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Correlates of psychotic like experiences (PLEs) during Pandemic: An online study investigating a possible link between the SARS-CoV-2 infection and PLEs among adolescents

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ABSTRACT

Background: This study investigated whether SARS-CoV-2 infection, depression, anxiety, sleep problems, cigarette, alcohol, drug usage contribute to psychotic-like experiences (PLEs) among adolescents during the pandemic. We also aimed to explore whether baseline inflammatory markers or the number of SARS-CoV-2-related symptoms are associated with PLEs, and the latter is mediated by internalizing symptoms.

Methods: Altogether, 684 adolescents aged 12–18 (SARS-CoV-2 group n = 361, control group (CG) n = 323) were recruited. The Community Assessment of Psychic Experiences-42-Positive Dimension (CAPE-Pos), Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), and Pittsburg Sleep Quality Index (PSQI) questionnaires were completed by all volunteers using an online survey. C-reactive Protein and hemogram values, and SARS-CoV-2-related symptoms during the acute infection period were recorded in the SARS-CoV-2 group. Group comparisons, correlations, logistic regression, and bootstrapped mediation analyses were performed.

Results: CAPE-Pos-Frequency/Stress scores were significantly higher, whereas GAD-7-Total and PSQI-Total scores were significantly lower in SARS-CoV-2 than CG. Among the SARS-CoV-2 group, monocyte count and the number of SARS-CoV-2-symptoms were positively correlated with CAPE-Pos-Frequency/Stress scores. Besides SARS-CoV-2, cigarette use, GAD-7, and PHQ-9 scores significantly contributed to the presence of at least one CAPE-Pos "often" or "almost always". PHQ-9 and GAD-7 fully mediated the relationship between the number of SARS-CoV-2 symptoms and CAPE-Pos-Frequency.

Conclusions: This study is the first to show a possible relationship between SARS-CoV-2 infection and PLEs among adolescents. Depression, anxiety, and cigarette use also contributed to PLEs. The number of SARS-Cov-2-symptoms and PLEs association was fully mediated by internalizing symptoms, but prospective studies will need to confirm this result.

1. Introduction

Psychotic-like experiences (PLEs), defined as positive psychotic symptoms experienced by the general population in the absence of a psychotic disorder, are not uncommon during adolescence (Kelleher et al., 2012). Kelleher et al. (2012) reported the median prevalence of PLEs as 7.5% among children aged 13 to 18. Although the great majority of PLEs are transitory during childhood (Thapar et al., 2012) and adulthood (Wiles et al., 2006), they are related to increased risk for psychotic disorders (Welham et al., 2009) and mood, anxiety,

; PLEs, Psychotic like experiences; SARS-CoV-2, The novel coronavirus; CAPE-Pos, The positive psychotic symptoms dimension of the Community Assessment of Psychic Experiences-42; PHQ, Patient Health Questionnaire; GAD-7, Generalized Anxiety Disorder-7; PSQI, Pittsburg Sleep Quality Index.

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behavioral, and substance use disorders (Healy et al., 2019).

Several shared risk factors associated with both psychosis and PLEs have been identified in the literature: (1) Genetic risk (Polanczyk et al., 2010), (2) migration (Scott et al., 2007), (3) adverse childhood experiences (Gawęda et al., 2019), (4) peer bullying (Wolke et al., 2014), (5) substance use (Mackie et al., 2011), (6) perinatal events (Zammit et al., 2009), (7) neuroanatomical changes (Schoorl et al., 2021), (8) neurocognitive changes (Kelleher et al., 2013), and (9) depressive symptoms (Barragan et al., 2011), anxiety symptoms, suicidal ideation, and self-harm (Nishida et al., 2008). Besides these factors, peripheral inflammation which can be caused by infections, auto-immune diseases, and psychosocial adversities, has been proposed as an etiological factor for PLEs (Khandaker et al., 2014) and psychosis (Fraguas et al., 2019). In the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (Khandaker et al., 2014), higher IL-6 level, an inflammation marker, at nine years of age was found to be related to an increased risk of PLEs at 18 years of age. Data from several studies have suggested that the novel coronavirus (SARS-CoV-2) can be associated with recent-onset psychotic symptoms (Correa-Palacio et al., 2020; Ferrando et al., 2020; Huarcaya-Victoria et al., 2020; Noone et al., 2020; Rentero et al., 2020). Despite the clinical continuum between PLEs and psychotic disorders, to the best of our knowledge, there is no published study investigating whether adolescents who had been infected with the SARS-CoV-2 experience PLEs more frequently when compared with those not affected by the SARS-CoV-2.

The SARS-CoV-2 pandemic has been detrimental to sleep quality and has increased stress, anxiety, depression, and social isolation among the general population (Casagrande et al., 2021; Hawes et al., 2021; Salari et al., 2020). These factors (i.e., social isolation, sleep problems, stress, anxiety, depression) are well-established risk factors for PLEs (Butter et al., 2017; Lee et al., 2012; Yung et al., 2006). A handful of studies have examined the impact of the Covid-19 pandemic on PLEs in the general population. Hajdúk et al. (2020) showed that depression, anxiety, perceived stress, and loneliness were associated with PLEs at follow-up. Moreover, childhood trauma, higher family income, and a single-parent family were predictive of new-onset PLEs during the pandemic among college and technical secondary school students (Sun et al., 2021). Simor et al. (2021) demonstrated that lower sleep quality predicted PLEs the following day among adults. Despite these studies, no study has investigated the effect of SARS-CoV-2 infection, depression, anxiety, sleep problems, cigarette, alcohol, and drug usage on PLEs during the pandemic among adolescents. In addition, a recent study demonstrated that PLEs were related to SARS-CoV-2 infection among college students, though much of the association is decreased when adjusting for anxiety and depression (Oh et al., 2021). In line with this, Francesconi et al. (2020) reported that a high level of internalizing symptoms mediated the association between inflammation during childhood and the future onset of PLEs. These previous research findings raise the possibility the relationship between PLEs and SARS-CoV-2 infection can be indirect and mediated by internalizing symptoms. However, this possible mediating pathway has not also been examined among adolescents.

The first purpose of this study was to examine whether there is a possible link between the SARS-CoV-2 infection and PLEs among adolescents. Secondly, we aimed to explore whether baseline inflammatory markers and SARS-CoV-2 related symptoms during the acute infection period were associated with PLEs. Thirdly, we aimed to examine the contributions of depression, anxiety, sleep problems, cigarette, alcohol, and drug usage on PLEs during the pandemic. Finally, based on Francesconi et al. (2020) and Oh et al. (2021)'s findings, we aimed to investigate whether depressive and anxiety levels mediated the association between the number of SARS-CoV-2 symptoms during acute infection and the frequency of PLE. We considered the following hypothesis: (1) Adolescents who have been infected with the SARS-CoV-2 exhibit a significantly higher frequency of PLEs than non-infected ones. (2) Baseline inflammatory markers such as C-reactive Protein (CRP) level, and neutrophil, lymphocyte, monocyte, and leucocyte counts, and the number of SARS-CoV-2-related symptoms during the acute infection period are correlated with the frequency of PLEs among adolescents exposed to SARS-CoV-2. (3) The association of the number of SARS-CoV-2 symptoms during the acute infection period and the frequency of PLEs is mediated by internalizing symptoms. (4) SARS-CoV-2 infection, depression and anxiety levels, sleep problems, cigarette, alcohol, and drug usage predict PLEs among adolescents during the SARS-CoV-2 pandemic.

2. Materials and methods

2.1. Participants and procedures

Inclusion criteria for the patient group were: (1) Adolescents aged 12–18 years, (2) RT-PCR positivity for the SARS-CoV-2 virus, and (3) adolescents and parents who were willing and able to give informed consent. Patients who had been diagnosed with schizophrenia spectrum disorder, bipolar disorder, autism spectrum disorder, or intellectual disability or who had a neurological disease were excluded. 1144 children who were infected with the SARS-CoV-2 virus between July 2020 and January 2021 were assessed regarding our inclusion and exclusion criteria. Patients were reached by phone at the Ministry of Health Ankara City Hospital Child Psychiatry Department between March 2021 and April 2021. 783 of them were excluded due to the following reasons: out of age range (<12 years or > 18 years) (n = 567), could not be reached by phone (n = 56), did not accept to participate (n = 2), had been diagnosed with autism spectrum disorder, intellectual disability or neurological disease (n = 6), did not complete the online survey (n = 152). Finally, we recruited 361 adolescents for the patient group (the SARS-CoV-2 group). All patients were examined at the Ministry of Health Ankara City Hospital Children's Emergency Department during acute SARS-CoV-2 infection, where they all underwent physical examination, blood analysis (complete blood cell count, biochemical analysis, and CRP), and reverse transcriptase polymerase chain reaction test (RT-PCR). Of the cases, 66 were hospitalized because of the SARS-CoV-2 infection. CRP level, and neutrophil, lymphocyte, monocyte, leucocyte, and thrombocyte counts during the acute infection period were extracted from the emergency department charts. Neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) (SII = platelets X neutrophils/lymphocytes) were calculated (Feng et al., 2020). Moreover, SARS-COV-2-related symptoms during the acute infection period (2 weeks) were recorded.

Adolescents from a community sample were recruited for the control group (CG). Inclusion criteria for the CG were: (1) Adolescents aged 12–18 years and (2) adolescents and parents who were willing and able to give informed consent. Exclusion criteria for the CG were: (1) History of SARS-CoV-2 infection, (2) diagnosis of schizophrenia spectrum disorder, bipolar disorder, autism spectrum disorder, intellectual disability, and (3) a neurological disease. We reached out to 12 middle and high school teachers and asked them to distribute our online survey to their students. 822 middle and high school students were invited to participate in the study. 42.7% (n = 351) of them responded to the questionnaire. Of the responders, 28 were excluded (SARS-CoV-2 infection (n = 22), schizophrenia (n = 1), and epilepsy (n = 5)). Consequently, 323 adolescents were recruited for the CG. Participation in the study was voluntary and anonymous for the CG.

An online questionnaire through a web-based survey tool (Google Forms) consisting of sociodemographic data form, the positive psychotic symptoms dimension of the Community Assessment of Psychic Experiences-42 (CAPE-Pos), Patient Health Questionnaire (PHQ), Generalized Anxiety Disorder-7 (GAD-7), and Pittsburg Sleep Quality Index (PSQI) were completed by both the SARS-CoV-2 group and CG.

Only the survey administrator had access to the personally identifiable information of participants. Informed consent of each participant was obtained before administering the questionnaire online. This study

was approved by the clinical research ethics review committee of the Ministry of Health Ankara City Hospital from Ankara, Turkey (E2-21–155, 10.03.2021). The study procedure adhered to the principles of the Declaration of Helsinki.

2.2. Assessments

2.2.1. Socio-demographic data form

Date of birth, gender, presence of a diagnosed psychiatric disorder, chronic disease, cigarette and alcohol usage within the last 30 days, lifetime drug use, history of SARS-CoV-2 infection (yes/no), SARS-CoV-2 virus related hospitalization (yes/no), and psychiatric disorders in the first degree relatives were acquired using a socio-demographic data form designed by the authors. We also asked individuals to rate their Covid-19-related anxiety on a 10-point likert scale (range from 1 to 10, higher scores show greater anxiety).

2.2.2. The Community assessment of psychic experiences (CAPE)

The CAPE, a self-report questionnaire to measure PLEs, consists of three dimensions: positive symptoms (20 items), negative symptoms (14 items), and depressive symptoms (8 items) (Stefanis et al., 2002). Only the positive symptoms dimension of the CAPE (CAPE-Pos) was used in the current study. Instead of questions searching for lifetime experiences of PLEs such as "In your lifetime, have you ever felt as if the thoughts in your head are not your own?", modified items were applied: "Since March 2020 (Covid-19 outbreak), have you … ….". Three factors of the CAPE-Pos including bizarre experiences, delusional ideas, and perceptual abnormalities were also calculated (Mark and Toulopoulou, 2017). The *meta*-analytical reliability of the CAPE was found as 0.91 (Mark and Toulopoulou, 2015). The questionnaire was also used to evaluate PLEs among adolescents (Mark and Toulopoulou, 2017). The reliability and validity of the Turkish CAPE was examined by Sevi et al. (2019).

2.2.3. Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 was designed to assess depressive symptoms as per the criteria for major depression in the DSM-IV. It comprises nine items scored on a scale of 0 to 3, with total scores ranging from 0 to 27. Higher scores indicate greater symptom severity. The Turkish reliability and validity of the PHQ-9 were demonstrated by Sari et al., 2016.

2.2.4. The Generalized Anxiety Disorder-7 (GAD-7): The GAD-7 questionnaire was designed to assess anxiety symptoms following the criteria for generalized anxiety disorder in the DSM-5. It comprises 7 items scored from 0 to 3 each, with total scores ranging from 0 to 21. Higher scores indicate greater symptom severity. Konkan et al., 2013 performed the Turkish validation and reliability of the GAD-7. Both the PHQ-9 and the GAD-7 have strong internal and test–retest reliability and construct and factor-structure validity. Moreover, both were used in adolescents before (Mossman et al., 2017; Richardson et al., 2010).

2.2.5. Pittsburg Sleep Quality Index (PSQI): The PSQI is a seven domain (19 item) self-rated questionnaire evaluating usual sleep habits during the past month. The seven domain scores include: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, daytime dysfunction, sleep fragmentation, and use of sleep aid medications, which altogether to provide a global sleep quality index score. The possible scores range from 0 to 21, with greater than five indicative of impaired sleep quality. The Turkish validity and reliability of the PSQI was conducted by Ağargün et al., 1996.

2.3. Statistics

Descriptive statistics (mean, standard deviation, median, interquartile range, and frequencies) and group comparison statistics were performed. The normality of the quantitative variables was assessed via histogram, skewness, kurtosis, normality plots, and the Kolmogorov Smirnoff test. Between-group comparisons of categorical variables were carried out using $\chi 2$ or Fisher's exact test. The Mann Whitney *U* test and the independent sample *t* test were utilized in non-normally and normally distributed quantitative data, respectively. Spearman correlation test was conducted to measure the correlation between baseline inflammatory markers, the number of SARS-COV-2 symptoms, and the CAPE-Pos, PHQ-9, GAD-7, and PSQI. A multivariate binary logistic regression analysis was conducted to identify which variables (SARS-CoV-2 infection, PHQ-9, GAD-7, PSQI, cigarette, alcohol and drug usage, and presence of a psychiatric disorder) were predictive of the presence of at least one CAPE-Pos with frequency of "often" or "nearly always" among adolescents. To assess for potential mediation of PHQ-9 and GAD-7 on the association of the number of SARS-CoV-2 symptoms during acute infection period and CAPE-Pos, Hayes' (2009) PROCESS mediator analysis Model 4 was utilized (Hayes, 2018). According to this model, the effect of the independent variable (i.e, number of SARS-CoV-2 symptoms) on CAPE-Pos-Frequency is presented in the total effect. The direct effect shows the impact of the number of SARS-CoV-2 symptoms on CAPE-Pos when controlling for the mediators (i.e, PHQ-9 and GAD-7). The indirect effect describes the total path over the PHQ-9 and GAD-7. Bias corrected 95% confidence intervals were generated using a bootstrapping approach with 10.000 re-sample. Data were analyzed with IBM SPSS Statistics for Macintosh, Version 17.0. Statistical significance was set at $\alpha < 0.05$.

3. Results

Age and gender distribution did not differ between the CG and SARS-CoV-2 groups (Table 1). The frequency of attention deficit and hyperactivity disorder (ADHD) was significantly higher in the SARS-CoV-2 group (Table 1). The rates of psychiatric disorders in family and of cigarette, alcohol, drug use, and Covid-19-related anxiety were

Table 1
Socio-demographic characteristics, cigarette, alcohol, and drug use, and Covid-19-related anxiety level of the groups (SARS-CoV-2 group and control group).

	SARS-CoV-2 group n = 361	Control group n = 323	Statistics *U*, X^2	p value	Effect size
Age (Median (IQR))	15.7 (3.43)	16.1 (2)	542221.000 [a]	0.11	n.a.
Gender (n(%))					
Male	161 (44.6)	168 (52)	3.940[b]	0.14	n.a.
Female	198 (54.8)	153 (47.4)			
Do not want to mention	2 (0.6)	2 (0.6)			
Diagnosed psychiatric disorder (n(%))	40 (11.1)	30 (9.3)	0.596[b]	0.44	n.a.
	9 (2.5)	14 (4.3)	1.257[b]	0.26	n.a.
		9 (2.8)	1.681[b]	0.30	n.a.
Depression	5 (1.4)	10 (3.1)	4.554[b]	0.03 *	0.082
Anxiety disorder	24 (6.6)	4 (1.2)	n.a.	0.71	n.a.
ADHD	3 (0.8)				
Other					
Psychiatric disorder in family (n(%))	17 (4.7)	42 (13)	14.878[b]	<0.001*	0.147
Chronic disease (n(%))	42 (11.6)	42 (13)	0.296[b]	0.58	n.a.
Cigarette use within 30 days (n(%))	19 (5.3)	55 (17)	24.455[b]	<0.001*	0.189
Alcohol use within 30 days (n(%))	6 (1.7)	37 (11.5)	26.113[b]	<0.001 *	0.201
Drug use in lifetime	2 (0.6)	13 (4)	8.024[b]	0.005*	1.118
Covid-19-related anxiety	5 (5)	6 (2)	48415.000 [a]	<0.001*	0.29

[a] Mann Whitney *U* test, [b] Chi-square test, ADHD = Attention-deficit/hyperactivity disorder.

significantly higher in the CG (Table 1).

Among individuals who were infected with SARS-CoV-2, 20.2% (n = 73) were asymptomatic. The frequency of symptoms during the acute infection period was: fatigue (n = 185, 51.2%), headache (n = 168, 46.5%), fever (n = 163, 45.2%), anosmia or ageusia (n = 158, 43.8%), arthralgia (n = 129, 35.7%), myalgia (n = 128, 35.5%), sore throat (n = 125, 34.6%), diarrhea (n = 95, 26.3%), cough (n = 82, 22.7%), chest pain (n = 48, 13.3%), conjunctivitis (n = 43, 11.9%), shortness of breath (n = 43, 11.9%), and rash (n = 21, 5.8%). The mean baseline CRP level and white blood cell differential counts were: CRP 0.43 mg/L ± 1.54 mg/L, neutrophil $2.87*10^9$/L ± $1.47*10^9$/L, lymphocyte $1.77*10^9$/L ± $0.66*10^9$/L, monocyte $0.38*10^9$/L ± $0.17*10^9$/L, leucocyte $5.03*10^9$/L ± $1.57*10^9$/L. The mean time interval between the onset of SARS-CoV-2 infection and online evaluation was 7.6 ± 0.8 months (min = 4.44 months, max = 10.02 months).

When compared with the CG group, the frequency and related stress of CAPE-Pos in the SARS-CoV-2 group were significantly higher, whereas PSQI and GAD scores were significantly lower (Fig. 1). Among the three dimensions of the CAPE-Pos, only bizarre experiences (U = 51689.500, p = 0.006) and delusional ideas (U = 48991.500, p < 0.001) significantly differed between the SARS-CoV-2 and CG groups. CAPE-Pos frequency and related stress were significantly correlated with PHQ-9, GAD-7, and PSQI scores (Table 2). Among the SARS-CoV-2 group, the number of symptoms during SARS-CoV-2 acute infection was positively correlated with CAPE-Pos frequency (rho = 0.269, p < 0.001), CAPE-Pos related stress (rho = 0.284, p < 0.001), PHQ-9 scores (rho = 0.308, p < 0.001), and GAD-7 scores (rho = 0.297, p < 0.001). CAPE-Pos frequency and CAPE-Pos related stress were not correlated with baseline inflammatory markers including CRP level, and neutrophil, lymphocyte, and leucocyte counts, NLR, MLR, and SII. On the other hand, the monocyte count was significantly correlated with the CAPE-Pos frequency (rho = 0.124, p = 0.04) and CAPE-Pos related stress (rho = 0.129, p = 0.03). The time interval between the onset of the SARS-CoV-2 infection and the online assessment was not significantly correlated with CAPE-Pos frequency/related stress, PHQ-9, GAD-7, or PSQI scores.

102 participants in the CG (31.6%) and 147 patients in the SARS-CoV-2 group (40.7%) endorsed at least one positive PLE with an "often" or "almost always" frequency ($X^2(2) = 6.153$, $p = 0.01$). Multivariate binary logistic regression analysis was performed to identify factors that were associated with at least one CAPE-Pos with the frequency of "often" or "almost always". Our logistic regression model explained 40.6% of the variance and correctly classified 78.8% of the cases, with a sensitivity of 90% and a specificity of 59.2%. SARS-CoV-2 infection and cigarette usage were related to a 2.42-fold and 2.11-fold increased risk of the presence of PLEs, respectively (Table 3). 1 point

Table 2
Correlates of psychotic like experiences among the whole sample (n = 684).

	CAPE-Pos-Frequency	CAPE-Pos-Stress	PHQ-Total	GAD-Total	PSQI
(1) CAPE-Pos-Frequency	1.000.				
(2) CAPE-Pos-Stress	0.982* <0.001	1.000			
(3) PHQ-Total	0.632* <0.001	0.630* <0.001	1.000		
(4) GAD-Total	0.578* <0.001	0.604* <0.001	0.748* <0.001	1.000	
(5) PSQI	0.225* <0.001	0.251* <0.001	0.427* <0.001	0.410* <0.001	1.000

Spearman correlation test, *p < 0.05. CAPE-Pos = Community assessment of psychic experiences positive subscale, PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized anxiety disorder-7, PSQI = Pittsburg Sleep Questionnaire Index.

Table 3
Multivariate binary logistic regression analysis to detect variables associated with the presence of psychotic like experience in often or nearly always frequency.

	B	S.E.	p value	Odds Ratio (OR)	95% C.I.for OR Lower	Upper
SARS-CoV-2 infection	0.884	0.222	<0.001*	2.421	1.566	3.743
GAD-7	0.188	0.035	<0.001*	1.207	1.127	1.293
PHQ-9	0.105	0.029	<0.001*	1.110	1.049	1.175
PSQI total	−0.033	0.037	0.37	0.968	0.900	1,041
Cigarette use	0.748	0.368	0.04*	2.112	1.027	4.346
Alcohol use	0.400	0.459	0.38	1.491	0.607	3.666
Drug use	−0.092	0.713	0.89	0.912	0.225	3.693
Presence of a diagnosed psychiatric disorder	0.206	0.327	0.52	1.229	0.648	2.331
Psychiatric disorder in family	−0.257	0.367	0.48	0.773	0.376	1.588
Age	0.058	0.064	0.36	1.060	0.935	1.202
Gender (Male) †	0.101	0.208	0.62	1.106	0.736	1.662
Constant	−3.556	1.032	0.001*	0.029		

*p < 0.05, PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized anxiety disorder-7, PSQI = Pittsburg Sleep Questionnaire Index. † Female coded as the reference.

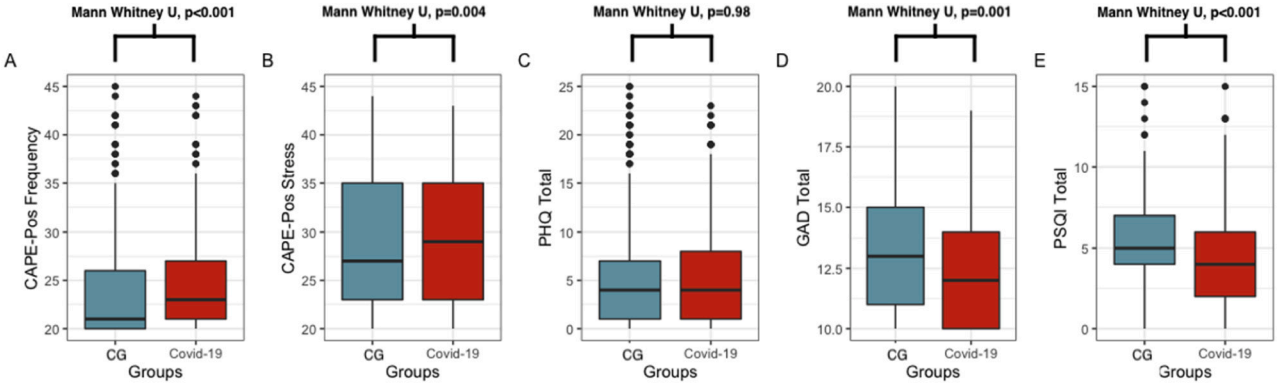

Fig. 1. Comparison between the SARS-CoV-2 and control groups in terms of psychotic-like experiences (PLEs), depression and anxiety levels, and sleep problems CAPE-Pos = Community assessment of psychic experiences positive subscale, PHQ = Patient Health Questionnaire-9; GAD = Generalized anxiety disorder-7, PSQI = Pittsburg Sleep Questionnaire Index, CG = Control group. A = Comparison of the frequency of PLEs, B = Comparison of PLEs-related stress, C = Comparison of depression level, D = Comparison of anxiety level, E = Comparison of sleep problems.

increase in GAD-7 and PHQ-9 was associated with 20% and 11% increased risk of PLEs, respectively (Table 3).

To test the assumption that PHQ-9 and GAD-7 mediate the association of the number of SARS-CoV-2 symptoms during acute infection and CAPE-Pos frequency, we conducted a mediation analysis among adolescents who had been infected with the SARS-CoV-2 virus. Due to missing data in 18 patients, mediation analysis was performed among 343 patients. While the number of SARS-CoV-2 symptoms had significantly indirect effect on CAPE-Pos frequency through PHQ-9 (indirect = 0.125, SE = 0.05, CI = 0.02–0.24) and GAD-7 (indirect = 0.334, SE = 0.08, CI = 0.18–0.51), it did not exhibit a significant direct effect on CAPE-Pos frequency (direct = 0.078, SE = 0.09, CI = -0.11–0.27) (Fig. 2). The non-significance of the direct effect of the number of SARS-CoV-2 symptoms on CAPE-Pos frequency suggests that the PHQ-9 and GAD-7 fully mediated the relationship between the presence of the number of SARS-CoV-2 symptoms and CAPE-Pos frequency (Nitzl et al., 2016). The total amount of variance accounted for by the overall model was 23%.

4. Discussion

To the best of our knowledge, this online study is the first study investigating whether SARS-CoV-2 infection is related to PLEs among adolescents. We also examined which variables (SARS-CoV-2 infection, depression and anxiety levels, sleep problems, cigarette, alcohol and drug use, and the presence of a psychiatric disorder) were predictive for PLEs among adolescents during the SARS-CoV-2 pandemic. Finally, we explored whether anxiety and depression levels mediate the relationship between the number of SARS-CoV-2 symptoms during acute infection and the frequency of PLEs.

The quasi-dimensional model conceptualizes PLEs as an indication of underlying vulnerability for psychosis (Yung et al., 2009). Moreover, psychotic disorders and PLEs share a broad range of risk factors, including social, environmental, developmental, neuroanatomical, cognitive, intellectual, and psychopathological (Kelleher and Cannon, 2011). A growing body of literature has investigated the onset of psychotic disorder in relation to the SARS-CoV-2 pandemic (Valdés-Florido et al., 2021). Ferrando et al. (2020) presented three patients with possibly SARS-CoV-2-associated inflammatory triggered psychosis. Despite the possible association between the SARS-CoV-2 infection and psychosis, to date, no study has investigated whether the SARS-CoV-2 infection is related to PLEs among adolescents. Consistent with our first hypothesis, adolescents exposed to the SARS-CoV-2 exhibited significantly higher frequencies of bizarre experiences and delusional ideas than those not affected by the SARS-CoV-2. Indeed, the SARS-CoV-2 infection was related to a 2.11-fold increased risk of at least one positive PLE "often" or "almost always" frequency in logistic regression analysis.

Recent *meta*-analytical evidence has demonstrated increased pro-inflammatory and pro-oxidative status in first-episode psychosis (Fraguas et al., 2019), in psychosis risk (Misiak et al., 2021), and in schizophrenia (Frydecka et al., 2018). Longitudinal studies have also established a link between inflammation and PLEs (Francesconi et al., 2020; Khandaker et al., 2014). Hence, our finding showing a possible relationship between SARS-CoV-2 infection and PLEs can be explained by this link. Boldrini et al. (2021) and Watson et al. (2021) proposed possible explanations of neuropsychiatric symptoms seen in some patients with the SARS-CoV-2. They suggested that systemic inflammation may cause decreased monoamines and trophic factors and activation of microglia, leading to increased glutamate and *N*-methyl-d-aspartate (NMDA) and excitotoxicity. Other possible mechanisms proposed by the authors were: (1) The leakage of viral particles through the blood–brain barrier, (2) direct viral invasion of brain and central nervous system vasculature, (3) hypoxic injury of brain, (4) micro-strokes caused by microthrombi, and (5) post-infectious autoimmune disorder. It is important to bear in mind that our study design was not sufficient to claim a direct association between SARS-CoV-2 infection and PLEs, instead it shows a possible link between PLEs and a systemic inflammation disease (Watson et al., 2021). Besides these biological reasons, severe stress related to SARS-CoV-2 infection and potential iatrogenic factors (e.g., isolated wards and personal protective equipment that limit normal social interaction, pharmacological agents like corticosteroids, etc.) can be related to an increased frequency of PLEs among adolescents exposed to the SARS-CoV-2 than controls (Turley et al., 2019; Watson et al., 2021). Thus, the association between SARS-CoV-2 and PLEs can be transitory and the trajectory of this relationship should be examined by prospective studies.

The results of this study indicated that the frequency of PLEs and PLEs-related stress were significantly positively correlated with monocyte count. Mao et al. (2021) showed that severely ill patients with SARS-CoV-2 exhibited monocytosis, leukocytosis, neutrophilia, lymphocytopenia, eosinophlia, and anemia compared to moderately ill patients. Gomez-Rial et al. (2020) suggested that monocytes can exert inappropriate activity and induce cytokine storm, which can lead to

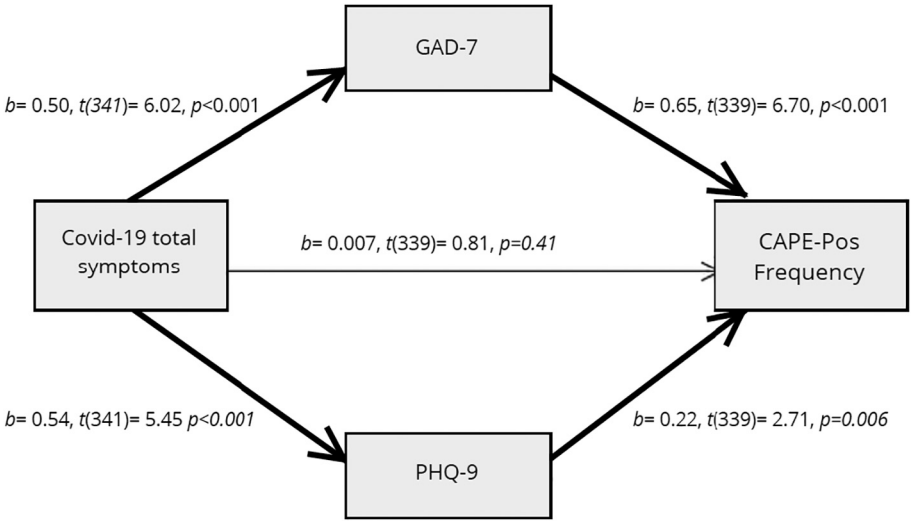

Fig. 2. The mediating effects of internalizing symptoms on the association between the number of SARS-CoV-2-related symptoms during acute infection and PLEs PROCESS mediator analysis Model 4. CAPE-Pos = Community assessment of psychic experiences positive subscale, PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized anxiety disorder-7.

severe tissue damage and disease worsening during SARS-CoV-2 infection. Our findings also showed that the number of SARS-CoV-2 symptoms during the acute infection period was associated with PLEs-frequency, PLEs-related stress, and depression and anxiety levels. Consistent with this finding, an increased number of SARS-CoV-2 symptoms at baseline, which may show illness severity, was found to be related to increased prevalence of depression, anxiety, and post-traumatic stress disorder (Ismael et al., 2020).

Our findings show that besides the SARS-CoV-2 infection, higher levels of depression and anxiety contribute to PLEs during the pandemic among adolescents. In line with this finding, Hajdúk et al. (2020) demonstrated a longitudinal relationship between depression/anxiety and PLEs among college students during the SARS-CoV-2 outbreak. However, the underlying mechanisms of the relationship between depression/anxiety and PLEs still need to be explored. Adolescents with PLEs can be more susceptible to depression and anxiety. Alternatively, depression and anxiety can increase the risk of PLEs among adolescents (Yamasaki et al., 2018). Furthermore, a shared underlying mechanism, such as hypothalamic–pituitary–adrenal axis dysregulation or inflammation, can lead to both depression/anxiety and PLEs (Francesconi et al., 2020; Yamasaki et al., 2018). We also found that depression and anxiety levels mediate the association between the number of SARS-CoV-2 symptoms and PLEs frequency among adolescents exposed to the SARS-CoV-2. Consistent with our finding, Francesconi et al. (2020) found a mediator effect of internalizing symptoms on the relationship between levels of IL-6 at age 9 and PLE at age 18. Importantly, Oh et al. (2021) also showed that PLEs were related to SARS-CoV-2 infection among college students, though much of the association is decreased when adjusting for anxiety and depression. Due to our cross-sectional design, we could not detect the causal relationship between the variables. A future prospective study should investigate whether internalizing symptoms mediate the association between SARS-CoV-2 severity and PLE among adolescents.

Moreover, we showed that cigarette usage was related to a 2.1 fold increased risk of PLEs during the pandemic. In line with our result, Jones et al. (2018) demonstrated that early-onset tobacco users were at a 1.78-fold greater risk of subsequent PLEs. The prodopaminergic effect of nicotine, impaired inflammatory functioning, or perturbation of acetylcholine receptors in tobacco smokers might explain the contribution of cigarette use to PLEs among adolescents (Mallet et al., 2018). Surprisingly, our CG exhibited higher anxiety levels and sleep problems when compared with the SARS-CoV-2 group. In addition, Covid-19-related anxiety was higher in the CG than in the SARS-CoV-2 group. Matalon et al. (2021) and Parker et al. (2021) found that anxiety symptoms significantly decrease in the month following hospitalization among SARS-CoV-2 patients. Therefore, surviving from SARS-CoV-2 infection and reducing unpredictability about the Covid-19 disease may be associated with lower anxiety levels in our SARS-CoV-2 group. A bidirectional relationship was proposed between sleep problems and Covid-19-related anxiety by Melillo (2021). On the one hand, disturbed sleep predicts greater pandemic-related perceived stress, and on the other, higher anxiety symptoms increase the odds of sleep problems among adolescents during the Covid-19 pandemic (Melillo, 2021). Consistent with this, we found a positive correlation between anxiety level and sleep problems, with a medium effect size. Contrary to expectations (Taylor et al., 2015), this study did not find the contribution of sleep problems on PLEs. We cannot exclude the possibility that the cross-sectional design of our study may have contributed to this negative result.

Several limitations should be considered. First, the cross-sectional design prevented us from determining the causal link between PLEs and the SARS-CoV-2. Secondly, our survey was self-selecting and only individuals who had access to the internet contributed to the study. Therefore, our population was not representative of the global adolescent population. We were also reliant on self-report data and could not confirm the presence of PLEs. Thirdly, up to 90% of pediatric cases infected with the SARS-CoV-2 can be completely asymptomatic (Naja et al., 2020). Thus, although we excluded cases who reported exposure to SARS-CoV-2 from our CG, we may have still included cases with asymptomatic SARS-CoV-2 infection or false-negative cases. Finally, it should be noted that we found a small effect size (Cohen's $d = 0.29$) for the difference between the SARS-CoV-2 group and CG in terms of the frequency of PLEs. Thus, our findings should be confirmed by future studies. Notwithstanding these limitations, to the best of our knowledge, this is the first study that showed a possible association between PLEs and SARS-CoV-2 infection among adolescents. The strengths of this study were the large sample size and the confirmation of the SARS-CoV-2 infection using an RT-PCR test.

5. Conclusion

Adolescents exposed to the SARS-CoV-2 virus reported a higher frequency and a higher proportion of PLEs than those not affected by the SARS-CoV-2. Besides SARS-CoV-2 infection, depression, anxiety, and cigarette use contributed to PLEs during the pandemic. PLEs were positively correlated with monocyte count and the number of SARS-CoV-2-related symptoms during the acute infection period. Furthermore, internalizing symptoms fully mediated the positive association between an increased number of SARS-CoV-2-related symptoms and PLE-frequency. Longitudinal studies are needed to determine the causal relationship between SARS-CoV-2 infection and PLEs. If this relationship is confirmed prospectively, close monitoring and early interventions may be necessary for adolescents exposed to the SARS-CoV-2 infection.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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