink to calm your nerves?	**Yes / No**
15.Have you ever wanted to quit **or** tried to cut down on your drinking and found that you couldn't?	**Yes / No**
16.Have people annoyed you by criticizing your drinking?	**Yes / No**
17.Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover [eye-opener]?	**Yes / No**

Screener Questions for Tobacco Use Disorder	
18. Over your lifetime, have you smoked more than 100 cigarettes? Include cigars, pipes, and chewing tobacco.	**Yes / No**
19. Have you ever had a period of one month or more when you smoked cigarettes every day?	**Yes / No**
20. Did you usually smoke your first cigarette within one hour after waking up?	**Yes / No**
21. Have you ever wanted to quit smoking **or** have tried to quit smoking and found that you couldn't?	**Yes / No**
Screener Questions for Post-Traumatic Stress Disorder	
32. Have you ever experienced a traumatic event in which you felt that your life might be in danger? *(Examples: serious car or other accident, natural disaster (like earthquakes or hurricanes), being physically attacked or threatened with a knife or gun,* being sexually assaulted or raped, experienced combat or been in a war zone, or observed sudden violent death (homicide or suicide.).	**Yes / No**
32a. Sometimes images or strong memories of traumatic events keep coming back in flashbacks, thoughts that you can't get rid of, or repeated nightmares. Has that ever happened to you?	**Yes / No**
32b. Did you make a special effort to avoid thinking or talking about what happened or deliberately stayed away from things or people that reminded you of the terrible experience?	**Yes / No**
32c. After this experience did you have trouble sleeping, have difficulty concentrating, were unusually irritable, have outbursts of anger, felt overly watchful or on guard, or been very jumpy or easily startled?	**Yes / No**

Figure 1. GPC screener questions. This figure illustrates the screening questionnaire items used in the GPC study to identify pPD, pAUD, pTUD, and pPTSD. The screener includes specific questions for each condition with yes/no response options. For pPD, participants were classified as positive if they answered "yes" to both items 11 and 11a, indicating experience of sudden anxiety attacks with physical symptoms and subsequent worry or behavior changes. The alcohol section includes six questions (items 12–17) addressing risky drinking patterns and consequences, while the tobacco section includes four items (18–21) addressing use patterns and quit attempts. PTSD screening (items 32–32c) focuses on traumatic experiences and subsequent symptoms.

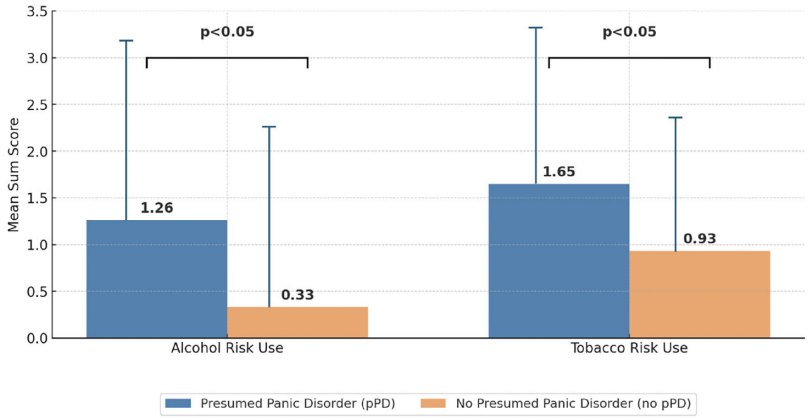

Figure 2. Mean sum scores for alcohol and tobacco risk use for participants with presumed panic disorder (pPD) and without presumed panic disorder (no pPD). This bar graph compares the severity of alcohol and tobacco use problems between individuals with and without pPD. Participants with pPD demonstrated significantly higher mean severity scores for both alcohol use (1.26 vs. 0.33, $p < 0.05$) and tobacco use (1.65 vs. 0.93, $p < 0.05$) compared with those without pPD. The blue bars represent individuals with pPD, while the orange bars represent those without pPD. Error bars indicate SDs.

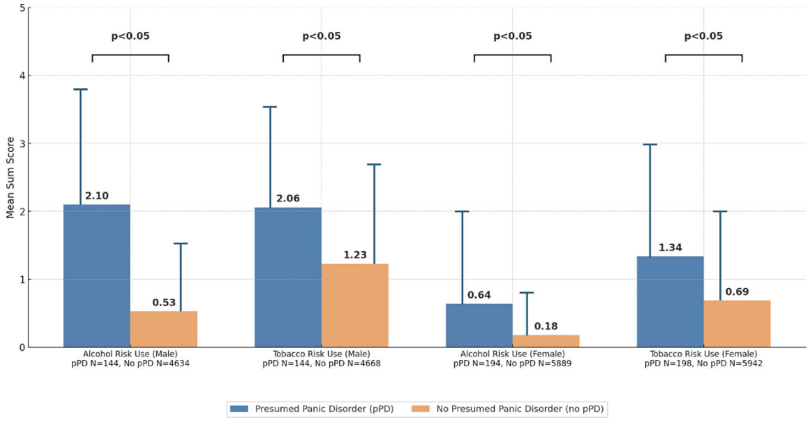

Figure 3. Mean sum scores for risky alcohol and tobacco use among male and female participants with presumed panic disorder (pPD) and without presumed panic disorder (no pPD). This figure illustrates the sex differences in alcohol and tobacco use problems among individuals with and without pPD. The data are stratified by both sex and pPD status, revealing significant interactions. Among males with pPD, mean alcohol risk scores (2.10) were substantially higher than among males without pPD (0.53). Similarly, males with pPD showed higher tobacco risk scores (2.06) compared with males without pPD (1.23). For females, those with pPD also demonstrated higher alcohol risk scores (0.64 vs. 0.18) and tobacco risk scores (1.34 vs. 0.69) compared with females without pPD. All comparisons were statistically significant ($p < 0.05$). Notably, males with pPD reported higher alcohol risk scores than females with pPD (2.10 vs. 0.64).

Discussion

This study stands out as one of the few that investigates the intersection of pAUD and pTUD within individuals with pPD. Moreover, it aims to delineate these groups more precisely by considering factors such as sex and ancestry/race, adding depth to our understanding of these complex relationships. To our knowledge, this is the first paper that looks at comorbid pPTSD in patients with pPD along with pAUD and pTUD. As aforementioned, the prevalence of people with PD in the United States is about 2.7%, which is similar to our sample's prevalence rate of 3.22%. Females are typically more afflicted with PD than males, which is confirmed in our data as well since in our overall case sample, about 58% of our cases with pPD were female, and 42% of our cases with pPD were male. We have also found, like others, that individuals with pPD have significantly more comorbidities, including pTUD, pAUD (Figures 2 and 3), and pPTSD (Tables 1 and 2).

Prior studies report that individuals with PD are two to four times more likely to smoke and drink compared with the general population (37). While our study does not measure prevalence directly, we found that among those who engage in these behaviors, individuals with pPD had a higher mean severity score for pTUD (1.65/4.0) compared with those with no pPD (0.93/4.0). Similarly, individuals with pPD had a higher mean severity score for pAUD (1.26/6.0) compared with those with no pPD (0.33/6.0). This suggests that individuals with pPD may experience more problematic use rather than just higher rates of use. Our analysis confirms the current literature that individuals with PD do smoke more tobacco and drink more alcohol (Figures 2 and 3) (16–19, 20, 23, 38–40).

Ancestry Differences in pPD and Comorbid pTUD or pAUD

Although past studies have reported ancestry/race differences in individuals with comorbid pPD + pAUD with AA individuals having higher prevalence than EA individuals, we found a lower prevalence in our AA sample (21, 30, 34, 41). Initially, it appeared that ancestry/race had an effect when looking at several covariates at once; however, this was not the case when we performed two-way and three-way interactions (Table 2). One possible explanation is that alcohol misuse and AUDs are less prevalent among AA individuals than those of EA, and therefore this may be driving these results. Ransome *et al.* (2017) (41) demonstrated that Black women with AUD had different health outcomes and drinking patterns than their White counterparts, potentially influenced by sociocultural factors and systemic barriers to care. While this study did not specifically examine PD or PTSD, its findings on racial disparities in alcohol use align with our observation of lower pAUD prevalence in AA individuals.

An alternative hypothesis could relate to the inherent nature of structural racism in the United States. For example, a recent study has highlighted the role of discrimination in influencing mental health and substance use outcomes. Vu *et al.* (2019) (42) demonstrated that intersecting identities, such as ancestry/race and sexual orientation, and experiences of discrimination significantly impact mental health outcomes, including depressive symptoms and substance use. This could further explain differences in comorbid substance use and PD across racial groups (42).

Additionally, AA children are more likely socialized to expect hostility, irrational restrictions, insults, and unfair treatment based on the color of their skin. Thus, to protect against this, AA children are taught to develop high levels of tolerance for unfair acts (43). This type of socialization has been shown to be protective of mental health symptoms (44). Although this socialization was not explicitly tied with PD, it could be postulated as a factor for the lower prevalence of PD. While this hypothesis is speculative, it warrants the need for further investigation.

Another possible explanation could be that limited access to mental health care and poor quality care when accessing care may be a factor for the lower prevalence of PD diagnoses (45, 46). Third, stigma and judgment also play a role in the lower rates of AA individuals receiving treatment. In a qualitative study by Alvidrez, one-third of black individuals regarded receiving treatment for mild depression and anxiety as "crazy" (47). In regards to comorbid substance use, studies have shown that even in precarious living situations comparably to their white counterparts, Black individuals with PD engaged in fewer unhealthy behaviors, such as tobacco, alcohol, and substance use (48, 49). Thus, the reasons for a decreased prevalence of PD and TUD or AUD in AA are multifactorial and are likely underreported in our sample (Table 1).

Sex Differences in pPD and Comorbid pTUD or pAUD

In our analysis, pPD is associated with increased pAUD and pTUD when looking at the main effect, adjusting for age, sex, ancestry/race, and pPTSD. When examining interactions between sex, ancestry/race, and pPTSD (two-way interactions), and sex and ancestry/race (three-way interactions) for pAUD and pTUD, only the interaction of sex with pAUD was significant, with it being greater among males compared with females (Table 2; Figure 3). This is in agreement with decades of research demonstrating a greater risk for alcohol use problems among males compared with females (50–52). General explanations for this male bias toward alcohol use problems include trends of male drinkers consuming alcohol more often and in larger quantities than female drinkers and, historically, limited opportunities for females to drink heavily due to societal norms, pregnancy, and child-rearing (53).

However, we should note that this contrasts with some recent studies that have shown that women with anxiety disorders, including but not limited to PD, drink more alcohol compared to men. For example, in a study in Germany, women with anxiety disorders tended to have an earlier onset of drinking, regular drinking, and occurrence of withdrawal symptoms when compared with women without anxiety disorders (54). They also noted there may be more severe physical symptoms among these women (54). Another study also found that women have more severe respiration-related symptoms and more severe agoraphobic avoidance symptomology compared with men (55). With both studies in mind, (54, 55) it could be hypothesized that females with anxiety disorders are already susceptible to significantly distressing withdrawal symptoms that could potentiate the desire to self-medicate with alcohol as a temporary measure to dampen panic disorder symptomology. However, Schneider's (54) study does not explicitly differentiate female individuals with PD from female individuals with other anxiety disorders. Therefore, the difference we found, wherein women with pPD were drinking less than men with pPD, is in agreement with the general literature on increased alcohol use problems in males compared with females and may not be in contradiction to these previous studies of women with anxiety including PD, since they had not separated women specifically with PD from other more common anxiety disorders (e.g., generalized anxiety disorder) (54, 55).

While studies like Schneider *et al.* (54) and Sheikh *et al.* (55) explored broader anxiety disorders rather than PD specifically, our findings align with their observations regarding differences in drinking behaviors. However, it is important to note that these studies utilized more comprehensive data collection methods. For instance, White *et al.* (2015) (53) captured longitudinal drinking patterns and detailed alcohol use history, whereas our study relied on a lifetime screener to assess drinking behaviors across both cases and controls. This difference in methodology could contribute to the observed discrepancies between studies.

With regard to tobacco use, there has been much research dedicated to understanding how substances may be used to alleviate feelings of anxiety, such as those that arise in PD. In an integrative model of smoking-anxiety comorbidity, smokers with anxiety disorders tend to be fearful of anxiety-related symptoms and bodily sensations, and they cope by using nicotine to achieve the "positive" sensations of nicotine in hopes of relaxing themselves. Alternatively, individuals may also use nicotine to escape and avoid emotionally distressing events (56, 57). This creates a feed-forward cycle that is difficult to break because the individual will inevitably feel nicotine withdrawal-related aversive interoceptive cues that occur routinely and cope by smoking some more (58, 59).

Historically, in the United States, males have always smoked more than females. Thus, at first glance, our finding of less smoking among women with pPD than men might seem supported by the literature. However, while smoking rates have decreased throughout most age groups, rates of smoking cessation in women have not. From a physiological standpoint, this may be due to the differences in nicotine metabolism observed between females and males. In a study by Benowitz, intravenous infusions of nicotine and cotinine showed higher clearance rates in females than

in males, and oral contraceptives further accelerated this clearance (60). Thus, one explanation of the notable higher smoking rates in females with PD versus women without PD could be a combination of this feed-forward cycle and the more rapid metabolic clearance of nicotine. Goodwin substantiates the hypothesis that female smokers likely smoke due to underlying anxiety spectrum diagnoses. In a sample of 4149 individuals, Goodwin examined the prevalence of mood and anxiety disorders among male and female current smokers in the United States using data from NCS and NCS-R and found that PD was significantly more common among female current smokers than in males in 2001 compared with 1990 (61).

We did not see this TUD interaction in our female sample (Table 2) and wonder whether this is simply due to the power limits of our sample size since, as Table 1 indicates, the overall female sample was only 198 pPD versus 5942 without pPD, and for males. A total of 144 with pPD versus 4668 without pPD. Another limitation includes the diagnoses for PD, PTSD, AUD, and TUD, which are based on screener/self-report items and not on a full diagnostic assessment for a DSM diagnosis. For this reason, AUD and TUD were treated as sum scores, representing the sum of the number of screening items endorsed. Although it may be considered a limitation, in our study, only 342 participants out of 10,611 answered yes to items 11 and 11a. The use of fewer questions could be implemented in clinical settings, where sometimes these questions are not asked, to screen out participants and direct them to appropriate services briefly.

Limitations

Findings should be considered within the context of this study's limitations. The diagnosis for PD and PTSD were based on screener items and not on a full DSM diagnosis. Further, screeners were self-reported and, therefore, subject to bias. However, even with the limited number of questions, only a very small portion met the criteria for PD or PTSD, and rates were comparable to those in the general population. In terms of pAUD and pTUD diagnoses in our sample, to measure severity, we used sum scores to represent the sum of the number of screening items endorsed. Future analysis should determine whether these findings extend to DSM diagnoses of AUD and TUD (e.g., DSM-V AUD, TUD). A larger sample size with PD in future studies would also strengthen our findings. Another limitation is that the cross-sectional study design for a lifetime of illness did not allow us to determine whether AUD or TUD preceded or followed PD or PTSD. Future studies of a more longitudinal nature could examine SUD diagnoses that precede or follow a diagnosis of PD. In terms of missing data, the overall dataset had minimal missing entries. Participants with incomplete data were excluded from analyses involving those variables. Given the low volume of missing data, imputation techniques were not necessary, and the results were not significantly impacted.

Conclusion

In our study, we found significantly more alcohol and tobacco use in those with pPD. By sex, females were more likely than males to have pPD (Table 1), but were less likely to have alcohol use problems compared with males (Figure 3; Table 2). We did not find that ancestry/race (AA vs. EA) had a moderating effect on alcohol and tobacco use problems among individuals with pPD. We did not find any differences in alcohol or tobacco use problems when we looked at interactions with comorbid pPTSD (Table 2). However, we did find significant comorbidity of pPTSD in the pPD sample compared with controls (Table 1). Continuing to document differences in risk factors for mental health conditions by ancestry/race and sex is important, as this can impact and guide national healthcare policy in the United States. Future research should look at specific genetic or environmental factors that reinforce the comorbidities of PD-AUD and PD-TUD. This will help guide future management and treatments. In summary, this study advances our understanding of the interplay between anxiety, SUD, and PD, particularly in the context of sex and ancestry/race differences, offering a foundation for future research and tailored clinical approaches.

Materials and Methods

Sample

The analytic sample is derived from the Genomic Psychiatry Cohort (GPC), a large and diverse sample of individuals screened for neuropsychiatric disorders. The primary focus of the GPC is on severe mental illnesses such as schizophrenia and bipolar disorder. However, it also includes a large cohort of participants who are unaffected by these disorders ($N = 10{,}953$), defined as individuals not diagnosed with schizophrenia or bipolar disorder and with no first- or second-degree relatives with these disorders. Controls also have no history of traumatic brain injury and no history of multiple depressive episodes (>4) (62). Further, individuals were identified as male and female based on genome, XX or XY, and self-identified as African or European Ancestry (AA, EA, respectively) were included in this analysis given the limited number of participants of Latino or mixed ancestry. This analytic sample is 56% female, 55% of EA, and 45% of AA (Table 1). One unique feature of the sample is a close to ~1:1 ratio of individuals of AA and EA in cases and control samples, making it a valuable dataset for the study of ancestry/race (and sex) differences in the comorbidity of these disorders. Participants are drawn from across the United States, Canada, Mexico, Portugal, and other regions of South America and Europe; however, only those who identified as AA or EA were included in the analytic sample.

Measures

Individuals who endorsed both PD screening items (i.e., responded "Yes" to items 11 and 11a) (Figure 1) are described as affected with pPD in this study, and individuals who endorsed 0–1 items, were described as unaffected with panic disorder (no pPD). Using these parameters, we identified 342 individuals with a pPD and compared these individuals with those unaffected noPD (Table 1). The screening questionnaire also includes six items (items 12–17) regarding alcohol use problems and four items (items 18–21) regarding tobacco use problems adapted from the "Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers"(CAGE) questionnaire (63). For both alcohol and tobacco use problems, screening items, sum scores for severity were computed, AUD ranged from 0 to 6 and TUD from 0 to 4. These specific cut-off points were chosen based on SAMHSA's Treatment Improvement Protocol recommendations, which aim to identify individuals at risk for SUD by casting a wider net. The graded scoring system allowed us to capture a spectrum of severity, where higher scores reflected a greater cumulative burden of alcohol or tobacco use. Of note, while PTSD screening items were included on the screening questionnaire, other anxiety disorders, including generalized anxiety, social phobia, separation anxiety, and specific phobia were not assessed. pPTSD was defined as responding yes to item 32 endorsing a traumatic event and then yes to at least two of the three screener questions 32a, 32b, 32c (Figure 1).

Statistical Analysis

First, Chi-squared and independent *t* test were used in Table 1 to assess the associations between pPD and demographic variables (Table 1). Significance was defined as a $p < 0.05$. Then, linear regression models were used to examine the association of pPD with pAUD, pTUD, and pPTSD. These models were computed separately for alcohol and tobacco use problems and included the following covariates: age, sex, self-reported ancestry/race, and pPTSD (Table 2). Further, all individuals identified as male and female and of AA and EA were included throughout this analysis, given the limited number of participants in other groups. All analyses were done using SPSS software (version 24).

Study Approval

The GPC study is approved by the Rutgers Institutional Review Board – Health Sciences, New Brunswick/Piscataway, located at 335 George St., Liberty Plaza Ste. 3100, New Brunswick, NJ 08901. This study involves human subject research, and written informed consent was obtained following a thorough explanation of the study's nature and potential outcomes.

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Author Contributions

M.J. Chung: conceptualization, writing – original draft. P. Georgakopoulos: formal analysis, project administration. J. Meyers: formal analysis, writing – original draft. S. Sharma: writing, project administration. C.N. Pato MD: conceptualization, funding acquisition, investigation, methodology.

M.T. Pato: conceptualization, funding acquisition, investigation, methodology, writing – original draft.

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Author Disclosures

The authors declare no conflict of interest.

References

1. De Jonge P, Roest AM, Lim CC, Florescu SE, Bromet EJ, Stein DJ, et al. Cross-national epidemiology of panic disorder and panic attacks in the world mental health surveys. Depress Anxiety. 2016;33(12):1155–77. DOI: 10.1002/da.22572. PMID: 27775828; PMCID: PMC5143159
2. Harvard Medical School. Table 2. 12-month prevalence of DSM-IV/WMH-CIDI disorders by sex and cohort 1. National Comorbidity Survey (NCS) website. 2007. Available from: https://www.hcp.med.harvard.edu/ncs/ftpdir/NCS-R_12-month_Prevalence_Estimates.pdf. Accessed March 25, 2024.
3. Levine DS, Himle JA, Taylor RJ, Abelson JM, Matusko N, Muroff J, et al. Panic disorder among African Americans, Caribbean blacks and non-Hispanic whites. Soc Psychiatry Psychiatr Epidemiol. 2013;48:711–23. DOI: 10.1007/s00127-012-0582-x. PMID: 22983664; PMCID: PMC3913268
4. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617–27. DOI: 10.1001/archpsyc.62.6.617. PMID: 15939839; PMCID: PMC2847357
5. Ziffra M. Panic disorder: a review of treatment options. Ann Clin Psychiatry. 2021;33(2):124–33. DOI: 10.127788/acp.0014. PMID: 33529291
6. D'Angelo M, Valenza M, Iazzolino AM, Longobardi G, Di Stefano V, Lanzara E, et al. Unraveling the complexity: exploring the intersection of panic disorder, dissociation and post-traumatic stress disorder. Behav Sci (Basel). 2024;14(3):166. DOI: 10.3390/bs14030166. PMID: 38540469; PMCID: PMC10968653
7. Markowitz JS, Weissman MM, Ouellette R, Lish JD, Klerman GL. Quality of life in panic disorder. Arch Gen Psychiatry. 1989;46(11):984–92. DOI: 10.1001/archpsyc.1989.01810110026004. PMID: 2684086
8. Weissman MM. Panic disorder: impact on quality of life. J Clin Psychiatry. 1991;52:6–8. PMID: 1995601
9. Simon NM, Otto MW, Korbly NB, Peters PM, Nicolaou DC, Pollack MH. Quality of life in social anxiety disorder compared with panic disorder and the general population. Psychiatr Serv. 2002;53(6):714–8. DOI: 10.1176/appi.ps.53.6.714. PMID: 12045308
10. Birchall H, Brandon S, Taub N. Panic in a general practice population: prevalence, psychiatric comorbidity and associated disability. Soc Psychiatry Psychiatr Epidemiol. 2000;35:235–41. DOI: 10.1007/s001270050233. PMID: 10939421
11. Zvolensky MJ, Kotov R, Antipova AV, Schmidt NB. Cross cultural evaluation of smokers risk for panic and anxiety pathology: A test in a Russian epidemiological sample. Behav Res Ther. 2003;41(10):1199–215. DOI: 10.1016/s0005-7967(03)00031-7. PMID: 12971940
12. Schuckit MA. Low level of response to alcohol as a predictor of future alcoholism. Am J Psychiatry. 1994;151(2):184–9. DOI: 10.1176/ajp.151.2.184. PMID: 8296886
13. Zvolensky MJ, Schmidt NB, Stewart SH. Panic disorder and smoking. Clin Psychol Sci Pract. 2003;10(1):29–51. DOI: 10.1093/clipsy.10.1.29
14. Zvolensky MJ, Feldner MT, Leen-Feldner EW, McLeish AC. Smoking and panic attacks, panic disorder, and agoraphobia: a review of the empirical literature. Clin Psychol Rev. 2005;25(6):761–89. DOI: 10.1016/j.cpr.2005.05.001. PMID: 15975699
15. Chang HM, Pan CH, Chen PH, Chen YL, Tai MH, Su SS, et al. Sex differences in incidence and psychiatric comorbidity for alcohol dependence in patients with panic disorder. Drug Alcohol Depend. 2020;207:107814. DOI: 10.1016/j.drugalcdep.2019.107814. PMID: 31887603
16. Amering M, Bankier B, Berger P, Griengi H, Windhaber J, Katschnig H. Panic disorder and cigarette smoking behavior. Compr Psychiatry. 1999;40(1):35–8. DOI: 10.1016/s0010-440x(99)90074-3. PMID: 9924875
17. McCabe RE, Chudzik SM, Antony MM, Young L, Swinson RP, Zolvensky MJ. Smoking behaviors across anxiety disorders. J Anxiety Disord. 2004;18(1):7–18. DOI: 10.1016/j.janxdis.2003.07.003. PMID: 14725865
18. Himle J, Thyer BA, Fischer DJ. Prevalence of smoking among anxious outpatients. Phobia Pract Res J. 1988;1(1):25–31
19. Breslau N, Kilbey MM, Andreski P. Nicotine dependence, major depression, and anxiety in young adults. Arch Gen Psychiatry. 1991;48(12):106974. DOI: 10.1001/archpsyc.1991.01810360033005. PMID: 1845224
20. Mathew AR, Norton PJ, Zvolensky MJ, Buckner JD, Smits JA. Smoking behavior and alcohol consumption in individuals with panic attacks. J Cogn Psychother. 2011;25(1):61–70. DOI: 10.1891/0889-8391.25.1.61. PMID: 21915160; PMCID: PMC3170754
21. Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry. 2004;61(11):1107–15. DOI: 10.1001/archpsyc.61.11.1107. PMID: 15520358
22. Pohl R, Yeragani VK, Balon R, Lycaki H, McBride R. Smoking in patients with panic disorder. Psychiatry Res. 1992;43(3):253–62. DOI: 10.1016/0165-1781(92)90058-B. PMID: 1438623
23. Fargamfar M, Moradnia M, Zolfaghari P, Shariyati Z, Sohrabi MB. Association between panic attacks and cigarette smoking among psychiatric patients. J Public Health. 2020;28:65–9
24. Dilsaver SC. Nicotine and panic attacks. Am J Psychiatry. 1987;144(9):1245–6. DOI: 10.1176/ajp.144.9.1245b. PMID: 3631336
25. West R, Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. Psychopharmacology (Berl). 2004;177:195–9. DOI: 10.1007/s00213-004-1923-6. PMID: 15179542
26. Beck JG, Berisford MA. The effects of caffine on panic patients: response components of anxiety. Behavior Therapy. 1992;23(3):405–22. DOI: 10.1016/S0005-7894(05)80166-2
27. Klevebrant L, Frick A. Effects of caffeine on anxiety and panic attacks in patients with panic disorder: a systematic review and meta-analysis. Gen Hosp Psychiatry. 2022;74:22–31. DOI: 10.1016/j.genhosppsych.2021.11.005. PMID: 34871964
28. Bakhshaie J, Zvolensky MJ, Goodwin RD. Cigarette smoking and the onset and persistence of panic attacks during mid-adulthood in the United States: 1994-2005. J Clin Psychiatry. 2016;77(1):2644. DOI: 10.4088/JCP.14m09290. PMID: 26845274; PMCID: PMC11846044
29. Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry. 1997;54:313–21. DOI: 10.1001/archpsyc.1997.01830160031005. PMID: 9107147
30. Smith SM, Stinson FS, Dawson DA, Goldstein R, Huang B, Grant BF. Race/ethnic differences in the prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med. 2006;36(7):987–98. DOI: 10.1017/S0033291706007690. PMID: 16650344
31. Grant BF, Hasin DS, Blanco C, Stinson FS, Chou SP, Goldstein RB, et al. The epidemiology of social anxiety disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2005;66(11):1351–61. DOI: 10.4088/jcp.v66n1102. PMID: 16420070
32. Grant BF, Hasin DS, Stinson FS, Dawson DA, Ruan WJ, Goldstein RB, et al. Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychol Med. 2005;35(12):1747–59. DOI: 10.1017/S0033291705006069. PMID: 16202187
33. Asnaani A, Richey JA, Dimaite R, Hinton DE, Hofmann SG. A cross-ethnic comparison of lifetime prevalence rates of anxiety disorders. J Nerv Ment Dis. 2010;198(8):551–5. DOI: 10.1097/NMD.0b013e3181ea169f. PMID: 20699719; PMCID: PMC2931265
34. Huang B, Grant BF, Dawson DA, Stinson FS, Chou SP, Saha TD, et al. Race-ethnicity and the prevalence and co-occurrence of Diagnostic and Statistical Manual of Mental Disorders, alcohol and drug use disorders and Axis I and II disorders: United States, 2001 to 2002. Compr Psychiatry. 2006;47(4):252–7. DOI: 10.1016/j.comppsych.2005.11.001. PMID: 16769298
35. Berenz EC, York TP, Bing-Canar H, Amstadter AB, Mezuk B, Gardner CO, et al. Time course of panic disorder and posttraumatic stress disorder onsets. Soc Psychiatry Psychiatr Epidemiol. 2019;54:639–47. DOI: 10.1007/s00127-018-1559-1. PMID: 30003310; PMCID: PMC6509003
36. Leskin GA, Sheikh JI. Lifetime trauma history and panic disorder: findings from the National Comorbidity Survey. J Anxiety Disord. 2002;16(6):599–603. DOI: 10.1016/s0887-6185(02)00125-1. PMID: 12405520
37. Smith JP, Randall CL. Anxiety and alcohol use disorders: comorbidity and treatment considerations. Alcohol Res. 2012;34(4):414–3. PMID: 23584108; PMCID: PMC3860396
38. Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. Clin Psychol Rev. 2000;20(2):149–71. DOI: 10.1016/s0272-7358(99)00027-6. PMID: 10721495
39. Kushner MG, Sher KJ, Beitman BD. The relation between alcohol problems and the anxiety disorders. Am J Psychiatry. 1990; 147:685–95. DOI: 10.1176/ajp.147.6.685. PMID: 2188513
40. Puddephatt JA, Irizar P, Jones A, Gage SH, Goodwin L. Associations of common mental disorder with alcohol use in the adult general population: a systematic review and meta-analysis. Addiction. 2022;117(6):154372. DOI: 10.1111/add.15735. PMID: 34729837; PMCID: PMC9300028

41. Ransome Y, Carty DC, Cogburn CD, Williams DR. Racial disparities in the association between alcohol use disorders and health in Black and White women. Biodemography Soc Biol. 2017;63(3):236–52. DOI: 10.1080/19485565.2017.1335589. PMID: 29035103; PMCID: PMC6045433
42. Vu M, Li J, Haardörfer R, Windle M, Berg CJ. Mental health and substance use among women and men at the intersections of identities and experiences of discrimination: insights from the intersectionality framework. BMC Public Health. 2019;19:108. DOI: 10.1186/s12889-019-6430-0. PMID: 30674293; PMCID: PMC6345035
43. Thornton MC, Chatters LM, Taylor RJ, Allen WR. Sociodemographic and environmental correlates of racial socialization by black parents. Child Dev. 1990;61(2):401–9. DOI: 10.1111/j.1467-8624.1990.tb02786.x. PMID: 2344778
44. Fischer AR, Shaw CM. African Americans' mental health and perceptions of racist discrimination: the moderating effects of racial socialization experiences and self-esteem. J Couns Psychol. 1999;46(3):395–407. DOI: 10.1037/0022-0167.46.3.395
45. Hunter LR, Schmidt NB. Anxiety psychopathology in African American adults: literature review and development of an empirically informed sociocultural model. Psychol Bull. 2010;136(2):211. DOI: 10.1037/a0018133. PMID: 20192561
46. SAMHSA. 2020. Results from the 2019 National Survey on Drug Use and Health: Mental Health Detailed Tables. Table 8.17B. [Online] Available from: https://www.samhsa.gov/data/report/2019-nsduh-detailed-tables [Accessed 27 March 2024]
47. Alvidrez J, Snowden LR, Kaiser DM. The experience of stigma among Black mental health consumers. J Health Care Poor Underserved. 2008;19(3):874–93. Doi: 10.1353/hpu.0.0058. PMID: 18677076
48. Jackson JS, Knight KM, Rafferty JA. Race and unhealthy behaviors: chronic stress, the HPA axis, and physical and mental health disparities over the life course. Am J Public health. 2010;100(5):933–9. DOI: 10.2105/AJPH.2008.143446. PMID: 19846689; PMCID: PMC2853611
49. Mezuk B, Rafferty JA, Kershaw KN, Hudson D, Abdou CM, Lee H, et al. Reconsidering the role of social disadvantage in physical and mental health: stressful life events, health behaviors, race, and depression. Am J Epidemiol. 2010;172(11):1238–49. DOI: 10.1093/aje/kwq283. PMID: 20884682; PMCID: PMC3025628
50. Naimi TS, Brewer RD, Mokdad A, Denny C, Serdula MK, Marks JS. Binge drinking among US adults. JAMA. 2003;289(1):70–5. DOI: 10.1001/jama.289.1.70. PMID: 12503979
51. Kanny D, Naimi TS, Liu Y, Lu H, Brewer RD. Annual total binge drinks consumed by US adults, 2015. Am J Prevent Med. 2018;54(4):486–96. DOI: 10.1016/j.amepre.2017.12.021. PMID: 29555021; PMCID: PMC6075714
52. Karaye IM, Maleki N, Hassan N, Yunusa I. Trends in alcohol-related deaths by sex in the US, 1999-2020. JAMA Netw Open. 2023;6(7):e2326346. DOI: 10.1001/jamanetworkopen.2023.26346. PMID: 37505494; PMCID: PMC10383009
53. White A, Castle IJ, Chen CM, Shirley M, Roach D, Hingson R. Converging patterns of alcohol use and related outcomes among females and males in the United States, 2002 to 2012. Alcohol Clin Exp Res. 2015;39(9):1712–26. DOI: 10.1111/acer.12815. PMID: 26331879
54. Schneider U, Altmann A, Baumann M, Bernzen J, Bertz B, Bimber UE, et al. Comorbid anxiety and affective disorder in alcohol-dependent patients seeking treatment: the first multicentre study in Germany. Alcohol Alcohol. 2001;36(3):219–23. DOI: 10.1093/alcalc/36.3.219. PMID: 11373258
55. Sheikh JI, Leskin GA, Klein DF. Gender differences in panic disorder: findings from the National Comorbidity Survey. Am J Psychiatry. 2002;159(1):55–8. DOI: 10.1176/appi.ajp.159.1.55. PMID: 11772690
56. Zvolensky MJ, Bernstein A. Cigarette smoking and panic psychopathology. Curr Dir Psychol Sci. 2005;14(6):301–5. DOI: 10.1111/j.0963-7214.2005.00386.x.
57. Trujillo MA, Khoddam R, Greenberg JB, Dyal SR, Ameringer KJ, Zvolensky MJ, et al. Distress tolerance as a correlate of tobacco dependence and motivation: incremental relations over and above anxiety and depressive symptoms. Behav Med. 2017;43(2):120–8. DOI: 10.1080/08964289.2015.1110559. PMID: 26651507; PMCID: PMC4903085
58. Brandon TH, Tiffany ST, Obremski KM, Baker TB. Postcessation cigarette use: the process of relapse. Addict Behav. 1990;15(2):105–14. DOI: 10.1016/0306-4603(90)90013-n. PMID: 2343783
59. Parrott AC. Does cigarette smoking cause stress? Am Psychol. 1999;54(10):817. DOI: 10.1037//0003-066x.54.10.817. PMID: 10540594
60. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P III. Female sex and oral contraceptive use accelerate nicotine metabolism. Clin Pharmacol Ther. 2006;79(5):480–8. DOI: 10.1016/j.clpt.2006.01.008. PMID: 16678549
61. Goodwin RD, Wall MM, Choo T, Galea S, Horowitz J, Nomura Y, et al. Changes in the prevalence of mood and anxiety disorders among male and female current smokers in the United States: 1990-2001. Ann Epidemiol. 2014;24(7):493–7. DOI: 10.1016/j.annepidem.2014.01.014. PMID: 24935462; PMCID: PMC4393820
62. Pato MT, Sobell JL, Medeiros H, Abbott C, Sklar BM, Buckley PF, et al. The genomic psychiatry cohort: partners in discovery. Am J Med Genet B Neuropsychiatr Genet. 2013;162(4):306–12. DOI: 10.1002/ajmg.b.32160. PMID: 23650244; PMCID: PMC3729260
63. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA. 1984;252(14):1905–7. DOI: 10.1001/jama.252.14.1905. PMID: 6471323