WOMEN IN PSYCHIATRY 2021: PSYCHOSOMATIC MEDICINE

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WOMEN IN PSYCHIATRY 2021: PSYCHOSOMATIC MEDICINE

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Table of Contents

04 ***Gender-Dependent Associations of Anxiety and Depression Symptoms With Eating Disorder Psychopathology in a Representative Population Sample***
Mareike Ernst, Antonia M. Werner, Ana N. Tibubos, Manfred E. Beutel, Martina de Zwaan and Elmar Brähler

13 ***Association of Loneliness and Wisdom With Gut Microbial Diversity and Composition: An Exploratory Study***
Tanya T. Nguyen, Xinlian Zhang, Tsung-Chin Wu, Jinyuan Liu, Collin Le, Xin M. Tu, Rob Knight and Dilip V. Jeste

21 ***Carer's Attachment Anxiety, Stressful Life-Events and the Risk of Childhood-Onset Type 1 Diabetes***
Anja Turin, Klemen Dovč, Simona Klemenčič, Nataša Bratina, Tadej Battelino, Jasna Klara Lipovšek, Katarina Uršič, Yael Shmueli-Goetz and Maja Drobnič-Radobuljac

29 ***Multidimensional Assessment of Interoceptive Abilities, Emotion Processing and the Role of Early Life Stress in Inflammatory Bowel Diseases***
Konstantina Atanasova, Tobias Lotter, Wolfgang Reindl and Stefanie Lis

47 ***Sexuality in Persons With Hidradenitis Suppurativa: Factors Associated With Sexual Desire and Functioning Impairment***
Rossella Mattea Quinto, Simona Mastroeni, Francesca Sampogna, Luca Fania, Roberta Fusari, Luca Iani and Damiano Abeni

54 ***The Effect of Yijinjing on the Cognitive Function of Patients With Chronic Schizophrenia***
Hui Gao, Chao Luo, Si-Jing Tu, Ru-Ping Lu, Lin-Na Jiang, Hui-Jun Qiao, Qu Lin, Ning-Ning Li and Jian-Hua Chen

60 ***The Relationship of Food Addiction With Other Eating Pathologies and Impulsivity: A Case-Control Study***
Ekin Sönmez Güngör, Cengiz Çelebi and Yildiz Akvardar

69 ***Loneliness in Young Adults During the First Wave of COVID-19 Lockdown: Results From the Multicentric COMET Study***
Gaia Sampogna, Vincenzo Giallonardo, Valeria Del Vecchio, Mario Luciano, Umberto Albert, Claudia Carmassi, Giuseppe Carrà, Francesca Cirulli, Bernardo Dell'Osso, Giulia Menculini, Martino Belvederi Murri, Maurizio Pompili, Gabriele Sani, Umberto Volpe, Valeria Bianchini and Andrea Fiorillo

79 ***Psychological Traits of Patients With Depression Comorbid With Chronic Pain: Are Complaint and Competitive Tendency Related to Pain?***
Koji Fujimoto, Masako Hosoi, Ryoko Katsuki, Toshio Matsushima, Keitaro Matsuo, Tomohiro Nakao, Nobuyuki Sudo and Takahiro A. Kato

86 ***Uric Acid Potential Role in Systemic Inflammation and Negative Symptoms After Acute Antipsychotic Treatment in Schizophrenia***
Milica M. Borovcanin, Slavica Minic Janicijevic, Natasa R. Mijailovic, Ivan P. Jovanovic, Nebojsa N. Arsenijevic and Katarina Vesic

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ORIGINAL RESEARCH
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Gender-Dependent Associations of Anxiety and Depression Symptoms With Eating Disorder Psychopathology in a Representative Population Sample

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Background: Evidence shows that anxiety and depressive disorders play an important role in eating disorder behavior. However, given the epidemiology of eating disorders, there is a need to investigate potentially gender-specific connections.

Method: This study tested the associations of anxiety and depression symptoms with eating disorder symptoms and behaviors and explored whether they differed between men and women. Within a population-representative survey (N = 2,510; ages 14–94), participants completed measures of depression symptoms (PHQ-2), anxiety symptoms (GAD-2), and eating disorder symptoms (EDE-Q8). We conducted linear regression analyses of the EDE-Q8 sum score and General Linear Models on the three behaviors overeating, binge eating, and compensatory behaviors (self-induced vomiting/use of laxatives/excessive exercising).

Results: Depression and anxiety symptoms were related to more eating disorder symptoms in men and women (irrespective of BMI, age, and income). The association of depression and eating disorder symptoms was slightly stronger in women. Overeating was more common in men and in depressed individuals, whereas compensatory behaviors were more common among anxious individuals, especially anxious women.

Conclusion: The study extends previous research by using gender-specific methods in a representative sample. It indicates similarities and differences between men and women regarding disordered eating on a population level.

Keywords: anxiety, depression, eating disorders, population, gender differences, representative survey

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INTRODUCTION

A large body of research has shown deviations from healthy emotional life in individuals with eating disorders. For instance, emotion regulation deficits (e.g., lack of emotional awareness) were found in all diagnosis groups (1). Emotion regulation can be summarized as the capacity to understand one's emotions and to modulate one's emotional response (2). Individuals do this in

different ways. For those who do not use adaptive strategies (such as reappraisal), eating disorder behavior can instead serve the purpose to attenuate difficult emotions. For example, Heatherton and Baumeister (3) proposed that binge eating serves as an escape from distressing self-perceptions, thus providing relief.

Indeed, a range of negative subjective states were initiating and/or maintaining factors of different kinds of eating disorder behavior (4). For instance, stress and experimentally induced negative mood increased the likelihood for female, obese study participants to lose control over the amount of food they consumed (5, 6). Likewise, anxiety (comprising symptoms of six anxiety disorders) exacerbated emotional eating and loss of control over eating in adolescents (7). Eating has been shown to alleviate distress in individuals who lacked other, more constructive coping mechanisms to calm themselves (e.g., after experiencing life stressors or experimental manipulations that led to anger or sad mood) (8, 9). Unpleasant emotions, namely sadness, anger, and fear were also related to *restrictive* eating behaviors (10, 11).

More generally, there is a substantial overlap between eating disorders and depressive (12, 13) and anxiety disorders (14, 15). There are different explanatory models for this observation. It has been hypothesized that depression and anxiety disorders are sequelae of eating disorders, or vice versa. Further, eating disorder symptoms could be manifestations of depression and anxiety disorders (depending on an individual's age and gender), or they could share common etiological factors (12, 16). Eating disorder, depression and anxiety symptoms belong to an internalizing phenotype of psychopathology that is much more common in women (17–19). Hence eating disorder research has heavily focused on women and only few studies have investigated large samples of men and women using gender-sensitive or gender-specific methods. However, such approaches are crucial to identify potential targets for prevention and treatment that are relevant in both men *and* in women, or only in men *or* in women [e.g., (20–23)].

The necessity for the investigation of gender-dependent patterns is underscored by previous research that has found different conditions underlying higher bodyweight in men and women. For instance, the association of anxiety and depression symptoms with higher bodyweight was moderated by gender (24) in the sense that women with anxiety and depression symptoms were more likely to have a higher bodyweight than men who reported anxiety and depression symptoms. Likewise, depression was more closely related to obesity in women in the community (25, 26). Similar results were reported by studies that contained measures of eating disorder symptoms or specific behaviors: In path models of binge eating within a sample of undergraduate students, negative affect (comprising e.g., depression symptoms) interacted with loss of dietary restraint in obese women, but not in obese men (27). Based on a large sample of American adults, Cotter and Kelly (28) reported that the association between stress and stress-related eating (eating more than usual as well as eating in order to feel better) was stronger in women. However, there is a lack of research analyzing gender-dependent associations (i.e., by modeling interaction terms) with more cognitive symptoms (including, e.g., preoccupation with food). There is also a research gap with respect to gender-dependent effects of anxiety and depression symptoms on both restrictive eating behaviors as well as compensatory behaviors (such as vomiting, or use of laxatives).

The aim of the present study was to expand previous research by using a large, representative population sample ($N = 2{,}510$) and by investigating eating disorder psychopathology (including cognitive symptoms such as guilt about eating) as well as actual behaviors of different kinds (overeating, binge eating, and compensatory behaviors). The sample included the entire adult age range, all bodyweight categories, and all income brackets. We investigated the relationships of depression and anxiety symptoms with eating disorder symptoms and behaviors measured by the EDE-Q8, a validated short form of the Eating Disorder Questionnaire (29) and whether these associations differed as a function of gender. In line with previous research cited above, which heavily focused on bodyweight (i.e., obesity), we expected more relevant relationships of the variables of interest within the women in our sample.

In particular, we tested the following hypotheses:

1) a) There are positive associations of depression symptoms and anxiety symptoms with global eating disorder psychopathology in the general population.
   b) These associations are modified by gender: they are stronger within women compared to men.

2) a) There are associations of depression symptoms and anxiety symptoms with specific behaviors (overeating, binge eating, compensatory behaviors).
   b) These associations are modified by gender, too: they are stronger within women.

MATERIALS AND METHODS

Participants

From September to November 2016, a representative sample of the German population was surveyed by the demographic consulting company USUMA (based in Berlin, Germany). Participants were chosen via a random route procedure. To be included, individuals had to be 14 years of age or older and to have sufficient understanding of the German language. The final sample used in the present investigation was representative of the German population regarding age, gender, and geographic region. Out of 4,902 designated addresses, 2,510 households participated (51.2%). Persons in multi-person households were randomly selected using a Kish-Selection-Grid. All participants provided informed consent. In the case of minors, participants gave informed assent with informed consent being provided by their parents/legal guardians.

Responses were anonymous. Socio-demographic information was obtained in an interview-format by the research staff and all other information was provided via a questionnaire (handed out with by a sealable envelope). Completed questionnaires were linked to respondent's demographic data without containing any identifying information. The study was conducted in accordance with the Declaration of Helsinki, and fulfilled the ethical guidelines of the International Code of Marketing and Social Research Practice of the International Chamber of Commerce

and of the European Society of Opinion and Marketing Research. The study was approved by the Ethics Committee of the Medical Department of the University of Leipzig. In total, 2,510 individuals participated (1,171 men and 1,339 women).

Measures

We used the eight-item version of the Eating Disorder Examination Questionnaire (EDE-Q8) to assess *eating disorder psychopathology*. It has previously shown excellent item characteristics and model fit indices as well as good reliability and convergent validity in large, representative samples of the population (30). In the present sample, internal consistency of the scale was also excellent ($\omega = 0.92$). The eight items cover the topics restraint over eating, food avoidance, preoccupation with food, feelings of fatness, desire to lose weight, guilt about eating, dissatisfaction with weight, and discomfort seeing one's body. With reference to the last 28 days, participants are asked to report how often they were affected by the respective item. Response options range from 0 = never to 6 = every time. Using the same format, three additional items assess the frequency of important *behavioral* aspects of eating disorders. They cover the frequency of overeating, binge eating (i.e., overeating with loss of control while eating), and self-induced vomiting/use of laxatives/excessive physical exercise (in the following summarized as compensatory behavior).

We used the GAD-2 (the two item short form of the Generalized Anxiety Disorder GAD-7) to assess *anxiety symptoms* (31). It starts with the question: "Over the last week, how often have you been bothered by the following problems?" and assesses two symptoms of generalized anxiety disorder: "Feeling nervous, anxious, or on edge," and "Not being able to stop or control worrying. Response options range from 0 = not at all to 3 = nearly every day, yielding a sum score from 0 to 6. A cut-off score of > =3 has yielded good sensitivity (86%) and specificity (83%) (32). In the present sample, the GAD-2 showed good internal consistency ($\omega = 0.79$).

Following the same instruction question, the PHQ-2 assesses the main criteria of major *depression* according to DSM-5: "Little interest or pleasure in doing things" and "Feeling down, depressed or hopeless" (33). Response options also range from 0 = not at all to 3 = nearly every day and yield a sum score between 0 and 6. A cut-off score of > =3 deemed ideal to identify clinically relevant symptom severity (with a sensitivity of 87% and a specificity of 78%) (33, 34). The PHQ-2 showed good internal consistency in the present sample ($\omega = 0.81$).

We used Body Mass Index (BMI) (kg/m^2) to control analyses for participants' bodyweight. It was calculated based on their self-reported height and weight.

We calculated equivalised income according to the OECD guideline (35) by dividing the household income through the square root of people in household. The result was then recoded into the following categories: 1 = <1,250€, 2 = 1,250–2,500€, 3 = >2,500€.

Other sociodemographic information such as age and gender were assessed via self-report.

Statistical Analyses

Sample characteristics are reported as means and standard deviations or percentage and number of cases, respectively.

To investigate research questions (1) (a) and (b), we conducted a hierarchical linear regression analysis of global eating disorder psychopathology (operationalized as the sum score of the EDE-Q8). Hierarchical linear regression allows for testing whether the introduction of new predictors adds to the explanation of the dependent variable's variance in a statistically significant way. Model 1 contained the sociodemographic variables age (as a continuous variable), gender (coded 1= men, 2 = women), and income. In model 2, the (centralized) PHQ-2 and GAD-2 sum scores were added to test specific associations of depression and anxiety symptoms and eating disorder symptoms. In model 3, we added an interaction of each of the two scores with gender to investigate possible gender-dependent differences in the depression and anxiety symptoms' associations with eating disorders. We performed a sensitivity analysis using the calculator provided by Soper (36). We tested the sample size required to observe a small effect ($f^2 = 0.02$) taking our largest regression model with eight predictors into account. It yielded a minimum sample size of 755, indicating that our investigation had sufficient statistical power. Regression models were checked for multicollinearity using the variance inflation factor (VIF). All VIF scores were below 3 [10 being the critical threshold (37)], indicating no concerning level of multicollinearity (The hierarchical linear regression analysis was followed by two gender-stratified models to gain a better understanding of gender-dependent associations).

To investigate research questions (2) (a) and (b), the association of depression and anxiety symptoms with diagnostically relevant behaviors, we calculated a General Linear Model (GLM) on each of the EDE-Q8's three items assessing the frequency of different behaviors: Overeating, binge eating, and compensatory behaviors (self-induced vomiting, use of laxatives, and excessive physical exercise). The GLMs contained the fixed effects gender, anxiety symptoms, depression symptoms, and the covariates age, income, and BMI. GLMs allow for a robust comparison of mean values (controlling the overall α-level), the modeling of covariates and interaction terms, and the ascertainment of the magnitude of observed effects. We chose separate GLMs as the three variables could not be aggregated in a meaningful way to form a sum score and were only weakly to moderately correlated with each other (overeating and binge eating: $r = 0.533$, $p < 0.001$; overeating and compensatory behaviors: $r = 0.118$, $p < 0.001$; binge eating and compensatory behaviors: $r = 0.255$, $p < 0.001$).

P-values correspond to two-tailed tests. Analyses were carried out using SPSS 24 for Windows. Regression coefficients and effect sizes are interpreted following Cohen (38).

RESULTS

Sample Description

The sample's age ranged from 14 to 94 years with a mean age of 48.4 years (SD = 18.2). It contained slightly more women ($N = 1{,}339$) than men ($N = 1{,}171$). The sample was

TABLE 1 | Means, standard deviations, and correlations among measures.

Variable	Mean (SD)/percentage	Gender	Income	BMI	PHQ-2	GAD-2	EDE-Q8	Overeating	Binge eating	Comp. behaviors
Age	48.4 (18.2)	0.030	0.245**	0.188**	0.051*	0.002	−0.019	−0.062*	−0.014	−0.031
Gender	$1_{Men} = 46.65$ $2_{Women} = 53.35$		−0.093**	−0.067**	0.088**	0.115**	0.202**	−0.097**	0.007	0.065**
Income	1.55 (0.55)			−0.009	−0.056**	−0.062**	−0.031	−0.026	−0.040	−0.031
BMI	25.76 (4.68)				0.119**	0.072**	0.381**	0.169**	0.182**	0.038
PHQ-2	0.69 (1.15)					0.38**	0.124**	0.101**	0.104**	0.031
GAD-2	0.69 (0.14)						0.344**	0.204**	0.232**	0.089**
EDE-Q8	7.17 (10.19)							0.270**	0.332**	0.153**
Overeating	1.20 (3.41)								0.593**	0.118**
Binge eating	0.56 (2.17)									0.255**
Comp. behaviors	0.08 (0.92)									

*Bivariate analyses are Pearson product-moment correlations, Spearman's Rho for categorical variables. *$p \leq 0.05$, **$p \leq 0.01$. Statistics of categorical variables indicate percentages. PHQ-2, GAD-2, and EDE-Q8 are reported as the sum score; for the three behaviors, frequency (over the last 28 days) is reported. Comp. behaviors = compensatory behaviors. Income: Equivalised income calculated according to the OECD guideline (35): household income/√(people in household); household income per month: 1 = <1,250€, 2 = 1,250–2,500€, 3 = >2,500€. N = 2,404.*

TABLE 2 | Hierarchical linear regression of eating disorder symptoms (dependent variable: EDE-Q8 sum score).

	Model 1 ($\Delta R^2 = 0.200$**; adj. $R^2 = 0.199$**)			Model 2 ($\Delta R^2 = 0.099$**; adj. $R^2 = 0.298$**)			Model 3 ($\Delta R^2 = 0.007$**; adj. $R^2 = 0.304$**)		
	β	95%CI B (L; U)	*p*	*β*	95%CI B (L; U)	*p*	*β*	95%CI B (L; U)	*p*
Gender	0.25	2.09; 2.83	**<0.001**	0.21	1.76; 2.46	**<0.001**	0.21	1.79; 2.48	**<0.001**
Age	−0.10	−0.07; −0.03	**<0.001**	−0.11	−0.08; −0.04	**<0.001**	−0.10	−0.08; −0.04	**<0.001**
Income	0.02	−0.29; 1.10	0.25	0.04	0.08; 1.38	**0.028**	0.39	0.06; 1.35	**0.032**
BMI	0.41	0.80; 0.96	**<0.001**	0.37	0.74; 0.89	**<0.001**	0.37	0.72; 0.87	**<0.001**
Depression symptoms				0.21	0.65; 1.61	**<0.001**	0.21	1.27; 2.21	**<0.001**
Anxiety symptoms				0.13	1.39; 2.32	**<0.001**	0.13	0.58; 1.55	**<0.001**
Depression symptoms × gender							0.08	−0.38; 0.59	**0.004**
Anxiety symptoms × gender							0.01	0.22 1.15	0.66

Effect coding for gender: men = −1, women = 1. Income: Equivalised income calculated according to the OECD guideline (35): household income/√(people in household); household income per month: 1 = <1,250€, 2 = 1,250–2500€, 3 = >2,500€. Bold values indicate statistically significant predictors.

representative for the German population in regard to age and gender. Bivariate correlations showed that female gender was related to reporting more depression symptoms, anxiety symptoms, and global eating disorders symptoms. All of these symptoms were also positively correlated with each other as well as with the reported frequency of the key behaviors overeating, binge eating, and compensatory behaviors (**Table 1**). Higher age was related to higher income, higher BMI, more depression symptoms and fewer episodes of overeating.

Eating Disorder Symptoms (EDE-Q8 Sum Score)

In order to investigate our first research question, we conducted a hierarchical linear regression analysis (**Table 2**). The inclusion of depression symptoms and anxiety symptoms in Model 2 and the inclusion of respective interactions with gender in Model 3 added statistically significant gains in explained variance. The final model explained 30% of the variance in eating disorder symptoms. Positive associations with a higher EDE-Q8 sum score were observed for lower age, female gender, higher BMI, anxiety symptoms, and depression symptoms. The interaction term of depression symptoms and gender was significantly associated with eating disorder symptoms: It indicated that the relation was stronger in women (**Figure 1**).

For a better understanding of the observed interaction effect, we conducted gender-specific analyses (**Table 3**). They showed that depression and anxiety symptoms added statistically significant gains in explained variance and were relevant predictors of eating disorder psychopathology. This was true in men and in women (with a larger beta weight for the predictor depression symptoms among women). The relations of younger age with more eating disorder symptoms were only present in women. In women, the model explained a larger proportion of variance (32 vs. 18%).

Diagnostically Relevant Behaviors

Figure 2 depicts the percentage of men and women who reported that the respective behavior occurred at least four times

over the course of the last month [the DSM-5 criteria state weekly occurrence (39)]. Overeating was most common, but not all individuals who reported having eaten large amounts of food reported to have felt a loss of control while doing so. Compensatory behaviors (self-induced vomiting, intake of laxatives, or excessive exercise) were the least common behaviors.

The results of the GLMs are shown in **Table 4**. All three diagnostically relevant behaviors were more common in younger individuals and in individuals with a higher BMI (with small effect sizes for these differences). Overeating was more common in men and compensatory behaviors were more common in women.

There was no association of gender with binge eating. Regarding depression and anxiety symptoms, we observed different patterns of relations with the three different behaviors: Overeating was more common in those with more anxiety symptoms and binge eating was more common in participants with more depression symptoms. Self-induced vomiting and other compensatory behaviors were more common among those with more severe anxiety. There was also an interaction, indicating that the latter association was stronger in women. All effects observed within the GLMs were small ($\eta^2 < 0.06$).

DISCUSSION

We used a large sample representative of the German population to explore the relations of eating disorder symptoms as well as specific behaviors with depression and anxiety symptoms in men and women. Global eating disorder symptoms (which included cognitive symptoms such as preoccupation with food and self-evaluations such as dissatisfaction with weight) were more common in women and in individuals with higher

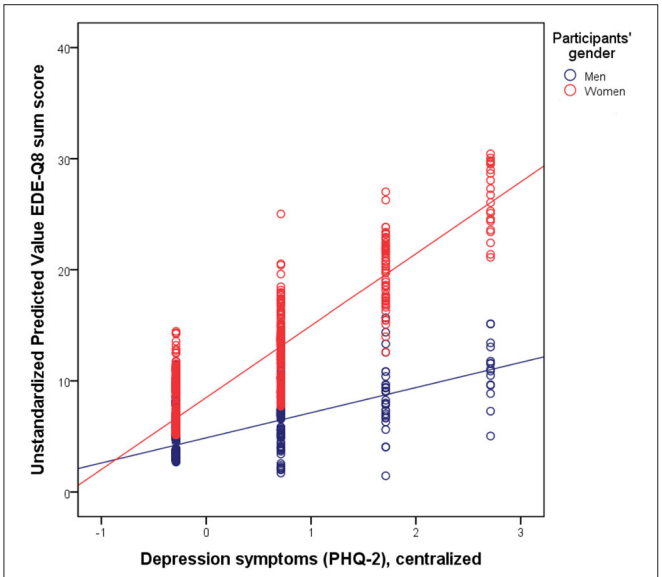

FIGURE 1 | Visualization of the interaction: there was a closer association of eating disorder symptoms as measured by the EDE-Q8 with depression symptoms as measured by the PHQ-2 in women.

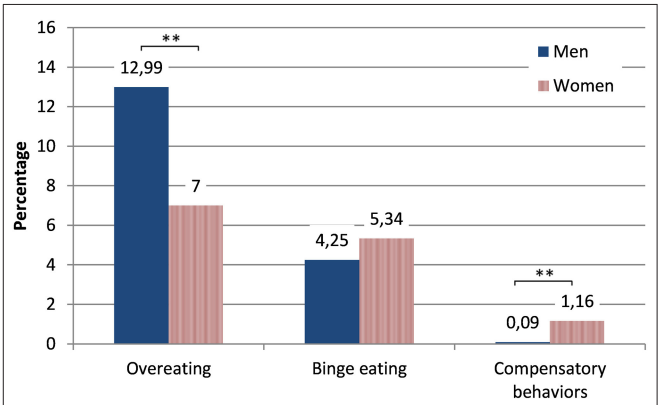

FIGURE 2 | Percentage of individuals of the general population who reported that the respective behavior had occurred at least four times over the course of the last month (stratified by gender). Asterisks indicate statistically significant differences.

TABLE 3 | Hierarchical linear regression of eating disorder symptoms (dependent variable: EDE-Q8 sum score), stratified by gender.

	Men						Women					
	Model 1 ($\Delta R^2 = 0.131$**; adj. $R^2 = 0.128$**)			Model 2 ($\Delta R^2 = 0.057$**; adj. $R^2 = 0.184$**)			Model 1 ($\Delta R^2 = 0.192$**; adj. $R^2 = 0.190$**)			Model 2 ($\Delta R^2 = 0.132$**; adj. $R^2 = 0.321$**)		
	β	95%CI B (L; U)	*p*	*β*	95%CI B (L; U)	*p*	*β*	95%CI B (L; U)	*p*	*β*	95%CI B (L; U)	*p*
Age	0.00	−0.03; 0.03	0.96	−0.01	−0.03; 0.02	0.63	−0.16	−0.13; −0.06	**<0.001**	−0.16	−0.13; −0.07	**<0.001**
Income	0.03	−0.38; 1.26	0.30	0.05	−0.14; 1.45	0.11	0.02	−0.65; 1.53	0.43	0.04	−0.22; 1.78	0.13
BMI	0.36	0.59; 0.82	**<0.001**	0.36	0.60; 0.82	**<0.001**	0.44	0.86; 1.09	**<0.001**	0.38	0.74; 0.95	**<0.001**
Depression symptoms				0.13	0.37; 1.64	**0.002**				0.27	1.75; 3.11	**<0.001**
Anxiety symptoms				0.13	0.36; 1.59	**0.002**				0.12	0.46; 1.84	**0.001**

Income: Equivalised income calculated according to the OECD guideline (35): household income/√(people in household); household income per month: 1 = <1,250€, 2 = 1,250-2500€, 3 = >2,500€. Bold values indicate statistically significant predictors.

TABLE 4 | Results of the General linear models of diagnostically relevant behaviors.

Model	*F*	*p*	partial η^2
1. Dependent variable: Overeating ($R^2 = 0.066$)			
Gender	6.23	**0.013**	0.003
Age	19.81	**<0.001**	0.009
BMI	68.38	**<0.001**	0.031
Income	0.08	0.78	0.000
Depression symptoms	15.11	**<0.001**	0.007
Anxiety symptoms	4.25	**0.039**	0.002
Gender x Depression symptoms	0.16	0.694	0.000
Gender x Anxiety symptoms	0.00	0.966	0.000
2. Dependent variable: Binge eating ($R^2 = 0.077$)			
Gender	1.40	0.237	0.001
Age	4.71	**0.030**	0.002
BMI	66.29	**<0.001**	0.030
Income	0.40	0.527	0.000
Depression symptoms	39.25	**<0.001**	0.018
Anxiety symptoms	1.55	0.213	0.001
Gender × Depression symptoms	0.93	0.334	0.000
Gender × Anxiety symptoms	0.01	0.934	0.000
3. Dependent variable: Compensatory behaviors ($R^2 = 0.018$)			
Gender	9.86	**0.002**	0.005
Age	3.09	**0.079**	0.001
BMI	13.99	**<0.001**	0.007
Income	0.29	0.592	<0.001
Depression symptoms	0.00	0.982	0.000
Anxiety symptoms	6.29	**0.012**	0.002
Gender × Depression symptoms	0.05	0.816	0.000
Gender × anxiety symptoms	3.87	**0.040**	0.002

Income: Equivalised income calculated according to the OECD guideline (35): household income/√(people in household); household income per month: 1 = <1,250€, 2 = 1,250-2500€, 3 = >2,500€. Bold values indicate statistically significant effects.

bodyweight. These findings corroborate previous research (23, 30, 40), including investigations that used the longer version of the EDE-Q in large population samples in other countries (41). Regarding the different behaviors, our results are also in line with previous epidemiological investigations which found that overeating was the most common type of disturbed eating in the general population. Previous studies also found that men were more likely to indicate overeating, however, more women reported binge eating (42, 43). The finding that compensatory behaviors were more common in women mirrors previous reports of higher prevalence rates of, for example, bulimia in women (18).

Evidence for the Association of Depression and Anxiety Symptoms With Global Eating Disorder Psychopathology and Differences Between Men and Women

The present study expands previous research by showing that global eating psychopathology was associated with depression symptoms (anhedonia and depressed mood) and anxiety symptoms (nervousness, not being able to stop/control worrying) in the German general population irrespective of participants' bodyweight, age, and income. The associations of eating disorder psychopathology and behaviors with anxiety and depression symptoms are in line with previous reports about psychological comorbidities among those with eating disorders (50% with anxiety disorders and 40% with mood disorders) (18). In our study, anxiety was also more closely related to eating disorder symptoms and behaviors than depression. Whilst we found that depression symptoms statistically predicted eating disorder symptoms in men and women, this association was comparatively stronger among women.

It has been proposed that negative, self-evaluating cognitions constitute the main overlap between depressive disorders and eating disorders (44, 45). Along these lines, previous research has stressed the relevance of sociocultural risk factors such as female gender role socialization in explaining the gender gap in eating disorders (46). As one's physical attractiveness, including the shape and weight of the body (which is judged against a thin ideal) is more relevant for women's social evaluation than men's (47), these aspects might be more closely related to negative affect in women (48, 49). Striving for thinness by the means of dieting, exercise, and other weight control behaviors might give the individual a sense of being in control, e. g. after a recent stressful life event (50). Moreover, there are other aspects of eating disorders that play a particularly important role for women that are not related to attractiveness. Among them are questions of self-determination, agency, and feminine identity (51) as well as problematic mother-daughter relationships (52).

The fact that the gender-specific regression model including anxiety and depression symptoms explained more variance in the female sample might indicate that the model lacked factors that are more relevant for men's eating psychopathology. Previous research has suggested that those might be weight history (20) and aspects of athletic achievement (53). Furthermore, the symptoms assessed by the EDE-Q8 comprise feelings of fatness and the desire to lose weight as opposed to, for example, muscularity-oriented diet and exercise and muscularity-oriented dissatisfaction. It thus omits concerns that were especially relevant for men with eating disorders (54–56).

Evidence for Associations of Depression and Anxiety Symptoms With Diagnostically Relevant Behaviors

In line with previous research, we observed associations of depression and anxiety symptoms with actual disturbed eating behavior which comprised overeating, binge eating, and compensatory behaviors. In our study, depression symptoms were especially common among individuals who reported binge eating. This corresponds to the substantial overlap of depression and binge eating disorder which is characterized not only by eating large portions, but also by a loss of control (57, 58). Congruently, negative affect, maladaptive cognitions, and inadequate coping strategies were related to its onset as well as

to its maintenance (59). Depression symptoms were also related to worse treatment outcomes in overweight individuals who tried to lose weight (57).

Regarding the frequency of overeating episodes, a small association with anxiety was present alongside the association with depression symptoms. Previous research has found that overeating might provide relief or a feeling of calm (7, 8). However, overeating improved participants' mood only for short time periods (9).

More anxiety symptoms (but not more depression symptoms) were observed among those reporting compensatory behaviors. This is in line with previous research that had investigated negative and positive affect as predictors of vomiting (60). We also observed an interaction of gender and anxiety symptom burden, indicating that anxious women might be at a particularly high risk to engage in these behaviors. Previous research has indicated that negative affect might trigger compensatory behaviors in women, but not in men (43). This interaction effect was the only one we observed; gender did not moderate the associations of depression and anxiety symptoms and overeating and binge eating, respectively. Thus, these analyses do not contribute to a better understanding of the univariate gender difference we observed with respect to the prevalence of overeating in the population.

However, all observed effects were small. This might be due to the sample (as most of the participants within the population survey reported neither eating disorder symptoms nor anxiety/depression symptoms). Also, as the present sample was representative of the population, participants' mean age was considerably higher than in many clinical investigations. Research has shown that the prevalence of eating disorders declines with age (61). Lastly, newer, more fine-grained methods such as Ambulatory Assessment give a better insight into chronological sequences of feelings and behaviors than questionnaire surveys capturing the last weeks.

STRENGTHS AND LIMITATIONS

Strengths are the large, representative sample (including individuals with and without eating disorder, depression, and anxiety symptoms), the broad age range, and the inclusion of all bodyweight categories. To our knowledge, it is the first population-representative, gender-specific investigation of the association of depression and anxiety symptoms with self-reported eating disorder symptoms comprising both cognitive symptoms (such as preoccupation with food) and behaviors (such as vomiting).

However, the results must also be judged against the backdrop of the study's limitations. First, the present investigation is a cross-sectional analysis of survey data. It does not allow for inferences with respect to cause and effect. BMI was assessed via self-report. Diagnostically relevant behaviors were assessed in terms of their frequency over the last month and not as "at least weekly" episodes in line with the DSM-5 criteria. The present study did not contain sufficient data to diagnose eating disorders. We did not inquire whether participants had ever received diagnoses of eating disorders either.

Further, given the fact that we used a community sample, some proportions were quite small (e.g., individuals reporting compensatory behaviors). An investigation of the study's research questions within large patient samples or high-risk populations (e.g., athletes) will help to ascertain the clinical relevance of our findings. It is another limitation that the behaviors were assessed using single items and that all questionnaires were screening measures (as the format of the large survey study did not allow for the inclusion of more time-consuming instruments). As a result, we can only report associations of eating disorder symptoms and behaviors with the symptoms contained in the short screeners, but not with other symptoms also present in the full manifestation of the disorders such as e. g. fatigue/loss of energy in the case of depression. Also, the GAD-2 only covers two main symptoms of generalized anxiety disorder. Our survey did not include measures of, for example, social anxiety disorder which has also been found to overlap with eating disorders [e.g., (62)]. This limitation might also have contributed to the relatively small proportions of explained variance within the different statistical models.

As noted above, many conceptions of eating disorder symptomatology (including the EDE-Q8) do not include specific features of men's eating disorders. As a consequence, currently used questionnaires might not be as sensitive to eating disorder symptomatology in men as in women and the present study might have underestimated men's symptom burden. Studies investigating differences between men and women will also benefit from collecting information such as the perception of gender roles, gender role self-concept, and gender role conflict. What is more, sexual orientation plays an important role as both non-heterosexual men and women were more vulnerable to body weight dissatisfaction (63). The present research did not include such measures which is why they could not be probed as potential risk factors. Moreover, gender was only assessed in a binary way (women/men).

Lastly, all reported effects observed within the General Linear Models were small and none of them explained more than 8% of the respective criterion's variance. Smaller proportions of explained variance are common in epidemiological research, large surveys, and other fields with greater amounts of unexplainable variation than in controlled experimental environments.

CONCLUSION

The present results from a representative sample of the German population show that depression as well as anxiety symptoms were related to eating disorder symptoms (comprising restraint, eating concern, weight concern, and shape concern) in men and women irrespective of their age, BMI, and income. Overeating was the most common behavior. It was more common among men than among women, but similar numbers of men and women reported binge eating episodes. Women were at a

higher risk for global eating disorder symptom burden and compensatory behaviors (self-induced vomiting, use of laxatives, and/or excessive exercise), although the latter behaviors were comparatively rare.

Our results indicate that specific behaviors observed in individuals with eating disturbances might be related to depression and anxiety symptoms. Overeating and binge eating might be relatively common among those coping with depression, while resorting to—in some instances self-damaging—compensatory measures might primarily serve to diminish anxiety/nervousness (e.g., regarding weight gain). The latter might be more common among women as women face greater societal pressure to be thin. Thus, individuals suffering from different eating disorder symptoms could benefit from learning strategies to cope with different kinds of symptoms, for example, nervousness or depressed mood.

As the observed gender-dependent effects were small, the study suggests some degree of clinical similarities between women and men with eating disorder symptoms. Going forward, the conceptualization of eating disorder psychopathology as a predominantly young, female problem should thus be superseded by more inclusive and differentiated approaches. Furthermore, the fact that we found the reported relations on a population level might indicate targets for prevention. Members of the general public who do not suffer from clinically relevant symptoms or who do not (yet) fall into extreme bodyweight categories might also benefit from guidance in dealing with negative emotions in daily life.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Department of the University of Leipzig. All participants provided informed consent. In the case of minors, participants gave informed assent with informed consent being provided by their parents/legal guardians.

AUTHOR CONTRIBUTIONS

ME, AW, and AT designed the study. EB and MdZ were involved in data acquisition. ME and AW drafted the manuscript. ME conducted the statistical analyses and produced the figures. AT, MB, MdZ, and EB revised the manuscript for important intellectual content. All authors were involved in the interpretation of the results, responsible for all aspects of the work, and have approved the final version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Association of Loneliness and Wisdom With Gut Microbial Diversity and Composition: An Exploratory Study

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Loneliness and wisdom have opposite effects on health and well-being. Loneliness is a serious public health problem associated with increased morbidity and mortality. Wisdom is associated with better health and well-being. We have consistently found a strong negative correlation between loneliness and wisdom. The present study aimed to investigate the association of loneliness and wisdom with the gut microbiome. One hundred eighty-four community-dwelling adults (28–97 years) completed validated self-report-based measures of loneliness, wisdom, compassion, social support, and social engagement. Fecal samples were collected and profiled using 16S rRNA sequencing. Linear regression analyses, controlling for age and body mass index, revealed that lower levels of loneliness and higher levels of wisdom, compassion, social support, and social engagement were associated with greater phylogenetic richness and diversity of the gut microbiome. Partial least squares (PLS) analysis to investigate multivariate relationships extracted two composite variables. Linear regression model predicting alpha-diversity with PLS components revealed that a linear combination of all psychosocial predictors (with negative loading for loneliness and positive loadings for all others, including wisdom, compassion, social support, and social engagement) was significantly associated with alpha-diversity. For beta-diversity, compassion and wisdom accounted for a significant proportion of variance in overall microbial community composition. Findings may have implications for interventions to reduce loneliness and possibly its health-related adverse consequences. Future research should explore whether increasing compassion and wisdom may improve loneliness and overall well-being as well as microbial diversity.

Keywords: microbiome, social isolation, compassion, social behavior, gut-brain-axis, bacteria

INTRODUCTION

Loneliness and social isolation are important public health risks, linked to worse emotional, cognitive, and physical health, functional decline, and premature death (1, 2). Loneliness is the subjective negative experience that results from a discrepancy between one's preferred and actual social relationships, whereas social isolation is the objective state of having few or infrequent social connections. Loneliness is generally conceptualized as having an acute, transient form or a persistent, stable form (3). The latter—i.e., persistent or chronic loneliness, rather than short-term fluctuations—is considered to be biologically toxic and is the focus in the present paper. Both loneliness and social disconnectedness are independently associated with worse physical health; however, the mechanisms responsible are not fully understood. Loneliness is associated with changes in cardiovascular, neuroendocrine, and immune function, including elevations in pro-inflammatory biomarkers and activation of the hypothalamic-pituitary-adrenal axis (1)—biological pathways that are associated with the microbiota-gut-brain-axis. On the other hand, wisdom, social support, and social engagement are associated with greater well-being and health (4, 5). Loneliness has been consistently found to be strongly inversely correlated with wisdom (6–8).

Wisdom is a multifaceted human characteristic with affective (or compassionate), reflective, and cognitive dimensions (9, 10). The affective dimension refers to the presence of positive emotions and behaviors toward others, such as empathy and acts of compassion. The reflective dimension is the ability to engage in reflective thinking and development of self-awareness. The cognitive dimension refers to one's knowledge about the world and comprehension of the deeper meaning of life events. Of the dimensions or components of wisdom, pro-social behaviors or compassion is most predictive of loneliness (6). Though wisdom has traditionally been viewed as a construct restricted primarily to philosophy or religion, empirical research in recent years has demonstrated that wisdom is partially influenced by biology (11, 12). Studies in behavioral genetics and neurobiology (13–16) suggest strong genetic and biological components of both loneliness and wisdom that underscore their evolutionary value (11, 17, 18) and public health implications, including their potential relationship with the gut microbiome.

The ability of gut microbes to communicate with the brain and modulate human behavior has emerged as an exciting concept in health and disease. The "microbiota-gut-brain-axis" involves bi-directional signaling between the gastrointestinal and central nervous systems and is regulated at neural, hormonal, and immunological levels (19). Alterations of these systems can result in disruptions of stress-response and behavior, from emotional arousal, affective behavior, and motivation, to higher-order cognitive functions such as decision-making (20). Studies in humans have found that the gut microbiota is associated with personality traits, such as neuroticism, openness, agreeableness, and conscientiousness, and psychological constructs, including subjective stress, self-compassion, affective empathy, and emotional well-being (21–24). Notably, compassion and empathy are important components of wisdom, and the putative neurocircuitry of wisdom overlap with structures that have been implicated in the microbiota-gut-brain axis, including fronto-limbic networks (25). Additionally, recent research has revealed connections between the gut microbiome and social behavior, and it has been proposed that the microbiome may be important to host sociality, particularly in the context of evolutionary-based theories of the benefits of mutualism in social survival (26–29). Social behavior and interactions can affect the composition of the gut microbiota (30, 31). Conversely, animal experiments have shown that gut microbes produce chemical signal used in social communication (32, 33) and that presence of the gut microbiota is necessary for social motivation (34). In humans, people with larger social networks tend to have more diverse gut microbiotas (22); however, the nature of and pathways that mediate this association are yet to be fully elucidated. Low microbial alpha-diversity has been associated with a number of diseases including obesity, inflammatory bowel diseases, and neurological and psychiatric disorders (35–37). No study to our knowledge has investigated gut microbial diversity with loneliness and wisdom. An investigation into the biological mechanisms underlying these psychological constructs is important to potential understanding of how loneliness may contribute to physical morbidity/mortality.

The present study sought to examine the relationship of microbial alpha-diversity and beta-diversity to loneliness and wisdom, as well as related psychosocial factors, in a sample of community-dwelling individuals across the adult lifespan. We hypothesized that higher levels of loneliness and lower levels of wisdom, compassion, social support, and social engagement would be associated with lower microbial diversity.

METHOD

Participants

The study included 184 community-dwelling adults (28–97 years). Inclusion criteria were age between 21 and 100 years, English fluency, and physical/cognitive ability to complete study assessments. This investigation was part of larger ongoing studies, including the SAGE (Successful AGing Evaluation) study and non-psychiatric comparison subjects from a study of aging and mental illness (38–40). Participants in the SAGE study were recruited using list-assisted random digit dialing of adults living in San Diego County, CA. The SAGE study originally targeted adults aged 50–100 years but was subsequently expanded to include participants aged 21–100 years to add younger individuals (39). Participants completed 25-min structured telephone interview that included questions about general health, depression and anxiety, and cognitive functioning. Exclusion criteria were residence in a nursing home or requiring daily skilled nursing care, diagnosis of dementia, or terminal illness or requiring hospice care. Non-psychiatric comparison participants from the study of aging and mental illness (38, 40) were recruited through multiple methods, including recruitment flyers in the community, www.ResearchMatch.org, and word-of-mouth. Participants were screened for major neuropsychiatric disorders using the Mini-International Neuropsychiatric Interview (MINI) (41). Exclusion criteria were past or present diagnosis of a

major DSM-IV-TR Axis I diagnoses, alcohol or other substance abuse or dependence within 3 months prior to enrollment, or diagnosis of dementia, intellectual disability disorder, or a major neurological disorder. Research protocols were approved by the UCSD Human Research Protections Program. All participants provided informed consent to participate.

Clinical Assessments

Participants completed validated scales of loneliness (UCLA Loneliness Scale) (42), wisdom (including cognitive, affective, and reflective dimensions; Three-Dimensional Wisdom Scale) (9), compassion (Santa Clara Brief Compassion Scale) (43), social support (Emotional Support Scale) (44), and social engagement (Cognitively Stimulating Questionnaire) (45). Additionally, depression (Center for Epidemiologic Studies Depression Scale) (46) and physical well-being (Medical Outcomes Study Health Survey) (47) were assessed.

Fecal Sample Collection and Analysis

Fecal samples were obtained from participants using at-home self-collection kits (BD SWUBE Dual Swab Collection System; BD Worldwide) and returned via mail. Samples were immediately frozen and stored at −80°C. DNA extraction and 16S rRNA amplicon sequencing were completed using the Earth Microbiome Project protocols (48, 49). In brief, DNA was extracted using the Qiagen MagAttract PowerSoil DNA kit (50). The 16S rRNA gene was amplified using unique reverse barcoded primers targeting the V4 region, and sequenced on Illumina MiSeq or HiSeq 4000 platforms, yielding paired-end 150 base-pair reads (median 17,160 reads/sample) (51, 52).

Sequencing data were processed using QIIME2 (version 2019.7) (53, 54). Raw sequences were demultiplexed and processed using Deblur (55), and previously recognized bloom sequences were removed (56). Deblur amplicon sequence variants were inserted into Greengenes 16S rRNA gene tree using SEPP (57, 58). Taxonomy was assigned using a pre-trained Naïve Bayes classifier (59). The output feature table was rarefied to 5,000 sequences per sample. Microbial community structure was characterized using measures of alpha-diversity and beta-diversity. Alpha-diversity is the ecological diversity (i.e., richness, evenness, compositional complexity) of a single sample and was quantified using Faith's Phylogenetic Diversity (PD), which measures the total length of branches in a reference phylogenetic tree for all species in a given sample (60). Beta-diversity measures the similarity (or dissimilarity) of microbial community composition between samples. Beta-diversity was characterized using Aitchison distance, a metric rooted in a centered log-ratio transformation and matrix completion called robust principal components analysis (PCA) that accounts for the sparse compositional nature of microbiome data sets (61).

Statistical Analysis

A two-sided alpha = 0.05 was used to determine statistical significance. The adaptive control of false discovery rate (FDR) procedure by Benjamini-Hochberg was used for multiple comparisons (62). Univariate linear regression models were first used to examine the relationship between alpha-diversity and psychosocial variables, controlling for age and body mass index (BMI). Associations between psychosocial variables and beta-diversity were performed using ADONIS (63) with significance calculated using PERMANOVA with 999 permutations (64). Subsequently, we used partial least squares (PLS) regression to investigate the multivariate relationship of all psychosocial variables and alpha-diversity in a single model. PLS constructs a series of composite variables that are linear combinations of the predictors such that the composite variables extract the most information from the predictors (i.e., has high variance, as is the case in PCA) and, at the same time, have high correlation with the response (which is not achieved in PCA) (65). We did not run PLS on beta-diversity since multivariable regression models require independence among dependent variables given the predictors, which is not the case for beta-diversity. For exploratory analyses, we examined age and gender as potential moderating factors by modeling an interaction term between psychosocial predictors on alpha- and beta-diversity in analyses.

TABLE 1 | Demographic and clinical characteristics of the sample.

	Total sample (*N* = 184)
Age (years)	62.39 (15.77)
Gender (female)	89 (48%)
Race/Ethnicity	
Caucasian	140 (76%)
Hispanic	25 (14%)
Asian	9 (5%)
African American	8 (4%)
Native American and Other	2 (1%)
BMI	26.43 (5.21)
Loneliness (UCLA-3)	35.86 (10.39)
Wisdom (3D-WS)	
Cognitive dimension	3.52 (0.53)
Reflective dimension	3.96 (0.51)
Affective dimension	3.40 (0.52)
Total score	3.62 (0.43)
Compassion (SCBCS)	4.73 (1.32)
Social support (ESS)	2.65 (0.55)
Social engagement (CSQ)	2.17 (0.61)

Data are presented as mean (standard deviation) for continuous variables or n (percent) for categorical variables.
3D-WS, Three-Dimensional Wisdom Scale; BMI, body mass index; CSQ, Cognitively Stimulating Questionnaire; df, degrees of freedom; ESS, Emotional Support Scale; SCBCS, Santa Clara Brief Compassion Scale; UCLA-3, UCLA Loneliness Scale, Version 3.

RESULTS

Demographic and clinical characteristics for the sample are presented in **Table 1**.

TABLE 2 | Coefficients from univariate linear regression models of each psychosocial factor predicting alpha-diversity (Faith's Phylogenetic Diversity), after controlling for age and body mass index.

	β	t	p	$q^{\dagger}$	Partial η^2
Loneliness (UCLA-3)	−0.170	−2.095	0.038*	0.021*	0.028
Wisdom (3D-WS)					
Cognitive dimension	0.012	0.132	0.895	0.336	<0.001
Reflective dimension	0.170	1.985	0.049*	0.021*	0.028
Affective dimension	0.200	2.396	0.018*	0.015*	0.040
Total score	0.194	2.188	0.021	0.015*	0.035
Compassion (SCBCS)	0.205	2.672	0.008*	0.015*	0.043
Social support (ESS)	0.180	2.338	0.021*	0.041*	0.033
Social engagement (CSQ)	0.201	2.478	0.014*	0.015*	0.040

† *Adjusted p-value controlling for adaptive false discovery rate.*
**p or q < 0.05.*
3D-WS, Three-Dimensional Wisdom Scale; CSQ, Cognitively Stimulating Questionnaire; ESS, Emotional Support Scale; SCBCS, Santa Clara Brief Compassion Scale; UCLA-3, UCLA Loneliness Scale, Version 3.

Alpha-Diversity

Univariate Analysis

Results of linear regression models indicated significant associations between alpha-diversity and loneliness, wisdom, social support, compassion, and participation in social engagement activities (**Table 2**). Lower levels of loneliness and higher levels of wisdom (total score and reflective and affective dimensions), compassion, social support, and social engagement were associated with greater alpha-diversity of the gut microbiome (**Figure 1A**). Effect sizes were small to medium. We also examined group differences in alpha-diversity based on loneliness severity categories, given that there are established cut-offs for loneliness severity: total score <28 = No/Low, 28–43 = Moderate, and >43 = High (66). Alpha-diversity significantly differed across severity categories ($F = 3.27$, $p = 0.041$), with lower alpha-diversity among individuals with high loneliness severity, compared to those with no/low ($p = 0.015$) and moderate ($p = 0.042$) severity (**Figure 1B**).

Considering the wide age range of participants and that age was significantly correlated with loneliness ($r = -0.233$, $p = 0.002$) and wisdom total score ($r = 0.235$, $p = 0.004$), we examined whether associations with microbial diversity were moderated by age [i.e., young/middle-aged adults (20–64 years) compared to older adults (>65 years)]. Loneliness significantly interacted with age on alpha-diversity ($\beta = -1.033$, $t = -3.05$, $p = 0.003$, $q = 0.021$), such that greater loneliness was associated with lower alpha-diversity in older adults ($\beta = -0.265$, $t = -3.99$, $p < 0.001$) but not in young/middle-aged adults ($\beta = -0.006$, $t = -0.013$, $p = 0.91$). There was no significant age interaction for wisdom ($p = 0.118$). Similarly, we examined gender as a potential moderating factor, and did not find any significant interactions between gender and psychosocial predictors on alpha-diversity ($ps > 0.183$). Finally, we explored other variables that could potentially explain or moderate the relationship between loneliness and alpha-diversity, including depression and physical well-being. Neither depression ($p = 0.665$) nor physical well-being ($p = 0.950$) was associated with alpha-diversity.

Multivariate Analysis

In multivariate analysis, we extracted composite variables from the PLS result and continuously added them into the linear regression model predicting alpha-diversity, examining the contribution of each composite component added by the size of explained variance in the outcome of alpha-diversity (from large to small). **Supplementary Table 1** presents results from the linear model predicting alpha-diversity with two PLS components, with age and BMI as covariates. This model was chosen because adding component 3 led to a decreased adjusted R^2. The model revealed that the effect of component 1 was significantly positively associated with alpha-diversity ($p = 0.008$), whereas component 2 was not ($p = 0.217$). Component 1 comprised of a linear combination of all psychosocial predictors (with a negative loading for loneliness and positive loadings for all others, including wisdom, compassion, social support, and social engagement) and accounted for 39.6% of the variance of the psychosocial predictors (**Supplementary Figure 1**; **Supplementary Table 2**). The effect sizes of composite predictors were small to medium. In exploratory analyses, neither age nor gender were significant moderators of psychosocial predictors on alpha-diversity ($ps > 0.238$).

Beta-Diversity

Beta-diversity was significantly associated with compassion, the cognitive and affective dimensions of wisdom, and wisdom total score (**Figure 2**). After adjusting for multiple comparisons, compassion, wisdom cognitive dimension, and wisdom total score remained significant. Effect sizes were small to medium. None of the psychosocial predictors interacted with age or gender on beta-diversity ($ps > 0.055$).

DISCUSSION

To our knowledge, this is the first study to show that loneliness and wisdom, including its important component of compassion, are related to gut microbial diversity and composition. As hypothesized, higher levels of loneliness and lower levels of compassion, wisdom, social support, and social engagement were associated with decreased phylogenetic richness and diversity of the gut microbiome. We further evaluated the multivariate relationship of alpha-diversity with psychosocial variables, and found that the PLS component comprising of all psychosocial variables were significantly associated with alpha-diversity. Wisdom and compassion were associated with both microbial diversity and microbial community structure and composition.

Gut microbial diversity and composition have been previously reported to be associated with personality traits and psychosocial constructs (21–23). Increased gut microbial diversity has been shown to be associated with greater emotional well-being, particularly positive affect, and larger social networks (22, 24). Our results expand upon previous findings, demonstrating that

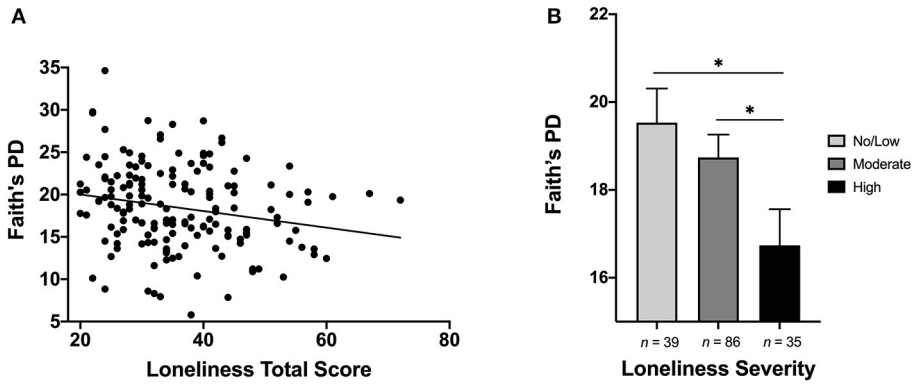

FIGURE 1 | (A) Scatterplot depicting the relationship between loneliness and alpha-diversity (Faith's Phylogenetic Diversity). Higher level of loneliness was associated with significantly lower alpha-diversity. **(B)** Bar plot illustrating differences in alpha-diversity based on loneliness severity categories. Individuals with High levels of loneliness exhibited significantly lower gut microbial alpha-diversity, compared to those with No/Low and Moderate levels of loneliness. *p or $q < 0.05$.

subjective loneliness or perceived social isolation and social support, beyond objective social network size, are associated with and may influence diversity of the gut microbiome. Additionally, we observed a relationship between alpha-diversity and compassion and social engagement, suggesting that pro-social attitudes and activities may positively influence microbial diversity or *vice versa*.

The mechanisms by which loneliness, compassion, and wisdom may be related gut microbial diversity is unknown. It is typically believed that reduced alpha-diversity represents worse physical and mental health, as low microbial diversity has been associated with various diseases, such as obesity, inflammatory bowel disease, and major depressive disorder (35, 36). The relationship between loneliness and microbial diversity is unlikely to be driven solely by physical health or depression, as neither depressive symptoms nor self-reported physical well-being were associated with alpha-diversity in this sample. A species-rich community may be less susceptible to invasion by exogenous pathogens and confer resilience and stability (37). It is possible that loneliness may result in decreased stability of the gut microbiome and, consequently, reduced resistance and resilience to stress-related disruptions, leading to downstream physiological effects such as systemic inflammation. Bacterial communities with low alpha-diversity may not manifest overt disease, but they may be less than optimal for preventing disease. Thus, lonely people may be more susceptible to developing different diseases. In line with our previous work (6, 7), age was negatively correlated with loneliness and positively correlated with wisdom, such that older individuals were less lonely and wiser. However, analyses examining the moderating effect of age revealed that greater loneliness was associated with lower alpha-diversity in older adults, but not young/middle-aged adults, suggesting that older adults may be especially vulnerable to health-related consequences of loneliness, consistent with prior research (67).

On the other hand, social support, compassion, and wisdom may confer protection against loneliness-related instability of the gut microbiome. Prior evidence suggests that perceived social support may buffer the negative effects of chronic stress on pro-inflammatory markers (68). Those effects may be mediated by the gut microbiome. An alternative hypothesis is that the microbiome may help shape social behavior, potentially leading to social isolation and loneliness or contributing to wisdom, which may ward off loneliness. Animal studies suggest that the gut microbiota may influence social behavior and interactions (26–29), although this hypothesis needs to be further explored in humans.

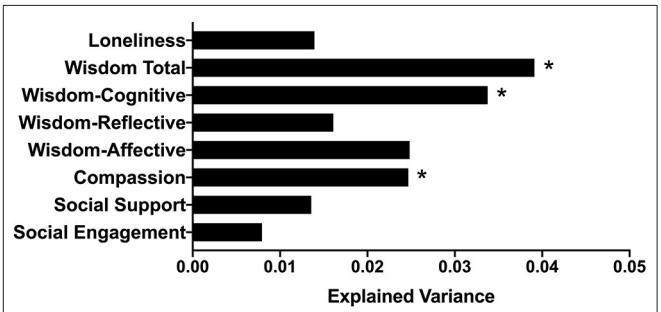

FIGURE 2 | Bar plot indicating the proportion of variance in beta-diversity (Aitchison distance) explained by each psychosocial factor, after controlling for age and BMI. *p or $q < 0.05$.

Different dimensions of wisdom were associated with microbiome diversity and composition. Alpha-diversity findings indicate that increased self-reflection, ability to regulate emotions, and pro-social attitudes and behaviors are associated with greater ecological diversity of the gut microbiome within individuals. Beta-diversity findings indicate that compassion and the cognitive dimension of wisdom account for a significant proportion of variance overall microbial community composition differences across individuals.

Our findings have potential clinical implications for developing interventions to reduce loneliness and its health-related consequences. Increasing perceived social support,

participation in social activities, and wisdom may improve loneliness by engaging overlapping biological targets. We have shown that it is possible to increase wisdom, particularly its affective and pro-social aspects, with behavioral interventions (69). Prior research also suggests that psychosocial interventions can reduce pro-inflammatory gene expression associated with loneliness (70). Conversely, probiotic and prebiotic interventions targeting the gut microbiome have been shown to reduce cortisol stress response, cognitive reactivity to sadness, and emotional processing bias (71, 72). This evidence presents the exciting possibility that future "psychobiotics" may be a novel therapeutic option for behaviors like loneliness (73).

This study had several important limitations. We did not have a measure of social network size or social interaction. It is important to dissociate subjective loneliness from objective social isolation, because more physical contact and interaction with others would provide increased opportunity to recolonize with more microbes. Additionally, as this was an exploratory study, we did not have measures of medical morbidity, diet, or other biological markers to further investigate relationships with health status. The sample size is modest considering the large age range. The effect sizes in this study were small to medium. A wide range of environmental and genetic factors can affect microbiome composition as well as psychological health. It is possible that some of the genetic and environmental effects on psychological well-being are via influence from the microbiome and *vice versa*. The bi-directionality of gut-brain communications and cross-sectional nature of this study limit interpretations of causality. Loneliness may lead to changes in the gut microbiome or, reciprocally, alterations of the gut milieu may predispose an individual to become lonely. Despite these limitations, the findings represent a step forward in understanding the relationships between the gut microbiome and psychosocial factors that have important consequences for health and well-being. Future longitudinal studies of diverse samples are needed to examine the relationship of changes in loneliness and wisdom with alterations in the gut microbiome as well as other inflammatory, neuroendocrine, and metabolic biomarkers. Similarly, the effects of psychosocial interventions on the microbiota should be examined as well as effects of probiotic treatments on loneliness and wisdom. This type of research will help improve our understanding of the microbiota-gut-brain-axis.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The name of the repository and accession number can be found below: European Molecular Biology Laboratory's European Bioinformatics Institute (EMBL-EBI) European Nucleotide Archive (ENA), https://www.ebi.ac.uk/ena/browser/home, PRJEB11419. Sample IDs and EBI accession numbers for individual subjects and additional metadata used in this study are available in **Supplementary Data**. Feature tables can be found in Qiita (https://qiita.ucsd.edu/) under study ID 10317.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by UCSD Human Research Protections Program. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TN: conceptualization, investigation, data curation, formal analysis, visualization, and writing – original draft. XZ, T-CW, JL, and XT: formal analysis, writing – review, and editing. CL: data curation, writing – review, and editing. RK: methodology, software, resources, supervision, writing – review, and editing. DJ: conceptualization, project administration, resources, funding acquisition, supervision, writing – review, and editing. All authors reviewed and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.648475/full#supplementary-material

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Carer's Attachment Anxiety, Stressful Life-Events and the Risk of Childhood-Onset Type 1 Diabetes

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Background/Objective: Type 1 diabetes (T1D) is among the most common chronic diseases in children/adolescents, and the incidence continues to rise worldwide. Different environmental factors have been evaluated in the etiology. In the present study, we investigated the role of attachment examining whether insecure attachment to carers or carers' own attachment insecurity was related to a higher risk of T1D in children.

Methods: We included 101 children with T1D (mean age 11.8 years), 106 healthy controls (11.6 years), and one of their carers. We assessed children's attachment using the Child Attachment Interview and carers' attachment using the Relationship Structures Questionnaire. We constructed binary multinomial logistic regression models using attachment to mothers, carers' attachment representations, and stressful life-events as T1D predictors.

Results: Higher carer attachment anxiety was associated with the child's T1D diagnosis ($p < 0.05$; $R^2 = 0.0613$) while security of attachment to mothers showed no significant association. When mothers' education was included in the model, both attachment anxiety in higher educated mothers and stressful life events showed a significant association with the child's T1D ($p < 0.001$; $R^2 = 0.293$).

Conclusions: Our findings suggest that higher attachment-related anxiety in carers with high education and stressful life events are associated with T1D in children.

Keywords: attachment—a strong affectional bond, child/adolescent, stress, stressful life events, type 1 diabetes mellitus, etiology

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INTRODUCTION

Type 1 diabetes (T1D) is among the most common chronic diseases in children and adolescents. The incidence continues to rise worldwide by ∼2–5% annually (1). T1D is a consequence of autoimmune destruction of pancreatic beta cells, which leads to a complete lack of insulin production (2). The environmental factors leading to the development of T1D in genetically susceptible individuals, either by triggering islet autoimmunity or progression from autoimmunity to overt T1D, have only been partially identified (3). Psychological stress is shown to be a possible

risk factor by increasing insulin resistance leading to increased demand on beta cells and by directly influencing immune response and causing alterations at the hypothalamic-pituitary-adrenal axis (4). Major life events (e.g., the death of a close relative or divorce) and psychological strain in the family have been consistently identified as risk factors for islet autoimmunity and T1D in a number of studies, including large population-based prospective studies (5, 6). One psychological factor that may be implicated in the development and maintenance of T1D in childhood is the quality of attachment relationships. Based on the caregiver's availability and sensitive responsiveness in relation to their infant's bids for proximity-seeking at times of distress, internal models of relationships are formed that guide behavior and expectations in a largely unconscious way (7). The parent-child attachment relationship serves as a context in which an infant's emotions and stress are regulated: as an interpersonal biobehavioral stress regulatory system. Individual differences in infant attachment are thought to reflect distinctive strategies for responding to and coping with interpersonal challenges (8, 9), exposing insecurely organized individuals to the deregulated autonomic nervous system and exaggerated hypothalamic-pituitary-adrenal activity, which, in turn, produces increased and prolonged exposure to stress hormones. Such stress responses may have considerable implications for the development of diverse health-risk conditions, such as insulin resistance and hyperlipidemia (10).

The evidence for these possible associations to date, however, is scant. Ciechanowski and colleagues demonstrated that dismissing attachment was related to poor glycemic control in adults with T1D (11). Sepa et al. investigated the association of mothers' attachment insecurity with the induction or progression of diabetes-related autoimmunity in early childhood using interviews with 18 mothers of antibody-positive infants and 32 mothers of antibody-negative infants. Their results showed a larger proportion of insecure mothers in the antibody-positive group, although the association was not statistically significant. They concluded that if an association between mothers' attachment and diabetes-related autoimmunity in children exists, it was not very strong, acknowledging their small sample size as well as a generally imperfect correlation between mother and child attachment (12). To our knowledge, no studies have examined the role of the child's and the carer's attachment security in the development of T1D.

To address this, the present study was undertaken in order to test associations between insecure attachment of children to their carers, carers' attachment insecurity, and T1D in children. We assumed insecure attachment of children or their parents together with stressful life events would be related to children's T1D.

MATERIALS AND METHODS

Participants and Procedures

All eligible children with T1D in Slovenia included in the Slovenian national childhood-onset T1D register and their parents/caregivers were invited to participate in this case-control observational study. An invitation to participate was sent by mail, followed by a personal phone call invitation from their diabetologist before attending one of the regular 3-monthly control visits.

The control group consisted of healthy pupils from 3rd to 9th grade from five randomly chosen primary schools from the entire country. The study was presented by one of the researchers or the school counselor during classes at school, and to the parents at the regular bi-yearly school meetings for parents. Parents were also given a written information sheet explaining the study. The invitation was followed by another inquiry to each invited class by the school counselors.

The main inclusion criteria were age between 8 and 15 years and diagnosis of T1D for over 1 year (the cases). The main exclusion criteria were intellectual disability and/or active psychosis and, in the controls, T1D.

The enrolment began in July 2015 and ended in December 2019. Participation was voluntary and anonymous, and all participants and/or their parents signed informed assents/consents prior to the enrolment. The interview recording and the assessments were completed at the University Children's Hospital (the cases) or at the school before the beginning of classes (control group). The protocol of the study was approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 60/08/13). Trial Registration: ClinicalTrials.gov (NCT02575001).

Measures

General demographic and family characteristics were acquired by a special questionnaire administered to the carers (13). The original questionnaire was modified by adding questions on early childhood development and diabetes management.

Subjects were administered the Child Attachment Interview (CAI) (14), a narrative-based assessment designed to elicit children's internal working models of attachment. Unlike semi-projective instruments, the CAI is a direct interview, calling on children to describe and reflect on their current attachment relationships and experiences. The interview is intended for use with 8–15-year-olds. It is assessed by analyzing the transcripts and video analysis of behavior for the presence of attachment disorganization. The subjects are then classified with respect to the relationship with each attachment figure either into two main groups (two-way classification: secure or insecure), three main groups (three-way classification: secure, preoccupied, or dismissing), or four main groups (four-way classification: secure, preoccupied, dismissing, or disorganized) (14, 15). CAI protocols were evaluated by three independent coders, all accredited by one of the CAI authors. Inter-rater reliability was conducted on 60 interviews for pairs of raters (20 interviews for each pair).

Children completed the Lifetime Incidence of Traumatic Events—Student Form (LITE-S) (16) to gauge exposure to adverse life events. The 16 items cover a broad range of potential trauma and loss events and ask for an estimate of emotional impact at both the time of occurrence and at the present. The questionnaire is available in student and parent forms (LITE-S, LITE-P), and its test–retest reliability for the total scale was found to be 0.76, and kappa per item ranged between 0.33 and 0.86 (16). LITE-S has been officially translated and validated in

the population of Slovene primary school students (unpublished data). We used the LITE-S All Events scale, reporting the cumulative number of stressful events.

The subjects' carers were administered the Social Readjustment Rating Scale (SRRS) questionnaire regarding stressful life events in the family from pregnancy to the present (17). The questionnaire was adjusted to assess 4 different life periods (from pregnancy to first year of life, the year before the diagnosis of T1D/before entering school for the controls, the past year, anytime in the child's life). Gerst et al. (17) tested the reliability of the SRRS by re-administration of the test after 3, 6, 12, and 24 months, and found high temporal consistency for healthy adults (r = 0.96–0.89) and psychiatric patients (r = 0.91–0.70). The questionnaire was previously translated and has been widely used in the Slovene population.

Carers' attachment patterns in close relationships (to each of their parents, to a partner, to a best friend, and general attachment) were assessed by the Relationship Structures Questionnaire (ECR-RS) (18). The scale assesses attachment to each of the four attachment figures by the same nine questions, and the general attachment is calculated as a mean of the results for all the figures. If the score for one of the attachment figures was missing, the mean was calculated from the remaining scores. Within each relational domain, the questionnaire assesses two dimensions: attachment-related anxiety (how worried the person is that the attachment figure may reject him or her) and attachment-related avoidance (what kind of strategies the person uses to regulate their attachment behavior in the relational context, from being comfortable using others as a secure base and safe haven, to being uncomfortable with closeness and dependency) (7). The securely attached person scores low on both of these dimensions. The reliability for the dimensions is from high to excellent (Cronbach's alpha above 0.7 for different attachment figures and domains) (18).

Data Analysis

The descriptive comparisons between two groups (cases vs. controls) were made using independent samples T-test, Mann–Whitney U-test, Pearson chi-square test, and Fischer's exact test predictor in the statistical package IBM SPSS for either continuous or categorical variables. The multivariate binomial logistic regression model in statistical program R was employed to predict T1D outcome depending on different predictors. The predictive variables used in the models were the following: (1) a two-way attachment classification (CAI), (2) attachment-related anxiety in carers (ECR-RS-anx-carers), (3) attachment related avoidance in carers (ECR-RS-avoid-carers), (4) stressful life events in the family during pregnancy with the child and the first year (SRRS_1y), (5) stressful life events in the family in their lifetime (Lifetime SRRS), (6) stressful life-events in the child (LITE-S), and (7) mothers' education level. Four models were tested in which different variables were used to predict T1D (primary outcome). Two-way attachment classification and stressful life events reported by children and carers were used in the first model; two-way attachment classification and stressful life events reported by carers in the second model; attachment-related anxiety in carers, attachment related avoidance in carers, and stressful life events reported by children and carers in the third model; and the mother's education level was added as the predictor in the fourth model. We decided to add the mothers' educational level to the fourth statistical model since there was a statistically significant difference between the groups (cases and controls). Education was used as an ordinal variable (level of education: 1 = unfinished primary school,

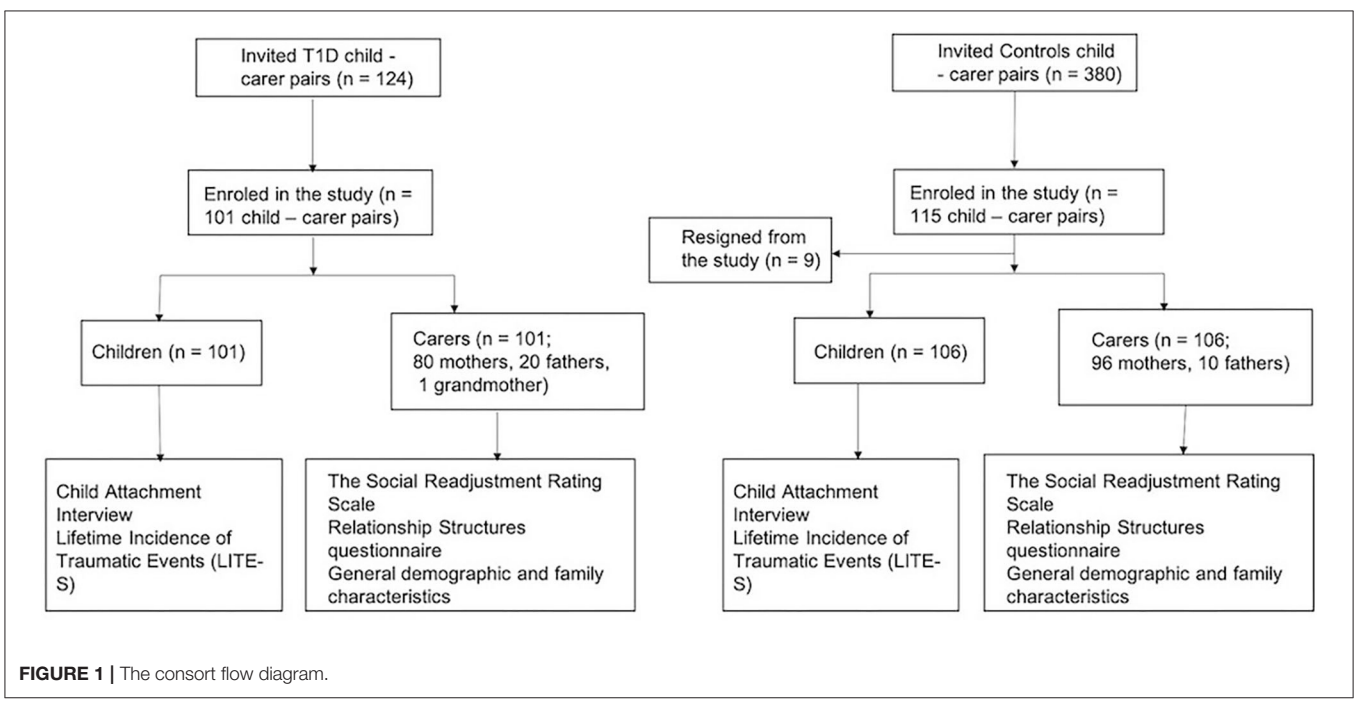

FIGURE 1 | The consort flow diagram.

2 = primary school, 3 = unfinished high school, 4 = high school, 5 = unfinished college, 6 = college, 7 = unfinished university, and 8 = university) and then three levels were analyzed according to median and quartiles. The differences were considered statistically significant for a *p*-value at or below 0.05.

All of the independent numerical scale variables in the binary multivariate logistic regression model were centered and both independent categorical variables were dummy coded. The logistic regression model was created with the backward stepwise procedure (19), where all of the second order interaction terms of the independent variables were included in the beginning. Thus, the final refined logistic regression model included only the main and the interaction terms of which removal would worsen the model.

RESULTS

Participants

One hundred and twenty-four families of children in the Slovenian national childhood-onset T1D register were invited to participate, of which 101 agreed to participate. Of the 380 pupils invited to be in the control group, 115 agreed to participate, with nine families dropping out shortly after the start of the study; 106 healthy pupils/families completed the study. The participation rate in the research group was 81.5% and in the control group 27.9% (**Figure 1** presents CONSORT Flow Diagram).

The study included 207 children, aged 11.7 ± 2.1 years; 109 were females. Of these 101 had T1D (aged 11.8 ± 2.1; 50 females), and 106 were in the control group (aged 11.6 ± 2.1; 59 females). The average duration of T1D was 5.2 ± 3.4 years. The majority of children with T1D (81.3%) were using an insulin pump. In the research group, the questionnaires were filled out by mothers in 79.3%, fathers in 19.8%, and other carers (grandmother) in 1%. In the controls, there were 90% mothers and 10% fathers. Baseline characteristics are presented in **Table 1**.

There were no statistically significant differences between the cases and the controls regarding age, gender, parent's employment, the security of attachment (CAI), presence of disorganization (CAI), lifetime stressful events in the family from the pregnancy of the child to child's first year or anytime in life (SRRS), lifetime stressful events as reported by the child (LITE-S), and carers' attachment (ECR-RS general anxiety or general avoidance). The groups were statistically significantly different in terms of parents' education level (**Table 1**). Namely, the education level of the parents in the control group was significantly higher than in the cases (see **Table 1**). Spearman correlation coefficient indicated that there was a moderate positive statistically significant correlation (rho = 0.629; $p < 0.001$) between the education levels of both parents. The inclusion of both parents' education in the model would therefore result in multicollinearity between the independent variables. Consequently, only the mother's education was used as a predictor in the subsequent statistical analyses.

Inter-rater reliability conducted on 60 interviews for pairs of raters was high for all main categories for mother (M) and father (F): for two-way M (*Kappa* = 0.89, $p < 0.05$), for three-way M (*Kappa* = 0.887, $p < 0.05$), for four-way M (*Kappa* = 0.708, $p < 0.05$), and all classifications F (*Kappa* > 0.7, $p < 0.05$).

Concordance between attachment to the mother and father was high, with 95.0% of children having the same two-way classification for both parents, 92.6% in the three-way, and 91.6% showing agreement in the four-way classification. Due to the high

TABLE 1 | Demographic data and results of the measured attachment to the mother, child stressful life events, family stressful events, and carers' attachment for children with T1D and healthy controls.

	Cases T1D (*N* = 101)	Controls (*N* = 106)	*p*
Age in years	11.8 ± 2.1	11.6 ± 2.1	0.656
Female gender	50 (49.5)	59 (55.7)	0.375
Duration of T1D in years	5.2 ± 3.4	/	/
Age of mother in years	41.1 ± 5.1	42.3 ± 4.4	0.112
Age of father in years	43.9 ± 6.3	45.1 ± 5.7	0.053
Divorced family/living with one parent/living outside the family	*N* = 96 19 (19.8)	*N* = 102 15 (14.7)	0.251
Mother education level	*N* = 93	*N* = 101	**0.0001**
Finished secondary school	48 (51.6)	18 (17.8)	
Finished University	22 (23.7)	70 (69.3)	
Father education level	*N* = 93	*N* = 98	**0.0001**
Finished secondary school	57 (61.3)	32 (32.7)	
Finished University	15 (16.1)	45 (45.9)	
Mother employed	*N* = 94	*N* = 99	
	80 (85.1)	93 (93.9)	0.068
Father employed	*N* = 93	*N* = 98	
	81 (87.1)	92 (93.9)	0.600
CAI	*N* = 101	*N* = 106	
CAI Secure (4-way)	65 (64.4)	56 (52.8)	0.093
CAI Insecure (4-way)	36 (35.6)	50 (47.2)	0.093
Dismissing	25 (24.7)	29 (27.4)	0.670
Preoccupied†	0†	0†	
Disorganized	11 (10.9)	21 (19.8)	0.076
Lifetime SRRS	*N* = 95	*N* = 101	
	215.3 ± 200.7	220.7 ± 237	0.644
Median (IQR)	170.5 (221)	154.0 (260)	
SRRS pregnancy-first year	*N* = 95	*N* = 101	
	17.2 ± 40.4	28.1 ± 63.8	0.077
Median (IQR)	0.00 (0)	0.00 (25)	
LITE−S	*N* = 95	*N* = 101	
	2.7 ± 1.8	2.9 ± 1.8	0.375
ECR-RS	*N* = 93	*N* = 101	
ECR-RS-avoid-carers	2.6 ± 0.9	2.5 ± 0.9	0.841
ECR-RS-anx-carers	1.8 ± 0.9	1.5 ± 0.7	0.076

Data are n (%) or Mean ± SD unless stated otherwise. The descriptive comparisons between two groups were made using independent samples T-test, Mann–Whitney U-test, Pearson chi-square test, and Fischer's exact test, statistical significance p < 0.05 (bold). CAI, Child Attachment Interview; SRRS, Social Readjustment Rating Scale; LITE-S, Lifetime Incidence of Traumatic Events—Student Form All Events scale; ECR-RS, Relationship Structures questionnaire; ECR-RS-avoid-carers, carers' attachment avoidance; ECR-RS-anx-carers, carers' attachment anxiety. †One (1%) of the cases and three (2.8%) of controls were classified as preoccupied in the 3-way classification but all of them were disorganized in the 4-way classification.

TABLE 2 | Results of the binary multinomial logistic regression model: carers' attachment anxiety/avoidance and stressful life events.

Names	Estimate	exp(B)	z	p
Parameter estimates				
(Intercept)	0.44025	1.553	11.359	<0.001
ECR-RS-anx-carers	0.13705	1.147	2.556	**0.012**
LITE-S	0.03400	1.035	1.454	0.148
SRRS_1y	−0.00104	0.999	−1.508	0.134
ECR-RS-avoid-carers	−0.03141	0.969	−0.708	0.480

ECR-RS-anx-carers, carers' ECR-RS general anxiety; ECR-RS-avoid-carers, carers' ECR-RS general avoidance; LITE-S, Lifetime Incidence of Traumatic Events—Student Form; SRRS_1y, stressful life events from pregnancy to the end of first year. Lifetime SRRS, which was initially included in the model, was removed due to the lower statistical significance comparing to the other variables, a process of backward stepwise procedure that is thus not shown in the table.
Statistical significant values are bolded.

TABLE 3 | Results of the binary multinomial logistic regression model: carer's attachment-related anxiety/avoidance and stressful life events—mothers' education level was used as one of the predictors.

Names	Estimate	exp(B)	z	p
Parameter estimates				
(Intercept)	0.4581	1.581	126.980	< 0.001
SRRS_1y	−5.08e−5	1.000	−0.0638	0.949
LITE-S	0.0481	1.049	22.646	**0.025**
ECR-RS-anx-carers	0.1038	1.109	20.147	**0.046**
ECR-RS-avoid-carers	−0.0288	0.972	−0.7202	0.473
Education	−0.1191	0.888	−62.175	**< 0.001**
SRRS_1y * LITE-S	−4.79e−4	1.000	−13.965	0.165
LITE-S * ECR-RS-anx-carers	−0.0536	0.948	−17.304	0.086
LITE_S * ECR-RS-avoid-carers	0.0524	1.054	19.333	0.055
ECR-RS-anx-carers* Education	0.0582	1.060	23.938	**0.018**
ECR-RS-avoid-carers* Education	−0.0350	0.966	−16.680	0.097

*SRRS_1y, stressful life events from pregnancy to the end of first year; LITE-S, Lifetime Incidence of Traumatic Events—Student Form; ECR-RS-anx-carers, carers' ECR-RS general anxiety; ECR-RS-avoid-carers, carers' ECR-RS general avoidance; Education, mothers' education level. *, represents interaction between two independent variables. Statistical significant values are bolded.*

concordance and the fact that most of the material was provided by the mothers, we used only attachment to the mother in the logistic regression models.

Of the T1D cohort, 64.4% were classified as secure with their mother, and 35.6% as insecure in the three-way classification (34.6% dismissing, 1% preoccupied). In the controls, 54.7% were classified as secure with their mother and 45.3% as insecure in the three-way classification (42.5% dismissing, 2.8% preoccupied). The differences were not statistically significant.

Primary Outcome

A binomial logistic regression was performed to ascertain the effects of two-way attachment classification (secure-insecure) in children or two-dimensional carers' attachment representation (anxiety-avoidance) and co-variates (stressful life events measured by SRRS from pregnancy to the end of the first year of the child's life or anytime in the family's life and stressful life events measured by LITE-S) on the presence of T1D (primary outcome).

In the first two models, the child's attachment to the mother (CAI two-way classification) with stressful life events from pregnancy to the child's first year or anytime in the family's life (lifetime SRRS) was not statistically significantly associated to child's T1D. The independent variables showed no statistically significant effects on the dependent variable ($p > 0.05$).

In the third model, carers' attachment anxiety was statistically significantly related to T1D ($p < 0.05$; $R^2 = 0.0613$), namely the higher the attachment anxiety, the higher the association with T1D in the child (**Table 2**). The model explained only 6.1% of the variance.

In the fourth model where mothers' education level was added as one of the predictors, the following variables were statistically significantly associated with the child's T1D: child's stressful life events, carer's attachment anxiety, mother's education level, and the interaction between the latter two. The higher the score on the LITE-S, carer's attachment anxiety, and the lower the mother's education, the higher the association with the child's T1D. **Table 3** shows the model in which mothers' level of education was added as one of the predictors [$X^2_{(10)} = 54.1, p < 0.001; R^2 = 0.293$]. The model explained 29.3% of the variance.

The results based on the simple slope analysis showed that the lower the mother's education, the higher the association with T1D for all levels of attachment anxiety (**Figure 2**). However, a higher level of attachment-related anxiety in carers was also positively related to T1D in children. This was the case for mothers with higher than secondary education level ($p = 0.007$ for finished University and $p = 0.01$ for unfinished or finished college, unfinished university), and not for mothers with lower education levels (**Figure 3**). Model $R^2 = 0.293$.

DISCUSSION

Our results showed that there was a statistically significant association between carers' (most often mothers') attachment anxiety and T1D. After adding mothers' education level to the model, the results showed a significant positive association between children's T1D and stressful events experienced by children, as well as carers' attachment anxiety. The positive association between carers' attachment anxiety and children's T1D was significant for mothers with higher education but not for mothers with secondary or lower education, with our model explaining 29% of the variance. We did not find a statistically significant association between children's attachment security and T1D.

To our knowledge, only one study to date has explored the relationship between carers' attachment and the occurrence of T1D in children. Sepa et al. investigated the relationship between maternal attachment (measured by the Adult Attachment Interview) and diabetes-related autoimmunity during infancy in 18 mothers of positive and 32 mothers of infants negative for diabetes autoantibodies. Whilst no statistically significant

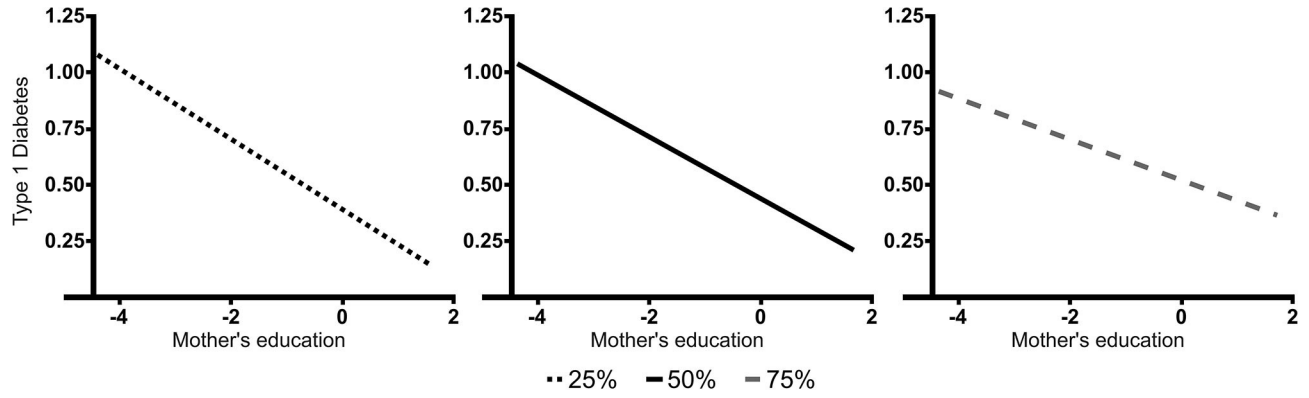

FIGURE 2 | The relationship between mothers' education level and children's T1D for different levels of carers' attachment anxiety. The figure shows significant slopes for the three levels of carers' attachment anxiety. The lower the mother's education, the higher the association with T1D for all levels of carers' attachment anxiety. Type 1 diabetes—type 1 diabetes in children; Education—level of mothers' education (−4—finished high school or less, 0—finished university); 25, 50, and 75%—levels of carers' attachment anxiety on ECR-RS (divided in three groups according to quartiles).

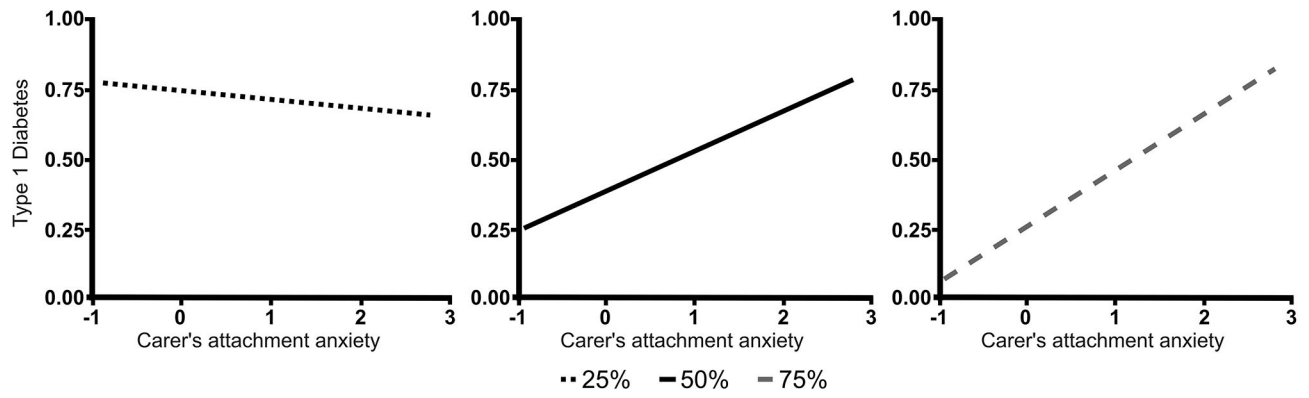

FIGURE 3 | The relationship between carers' attachment anxiety and children's T1D for different levels of mothers' education. The figure shows significant slopes for the three levels of mothers' education. In the mothers with higher than secondary education, higher level of carers' attachment-related anxiety was positively associated to T1D in children. This was not the case for mothers with secondary or lower education. Type 1 diabetes—type 1 diabetes in children; Carers' attachment anxiety—carers' ECR-RS general anxiety; 25, 50, and 75%—7 levels of education presented as median and quartiles (25%—finished high school or less, 50%—unfinished or finished college, unfinished university, 75%—university).

association was found, the results showed a higher proportion of insecure mothers in the autoantibody positive group (12). The development of T1D in children of caregivers with high attachment anxiety could be mediated by the caregivers' lower capacity for stress regulation, which in turn can lead to their reduced capacity for regulation of their child's stress response. This would be most acute at times wherein the attachment system is activated (perceived danger to the child) (20, 21). Carers with higher level of attachment related anxiety might show overconcern in relation to their children and thus upregulate instead of downregulating stress experienced by their children (21). Due to the observational design of the present study, it is also possible that attachment-related anxiety in carers could be a result of the stress related to the chronic illness of their children and the constant threat of possible serious medical complications related to it (22). The relationship of attachment-related anxiety and T1D could thus be seen as bidirectional (23).

Our results showed that the mothers' educational level negatively correlated with the probability of T1D: the higher the educational attainment, the lower the association with the child's T1D. The research of Virk et al. (24) on a large population-based sample showed an association between bereavement (loss of a mother, father, or sibling from age 5 years onwards) and increased rate of T1D when exposure onset began after 11 years of age. This association only persisted among children born to mothers with low educational attainment. They suggest that a lower maternal education level might be associated with increased vulnerability. These results, however, should be interpreted with caution, since the groups in our study differed in the parents' educational level in the first place and could be a result of selection bias.

Our results showed a statistically significant association between stressful life events in children (but not in the carers) and T1D in the model in which carers' attachment was the

predictor of T1D. Therefore, our results partly support previous studies that showed a positive correlation between stressful life events in the life of parents or children and T1D-related autoimmunity or occurrence of T1D (8, 25). In a sample of 5,986 children and their families (the prospective population-based All Babies in Southeast Sweden project), Sepa and colleagues showed that maternal experience of serious life events (such as divorce or violence) was involved in the induction or progression of diabetes-related autoimmunity in children at age 2.5 years, independent of a family history of T1D (6). In the same project, childhood experience of a serious life event was associated with a higher risk of a future diagnosis of T1D (8). One possible explanation for our results might be the retrospective and not prospective nature of the stressful life-events evaluation, so the subjectivity and the change in certain experiences through time must be taken into account (26).

Our findings did not show a significant association between attachment insecurity in children and T1D. Thus, the hypothesis that insecurity of attachment in children represents a stress-related vulnerability and as such means, a greater risk for T1D was not confirmed in the current study. To date, no other studies have supported this hypothesis. Given that attachment representations are susceptible to change with time, being less stable in childhood than adulthood (7, 27), it is also possible that some children assessed as secure at the time of the study may have been insecurely attached before they developed diabetes. The availability, consistency, and responsiveness of medical professionals, such as the diabetes pediatrician (24-h phone availability) and the availability of care offered by other professionals from the diabetes team (nurses, educators, dietitians, psychologists, child psychiatrists, group and family therapists), could provide a safer environment for the families of children with T1D. The latter is also supported by previous reports of lower suicidality in adolescents with T1D (from the same hospital) compared to healthy adolescents (13).

The strengths of this study were the inclusion of almost the entire cohort of Slovene children with T1D within the specified age range, using an interview measure instead of a self-report for the assessment of child attachment, and large sample size as compared to similar studies. Using a case-control design enabled us to compare and also control for possible bias of the effect of different predictors on the primary outcome. The first limitation is the observational approach of the study. Even though the case-control design enabled us to control for the bias, from our sample we can only determine the associations, not the causality of the observed factors in the development of T1D. Even though we gathered very high-quality information on attachment in the children, the carers' attachment was only assessed by a self-reported questionnaire. Nevertheless, the questionnaire itself proved highly reliable (18) and our results add considerably to previous studies on the influence of parents' attachment (assessed by Adult Attachment Interview) to diabetes-related autoimmunity in children (12). The third limitation was the different recruitment and resulting differences in participation rates between the groups. This could have had an effect on the type of families who were part of the study and is also reflected in the differences in the parents' education levels. The groups did not differ in any other demographic or studied factors and the models were designed to overcome possible biases.

In conclusion, our findings suggest that some of the risk factors associated with T1D in children may be reduced by helping families under higher levels of stress, especially if there are indices of high attachment anxiety in the carers. Offering support for families early in the caregiving process, bearing in mind the role of the caregivers in children's stress regulation, would be a possible approach. Such interventions as well as longitudinal studies on the effects of parental attachment on the development of chronic disease in children should be evaluated in future studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 60/08/13). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MD-R, SK, TB, NB, and YS-G designed the study. AT, KD, SK, NB, JL, KU, TB, YS-G, and MD-R were involved in the acquisition and interpretation of data. The first draft of the paper was written by AT, with the support of MD-R, who is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to conception of the work and approved the final version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Multidimensional Assessment of Interoceptive Abilities, Emotion Processing and the Role of Early Life Stress in Inflammatory Bowel Diseases

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Perception of internal bodily sensations includes three dissociable processes: interoceptive accuracy, interoceptive sensibility, and interoceptive awareness. Interoceptive abilities play a crucial role in emotion processing and impairments of these processes have been reported in several psychiatric disorders. Studies investigating interoceptive abilities and their role in emotional experience in individuals with somatic disorders such as inflammatory bowel diseases (IBD) are sparse. Recent findings suggested an association between adverse childhood experiences (ACE) and the development of gastrointestinal disorders. The aim of the current study was to investigate the associations between the different dimensions of interoception and emotional processing in IBD while taking ACE into account. We recruited IBD patients in clinical remission (n = 35) and 35 healthy control participants (HC) matched for age, education and IQ. Interoception was measured as a three-dimensional construct. Interoceptive accuracy was assessed with the heartbeat tracking task and interoceptive sensibility with a self-report measure (Multidimensional Assessment of Interoceptive Awareness questionnaire). Emotional processing was measured using an experimental task, where participants were asked to rate the subjectively perceived valence and arousal when presented with positive, neutral and negative visual stimuli. IBD patients significantly differed in two interoceptive sensibility domains, Emotional awareness and Not-distracting. Patients reported greater awareness of the connection between bodily sensations and emotional states, while showing a stronger tendency to use distraction from unpleasant sensations compared with HC. Higher emotional awareness was linked to higher perceived intensity and arousal of negative stimuli. The strength of this relation was dependent on the severity of ACE, with severer traumatization being associated with a stronger association between emotional awareness and perceived valence and arousal. Our findings suggest that it is the subjective component of interoception, especially the one assessing interoceptive abilities within the scope of emotional experience, which affects emotional processing in IBD. This is the first study providing

evidence that IBD patients did not differ in their perception of visceral signals *per se* but only in the subjective ability to attribute certain physical sensations to physiological manifestations of emotions. Our findings support the hypothesis that ACE affect the association between interoception and emotional processing.

Keywords: inflammatory bowel diseases, interoception, interoceptive sensibility, emotion processing, emotional awareness, early life stress, childhood trauma, heartbeat tracking

INTRODUCTION

Inflammatory bowel diseases (IBD) are immune mediated chronic diseases with a prevalence of 6.8 million cases globally. The incidence of IBD is continuously rising not only in industrialized countries of the northern hemisphere but also in developing countries (1). IBD include primarily Crohn's disease and Ulcerative colitis, both characterized by various physical and psychological symptoms such as abdominal pain, diarrhea, unwanted weight loss, depression, and anxiety (2). The etiology of IBD is multifactorial including genetic, immune, and environmental factors. While the impact of the environment on the development of IBD is substantial, the role of specific factors is still poorly defined, one candidate being early life stress (3–5). Newer studies in IBD have suggested alterations in the brain-body communication, directly influencing the sensory and immune functions of the gastrointestinal tract (6–8). In line, gastrointestinal pathologies have been recently linked to altered interoceptive processes (9). Interoception is closely linked to emotional processing (10, 11) and might influence the severity of IBD symptoms and disease course by increasing the level of stress through an increased sensitivity toward negative emotional stimuli. So far, studies on changes in interoception and their relation to emotion processing in IBD are sparse (12). The present study aims to contribute to the better understanding of these domains of functioning in IBD by investigating interoception as a multidimensional concept together with changes in emotion processing while taking the influence of early life stress into account.

Interoception refers to the sense through which bodily changes are signaled and perceived (13). It is conceptualized as a three-dimensional construct, comprising interoceptive accuracy (IACC), interoceptive sensibility (IS), and interoceptive awareness (IAw) (14). Interoceptive accuracy refers to the correspondence between the actual and the perceived bodily signals. In contrast, IS is defined as the subjective belief to be internally focused and represents the extent to which individuals feel engaged by interoceptive signals (14). IS includes not only individual's general awareness of bodily sensations but also beneficial and maladaptive forms of interoceptive engagement (15). Finally, interoceptive awareness represents the correspondence between interoceptive accuracy measured *via* behavioral tasks (e. g heartbeat tracking task) and subjectively reported general IS (16). It should be mentioned that the metacognitive component of interoceptive awareness should be measured only using interoceptive accuracy scores and respondent's ratings of the confidence in the accuracy of their performance in the applied task [for discussion see (107)]. In the present manuscript we retain the use of the term interoceptive awareness to refer to the correspondence between interoceptive accuracy scores and IS as measured *via* self-report measures. Interoceptive impairments have been linked to specific physical and mental health conditions, emphasizing the importance of precise body signals perception for the physical and mental well-being (17). Although impairments in interoception may contribute to the pathophysiology of gastrointestinal disorders, there is, to our knowledge, no study that investigated interoceptive processing in IBD as a multidimensional concept. Enhanced visceral perception sensitivity ("visceral hypersensitivity") refers to the altered processing of visceral stimuli in gastrointestinal disorders (18). Current findings support the view that it results from disturbances along the brain-gut axis (19) and is related to functional alterations in brain regions involved in visceral afferent processing, emotional arousal and pain perception (20, 21). Visceral sensitivity in irritable bowel syndrome patients have been characterized by a biased appraisal of perceived bodily signals and enhanced selective attention to gastrointestinal sensations (20–23). Even though so far there is—to our best knowledge—no study investigating the link between visceral hypersensitivity and interoceptive processing, we suggest that IBD patients might exhibit stronger and more selective attention toward their bodily signals in order to recognize early signs of worsening disease activity and upcoming relapse, which might result in superior interoceptive abilities. To date, there are only few studies, which investigated interoceptive abilities in populations with gastrointestinal disorders. Findings suggest no alterations in the behavioral performance in interoceptive accuracy tasks, but only in self-reported IS in irritable bowel syndrome patients (24). In contrast, a study by Fournier et al. (25) found no differences in the interoceptive abilities of IBD patients measured with the Toronto Alexithymia Scale (26). Although it can be assumed that chronic exposure to visceral pain in IBD might be associated with superior abilities to detect bodily signals, experimental studies examining this association using both behavioral and self-report measures are missing. In IBD patients, the perception of physiological stimuli is critical for the regulation of psychological mood, which in turn may affect the appraisal of gastrointestinal symptoms and also the disease course.

Besides their role in symptoms perception, interoceptive abilities are of particular importance for many higher order cognitive processes such as learning, decision making, and emotion processing (27). The perception of physiological changes

in the body is posited as a core component of emotional experience (13, 28). Based on neurobiological findings, Craig (29) postulated that interoception reflects the physiological condition of the entire body, including also the perception of the response of the body to different affective stimuli and its impact on emotional experience (29). Deficits in interoceptive abilities are associated with difficulties in identifying emotions, reduced emotional reactivity and inferior ability to downregulate negative emotions (30). In contrast, superior interoceptive abilities are linked to stronger associations between individual's body response to emotional stimuli and subjective ratings of perceived arousal (30, 31). Thus, altered processing of visceral signals, as observed in gastrointestinal disorders, may contribute to changes in patients' emotional functioning. A study by Vianna et al. (12) suggested the relevance of this link in IBD: the association between stronger visceral responses and higher subjective arousal to emotional stimuli was significantly increased in acute Crohn's disease patients compared to healthy controls (HC), particularly for negative stimuli (12). Additionally, findings from neuroimaging studies have indicated decreased sensitivity to positive emotional content in patients with Ulcerative colitis, suggesting the close connection between brain regions involved in the processing of interoceptive as well as emotional stimuli (32). Impairments in emotional functioning may have crucial negative impact on patients' well-being (e.g., depression, anxiety). Although it is conceivable that alterations in interoceptive abilities may partially explain impairments in emotion processing in IBD, studies investigating this link are sparse (25, 33).

One environmental factor that has been linked to an increased risk for mental and somatic disorders is a history of adverse childhood experiences (ACE). ACE, including emotional and physical abuse as well as neglect, have permanent consequences for the mental and somatic health in adulthood (34, 35). Individuals who report experiences of early life stress are more prone to developing chronic inflammation, cardiovascular disease and affective disorders compared to non-traumatized controls (36). Some authors emphasized a potential role of ACE in gastrointestinal disorders (4, 37). A cohort study revealed that the prevalence of at least one type of childhood adversity in IBD patients is above 70% with most of the patients reporting death of a family member during childhood and 12–13% reporting sexual or physical abuse (37). One biological mechanism, which may explain the negative impact of ACE on physical health in later life is the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and alterations of the stress-response in individuals exposed to early life stress. Impaired physiological stress response affects the brain-body signaling, which in turn might lead to altered perception of bodily signals (38, 39). Beyond its negative impact on body signals perception, ACE have been also linked to impaired emotion regulation and emotional processing (40, 41). Thus, early life stress might lead to dysregulation of the brain-body axis and altered interoception, leading to impairments of emotional processing (42). However, the role of childhood adversity as vulnerability factor for altered perception of bodily signals and impaired emotional functioning in IBD is still unclear (43). Besides higher rates of ACE, newer findings suggest that one third of the IBD patients meet the criteria for clinically important symptoms of a post-traumatic stress disorder (PTSD), and patients attribute these to their disease (44). Thus, histories of childhood traumatization, as well as chronic stress associated with the disease experience itself constitute stressors, which may lead to changes in arousal, physiological reactivity and emotional experience.

The aim of the current study was to investigate alterations of interoceptive abilities and emotion processing in IBD compared to healthy participants. We proposed that the chronic exposure to gastrointestinal symptoms may lead to enhanced attention toward bodily signals, resulting in superior interoceptive abilities in IBD. The perception of physiological changes in the body is a core component of emotional experience and greater interoceptive accuracy is linked to more intense emotional experience and greater perceived arousal. Therefore, changes in visceral signals perception might explain altered emotional processing among IBD patients. To the best of our knowledge, this is the first study investigating interoception as a multidimensional construct and its effects on emotion processing in IBD by combining behavioral and self-report measures. Measures of interoception included interoceptive accuracy using the heartbeat tracking task (HBT) (45), IS assessed *via* self-reports (46) and interoceptive awareness as the correspondence between interoceptive accuracy and IS. We focused on IBD patients in clinical remission to avoid a potentially confounding effect of active disease symptoms on the interoceptive measures. For the same reason we chose to assess interoceptive accuracy using the HBT. A high correlation between measures of cardiac and gastric interoception points to the presence of a general sensitivity for interoceptive cues across different sensory modalities (47, 48). In line, we used the HBT as a substitute for measures of gastric interoceptive accuracy, since it is less susceptible to confounding effects of abdominal pain in this patients' group. HBT is a well-established method to measure interoceptive accuracy that is typically performed under conditions of physical rest (45). However, when studying the relationship between interoception and emotional experience, an assessment of interoceptive accuracy under physical rest might fail to measure important characteristics of the cardiovascular system such as its dynamic responses to arousing stimuli (49). To overcome this shortcoming, we implemented a short physical exercise with the purpose of inducing a physiological reaction in our participants. According to previous findings by Schaan et al. (38), increased heartrate resulting from a physical activation should lead to improvement in participants' interoceptive accuracy (50).

According to this rationale, we hypothesized that IBD patients will (I.) demonstrate superior interoceptive accuracy and IS, as well as greater congruency between these constructs and (II.) report higher arousal and emotional intensity when evaluating negative stimuli compared with a healthy control group. We hypothesized that (III.) greater interoceptive accuracy will be associated with higher arousal and emotional intensity ratings during emotional processing. Moreover, we expected that ACE will modulate alterations in interoception and emotional processing and strengthen the association between interoceptive accuracy and emotional processing. (IV.) We expected the

performance of a short physical exercise to result in improved interoceptive accuracy. Therefore, we explored whether group differences in interoceptive accuracy increased after performing a physical challenge. Finally, we investigated whether heart rate and heart rate variability during the interoception and emotion processing tasks differed between IBD patients and healthy individuals and expected (V.) a decreased heart rate variability (HRV) in the IBD group compared with healthy participants as repeatedly shown in the literature before (51).

MATERIALS AND METHODS

Participants

The study was approved by the Ethics Committee of the Medical Faculty Mannheim at Heidelberg University and all participants gave their written informed consent before participating in the study. The hypotheses, sample size, methods, exclusion criteria and planned analyses were preregistered before data collection and can be accessed at: https://aspredicted.org/blind.php?x=dj6fz9. All aspects of the study were carried out in accordance with the pre-registered protocol unless otherwise stated.

In total, 70 individuals in age 18-65 years participated in the study. Of these, 35 met the diagnostic criteria for IBD and 35 were HC. Both groups were matched for age, IQ [Multiple-Choice Word Test-B (MWT-B); (52)] and education. For age, we accepted a difference of ± 5 years in pairwise matches between patient's and HC's age. We aimed to achieve two samples comparable on a group level. Since equal education level was of particular importance for our matching procedure, we matched each healthy participant with the same education as the one reported by the IBD patient. Therefore, the final sample included more female participants in the HC group than in the IBD group. For further details, see **Table 1**. We excluded one participant of the IBD group from further analyses, since she/he reported no perceived heartbeats during the HBT. Thus, the final sample consisted of 34 IBD patients and 35 HC. According to our preregistered analyses a sample size of 120 participants was planned. However, due to the Covid-19 outbreak and the pandemic-related restrictions the number of participants was reduced.

IBD patients were recruited from the IBD outpatient unit at the University Medical Center Mannheim. Overall, 23 patients with Crohn's disease and 11 with ulcerative colitis in clinical remission were included in the IBD group. Crohn's disease patients exhibited mean Harvey-Bradshaw Index score of 1.43 ± 1.56 and UC patients mean Partial Mayo Score of 1.73 ± 1.49. The average age for disease onset was 25.65 ± 10.83 years. The average disease duration was 15.67 ± 13.55 years. Overall, 10 IBD patients reported a history of Extraintestinal manifestations (Enteropathic arthritis $n = 6$, Dermatitis $n = 4$). Nineteen patients did not report histories of previous surgeries, while the remaining IBD patients underwent surgeries including ileal resection, ostomy, fistula removal and abscess drainage. Diagnostic procedures and gastroenterological examinations were carried out on all patients by fully trained physicians specialized in the care of patients with IBD. Exclusion criteria were biological signs of disease activity (fecal calprotectin level in mg/L > 200), current use of corticosteroids, use of psychotropic medications other than SSRIs or SNRIs, and current or prior history of neurological or mental disorders. Thirty-three patients reported a current treatment with biologics and one using Mesalazine. Lastly, ten IBD patients reported having histories of further somatic diseases (pulmonary embolism $n = 2$, pancreatitis $n = 2$, diabetes $n = 1$, chronic cystitis $n = 1$, thrombocythemia $n = 1$, asthma bronchiale $n = 1$, and hypothyroidism $n = 2$). Exclusion criteria for the HC group were chronic medical conditions, chronic medication intake, use of psychotropic medication, and current or prior history of neurological or psychiatric disease and general gastrointestinal complaints (e.g., abdominal pain, diarrhea) during the last 4 weeks prior to testing. For further details on sample characteristics, see **Table 1**.

To characterize the sample, we assessed psychological distress with the Brief Symptom Inventory (BSI-18) (53). BSI-18 is a is an 18 Items self-report instrument that measures somatization, depression, and anxiety in three subscales with 6 items each and a global symptom severity score [Global Severity Index (GSI)]. BSI-18 is a reliable instrument for measuring psychological distress and comorbidities in patients with mental and somatic disorders (54, 55). The scores for the GSI range from 0 to 72 points and from 0 to 24 points for each subscale with higher scores indicating higher symptom severity. GSI total scores showed acceptable reliability in the present study, however the reliability of the subscale scores suggests that they have to be interpreted with care (IBD: Cronbach's $\alpha = 0.88, 0.61, 0.76, 0.83$; HC: $\alpha = 0.85, 0.66, 0.87, 0.66$).

Prior to testing, participants evaluated their current affective state with the state version of the State-Trait Anxiety Inventory [STAI; (56)]. It is a 20 items scale, which measures subjective feelings of apprehension, tension, nervousness, worry, and activation/arousal of the autonomic nervous system on a 4-point Likert scale (1 "not at all" to 4 "very much so"). Items scores are added to obtain scale total score (range from 20 to 80) with higher scores indicating greater anxiety. Cronbach's α in the current study was $\alpha = 0.79$ in the IBD sample and 0.91 in the HC group. Additionally, arousal, valence, and dominance levels were assessed *via* the Self-Assessment Manikin [SAM; (57)]. SAM is a non-verbal pictorial assessment technique that measures valence/pleasure, perceived arousal, and perceptions of dominance on a 9-point Likert scale. Higher scores indicate greater positive valence, higher arousal and higher perceived dominance.

Finally, visceral sensitivity was measured with the Visceral Sensitivity Index [VSI; (58)]. The 15-item scale assesses gastrointestinal symptom-specific anxiety, comprising Worry, Fear, Vigilance, Sensitivity, and Avoidance as gastrointestinal-related cognitions and behaviors. Items are scored on a reversed 6-point scale ranging from 0 "strongly agree" to 5 "strongly disagree." VSI has been developed specifically for patients with functional gastrointestinal disorders. Since the VSI is not a suitable measure for healthy individuals,' we utilized this self-report measure in the IBD group only. The overall VSI score ranges from 0 to 75 points with higher scores indicating more severe gastrointestinal-specific anxiety, as well as lower tolerance

TABLE 1 | Sample characteristics including demographic data, affective state prior measurement and psychological well-being.

	IBD (M ± SD)		HC (M ± SD)		Test-statistics	*P*-value
Demographics						
Age	41.32	±14.36	37.06	±11.96	1.34[a]	0.184
Sex (female/male)	18/16		20/15		0.12[b]	0.726
BMI	25.09	±3.32	24.59	±4.52	0.52[a]	0.607
Years of education	12.44	±3.11	12.97	±2.62	−0.77[a]	0.445
MWT-B	29.79	±4.05	30.51	±3.71	−0.77[a]	0.443
Affective state						
STAI Anxiety (state)	34.35	±5.82	32.23	±8.39	0.99[a]	0.327
SAM-Valence	3.64	±0.99	3.81	±0.85	−0.69[a]	0.492
SAM-Arousal	2.51	±0.98	2.03	±0.93	2.06[a]	0.043*
SAM-Dominance	3.48	±0.62	3.70	±0.70	−1.04[a]	0.302
Psychological distress						
GSI	28.90	±9.38	23.50	±5.94	2.71[a]	0.009**
Somatization	9.63	±3.11	6.94	±1.56	4.29[a]	<0.001***
Depression	9.47	±3.71	8.00	±3.24	1.69[a]	0.096
Anxiety	9.80	±3.84	8.56	±2.60	1.53[a]	0.131
Visceral sensitivity						
VSI	28.87	±14.95	–		–	–

*IBD, inflammatory bowel diseases group; HC, healthy controls group; BMI, body-mass index; MWT-B, multiple choice word test-B; STAI, state-trait anxiety inventory; SAM, self-assessment manikin; GSI, general symptom index; VSI, visceral sensitivity index. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, [a]T-value, [b]Chi^2 statistic.*

to visceral pain. Reliability in the current sample was Cronbach's $\alpha = 0.89$.

Procedure

Participants evaluated their general interoceptive sensibility by a self-report questionnaire. Afterwards, the ECG assessment was started, and participants were asked to perform three experimental tasks, including an emotional processing task and the heartbeat tracking task followed by a time estimation task (see **Figure 1**).

Questionnaires

Interoceptive Sensibility: MAIA

We assessed IS using the Multidimensional Assessment of Interoceptive Awareness [MAIA; (46, 59)]. The 32 items self-report questionnaire measures eight different facets of interoceptive sensibility on a 6-point Likert-scale (0 = "never"− 5 = "always") with higher scores indicate greater sensitivity to signals from the body. MAIA provides a multidimensional profile of body awareness including the following eight subscales: *Noticing* (being aware of body sensations), *Not-Distracting* (being inclined to not distract or ignore painful or uncomfortable sensations), *Not-Worrying* (inclination to not be emotionally distressed by uncomfortable sensations), *Attention Regulation* (paying attention to and controlling attention on body sensations), *Emotional Awareness* (being aware of the connection between emotions and body sensations), *Self-Regulation* (regulating distress through paying attention to body sensations), *Body Listening* (purposefully listening for insight from the body) and *Trusting* (experiencing trust with and safety in the body) (46). MAIA revealed good internal consistency in the current experiment with Cronbach's $\alpha = 0.91$ in the IBD group and 0.94 in the HC group. A key advantage of MAIA is the possibility to assess various aspects of IS, including subscales distinguishing between beneficial and dysfunctional forms of IS. While "*Noticing*" assesses the awareness of bodily sensations in general, "*Attention Regulation*" and "*Not-Distracting*" measure individual differences in how engaged a person is regarding interoceptive cues (59). Moreover, previous findings indicated that general IS ("*Noticing*" subscale) did not benefit from body-focused interventions, aiming at improving interoceptive abilities, while the ability to sustain and control attention to bodily sensations ("*Attention Regulation*" subscale) showed a significant improvement (15). The postulated association between bodily sensations and emotional experience is assessed by the subscale *"Emotional Awareness."* Since discrete emotions are linked to physiological reactions, individuals might differ in terms of their ability to recognize these mind-body associations, which might lead to difficulties in recognizing their emotional state.

Childhood Traumatization and PTSD Symptoms Severity

We assessed traumatization during childhood and adolescence as well as traumatic experiences during lifetime using a battery of psychometric measures. Severity of ACEs were measured with the German version of the Childhood Trauma Questionnaire [CTQ; (60)]. This 28-item questionnaire (five-point Likert scale ranging =1 "not at all" −5 = "very often") has been shown to have good psychometric properties in previous research (60). The CTQ consists of five subscales including emotional abuse (Cronbach's α in this study 0.79), physical abuse ($\alpha = 0.73$), sexual

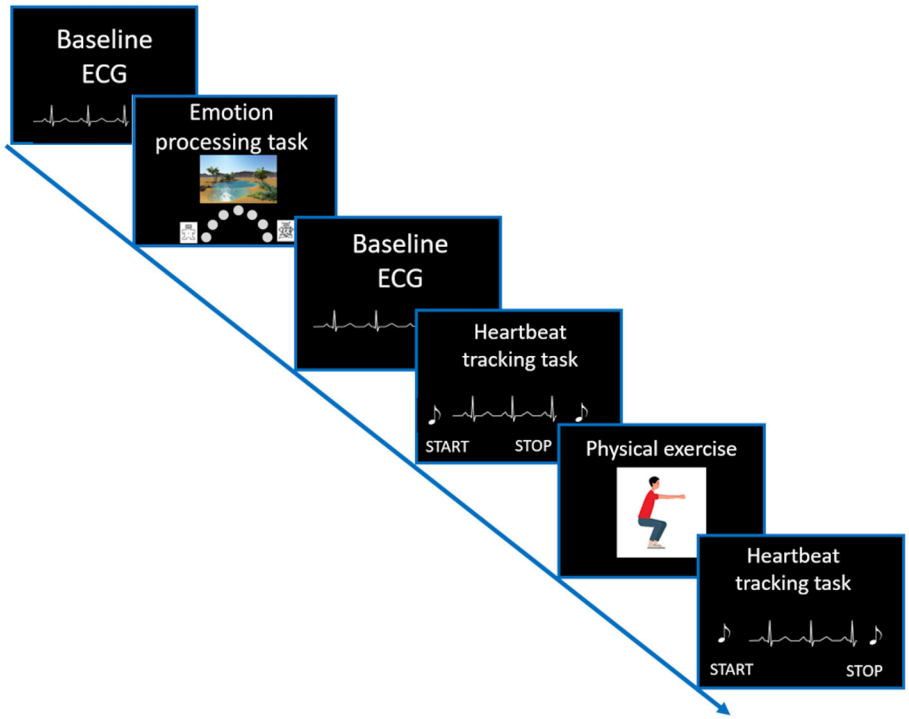

FIGURE 1 | Visualization of the study setup. After completing all questionnaires, a resting ECG (duration of 2 min) was recorded. Afterwards, participants performed an emotion processing task. Again, before starting the Heartbeat tracking task, a resting ECG recording was conducted. For more details on the trial structure of the Heartbeat tracking task please see **Figure 2**.

abuse ($\alpha = 0.88$), emotional neglect ($\alpha = 0.84$), and physical neglect ($\alpha = 0.45$) and a total score (Cronbach's α in IBD: 0.86; HC: 0.73). Each subscale is represented by five questions with a score from 5 to 25. Scores fall into four severity categories: none to low, low to moderate, moderate to severe and severe to extreme traumata exposure for each subscale (see **Table 2**).

Furthermore, to assess additional types of early life stress such as parental loss, continuous separation from one or both parents and foster care experiences we used selected items (1a, 1b, 2a, 2b) of the Childhood Experience of Care and Abuse Questionnaire [CECA.Q, (61); German version: (62)].

Additionally, all participants were screened for potentially traumatic life events using the Life events Checklist for DSM-5 [LEC-5; (63)]. It is a self-report measure, which assesses exposure to 16 events known to potentially result in symptoms of posttraumatic stress disorder (PTSD) or distress. LEC-5 distinguishes not only between event types (e.g., physical or sexual assault, accident) but also between the ways a person was exposed to the stressor (e.g., direct exposure or witnessing the traumatic event). For each participant, the number of personally experienced traumatic events (direct exposure) were summed up, resulting in one sum score.

Severity of PTSD symptoms was evaluated with the PTSD Checklist for DSM-5 [PCL-5; (63)]. It is a 20-item self-report measure that assesses the presence and severity of symptoms after experiencing a traumatic event. Items correspond with DSM-5 criteria for PTSD including intrusion symptoms, avoidance, negative alterations in cognitions and mood and alterations in arousal and reactivity during the last 4 weeks. The rating scale ranges from 0 "not at all" to 4 "extremely" for each symptom. A total symptom severity score is obtained, with higher scores indicating higher PTSD symptoms severity. PCL-5 revealed high reliability in the current study with Cronbach's $\alpha = 0.91$ in IBD and.87 in HC. See **Table 2**.

Experimental Tasks

Interoceptive Accuracy: HBT

Interoceptive accuracy was measured with a standard heartbeat tracking task [HBT, (45)]. Participants were seated upright in a quiet room with their eyes closed. They were asked to silently count the number of heartbeats occurring during five discrete time intervals of 25, 35, 45, 55, and 100 s. Participants were explicitly told not to estimate their heartbeats, but to count only those heartbeats they actually perceived. Intervals varied in their length and were presented in a randomized order counterbalanced across both groups. Before starting with the experimental task, a baseline measurement of cardiac activity was performed (**Figure 1**). Each HBT interval started after a resting period of 20 s. While counting their heartbeats, participants were not allowed to use a manual pulse. To explore the effects

TABLE 2 | Sample characteristics including childhood traumatization, traumatization in later life, and PTSD symptoms severity.

	IBD (M ± SD)		HC (M ± SD)		Test-statistics	*P*-value
TRAUMA HISTORY						
Childhood trauma						
CTQ total	35.73	±10.77	36.06	±7.00	−0.15[a]	0.881
None to minimal ACE	*n* = 21		*n* = 21		0.10[b]	0.758
Low to moderate ACE	*n* = 10		*n* = 13		0.36[b]	0.551
Moderate to Severe ACE	*n* = 2		*n* = 1		0.41[b]	0.520
CTQ—EA	8.18	±3.73	8.51	±2.96	−0.41[a]	0.684
CTQ—PA	6.27	±2.53	5.80	±1.60	0.92[a]	0.362
CTQ—SA	5.55	±2.00	5.14	±0.55	1.12[a]	0.272
CTQ—EN	8.91	±3.79	9.63	±3.29	−0.84[a]	0.405
CTQ—N	6.81	±2.34	6.97	±1.71	−0.31[a]	0.758
CECA (loss/death of a parent)	*n* = 10		*n* = 9		0.26[b]	0.608
Lifetime trauma						
LEC-5	1.52	±1.56	1.11	±1.30	1.15[a]	0.254
PTSD symptoms						
PCL-5 total	15.47	±12.37	5.54	±5.94	4.13[a]	<0.001***
Cluster B	4.25	±3.69	1.43	±1.95	3.86[a]	<0.001***
Cluster C	1.81	±2.13	0.74	±1.20	2.50[a]	<0.013*
Cluster D	4.16	±3.55	1.86	±2.79	2.96[a]	0.004**
Cluster E	4.84	±4.52	1.43	±1.70	4.02[a]	<0.001***

IBD, inflammatory bowel diseases group; HC, healthy control group; CTQ, childhood trauma questionnaire; EA, emotional abuse; PA, physical abuse; SA, sexual abuse; EN, emotional neglect; PN, physical neglect; ACE, adverse childhood experiences; CECA, childhood experience of care and abuse; LEC-5, life events checklist; PTSD, post-traumatic stress disorder; PCL-5, post-traumatic stress disorder checklist for DSM-V; Cluster B = intrusion symptoms, Cluster C = avoidance, Cluster D = negative alterations in cognitions and mood, Cluster E = alterations in arousal and reactivity, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, [a]T-value, [b]Chi^2 statistic.

of dynamic alterations in the cardiovascular homeostasis on interoceptive accuracy, all participants were asked to perform a short physical exercise comprising 10 squats (**Figure 2**). However, some of the IBD patients reported pain in the knees and refrained from performing this exercise. Therefore, data for the second run of the task was available only for a subsample of participants (24 IBD patients and 24 HC). To compute interoceptive accuracy scores, the ratio of the number of reported heart beats and number of R-waves in the ECG was calculated for each of the time intervals of the HBT and averaged across the five intervals [1/5 $\sum$ (1-|actual heartbeats-counted heartbeats|/actual heartbeats)]. In the present sample, interoceptive accuracy scores ranged from 0 to 1 (no over-reporters observed) with higher scores indicating greater interoceptive accuracy.

Time Estimation Task

Subject's performance on the HBT might be confounded by individuals' abilities to estimate time, and their knowledge about their own heart rate (64, 65). Therefore, we extended the experimental task by an additional time estimation task (**Figure 2**) (10). Participants were asked to estimate the elapsed time during five discrete time intervals of 25, 35, 45, 55 and 100 s. Time intervals were presented in pseudorandomized order, counterbalanced across the experimental groups. The time estimation task was performed after the HBT prior and following the physical challenge. Similar to the computation of interoceptive accuracy scores, time estimation (TE) accuracy was calculated using the following formula [1/5 $\sum$ (1–|actual elapsed time—estimated elapsed time|/actual elapsed time)] (10).

Emotional Processing Task

Emotional processing was measured by ratings of subjective intensity of arousal and valence when being presented with emotional stimuli. The task involved 90 pictures of three categories (30 positive, 30 negative, and 30 neutral pictures) from the OASIS data base [(66) www.benedekkurdi.com/#oasis], presented in a pseudorandomized order. Based on existing norms, "negative" stimuli were selected based on high arousal (M = 4.12, SD = 0.45) and low valence ratings (2.58 ± 0.35), "positive" pictures had high arousal (4.15 ± 0.48) and high valence ratings (6.04 ± 0.23), and "neutral" stimuli had low arousal (2.36 ± 0.53) and moderate valence rating (4.08 ± 0.10). Emotional stimuli were presented on a computer screen and participants were asked to rate their subjectively experienced level of arousal and valence for each stimulus. Arousal and valence ratings were made in two separate blocks, each one consisting of 90 pictures, resulting in overall 180 trials. All ratings were performed on an 8-point scale (valence: 1 = "very unpleasant" − 8 = "very pleasant"; arousal: 1 = "not aroused at all" − 8 = "highly aroused") by moving a mouse cursor to one of the eight target buttons. Trials were self-paced, with participants signaling the start of the trial by moving the cursor to a start button that was placed in equal distance from the semicircular arranged target buttons.

ECG Recording and Preprocessing

Electrocardiogram (ECG; Einthoven II) was obtained by attaching two one-way hydrogel electrodes (Kendall™ Covidien, Germany) under the right and the left clavicle, respectively,

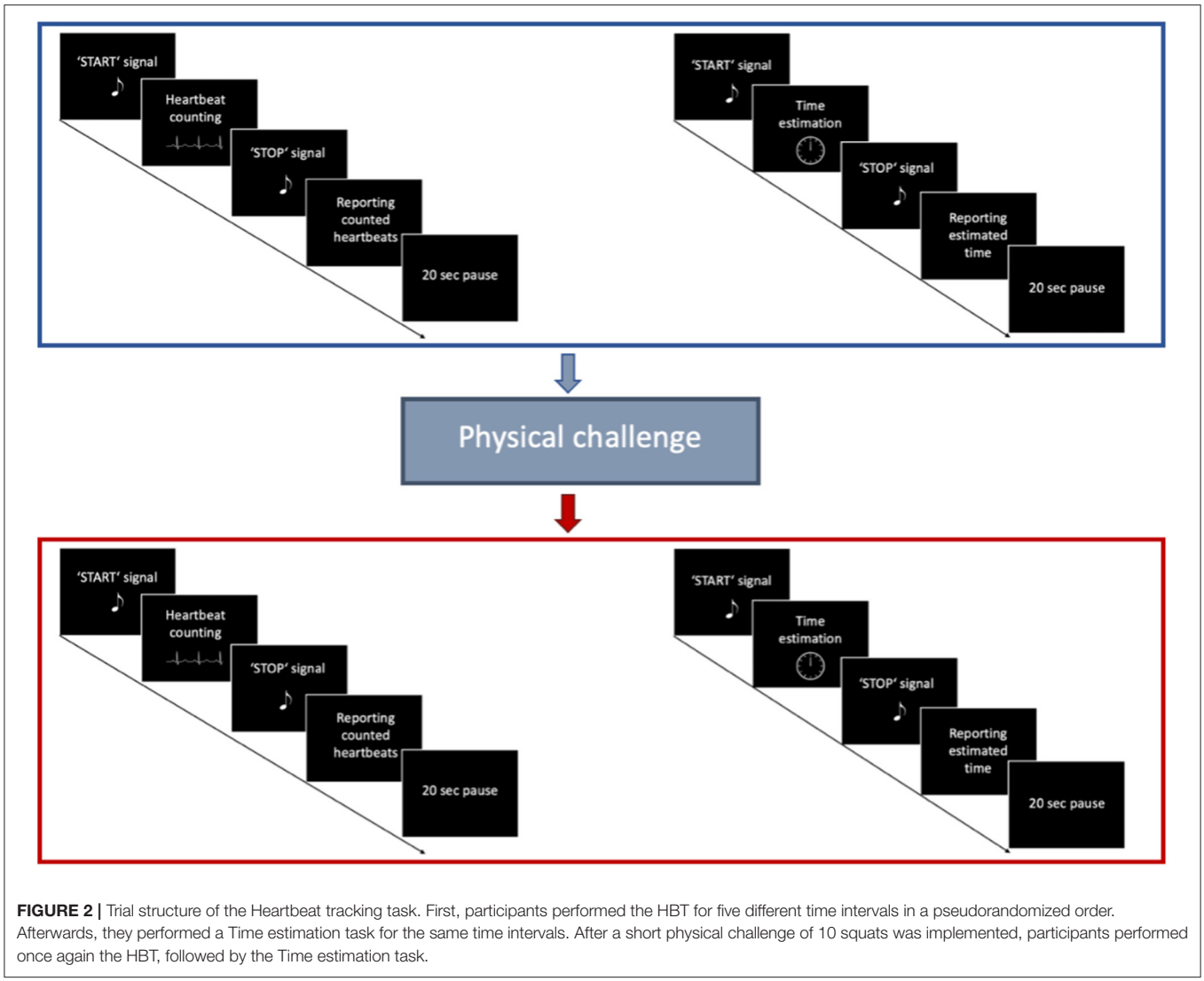

FIGURE 2 | Trial structure of the Heartbeat tracking task. First, participants performed the HBT for five different time intervals in a pseudorandomized order. Afterwards, they performed a Time estimation task for the same time intervals. After a short physical challenge of 10 squats was implemented, participants performed once again the HBT, followed by the Time estimation task.

and a third electrode was placed on the left side under the lowest rib. Signals were recorded with a sample rate of 1,024 Hz using a Varioport system (Becker, meditec). Participants were instructed to avoid body movements and to breathe in their natural manner. ECG was recorded during each experimental task as well as during two resting periods with a duration of 2 min each (**Figure 1**).

R-waves of the QRS-complex were determined by the Pan-Tompkins algorithm (67, 68) using custom written scripts in Matlab 2020a (The Mathworks, Inc.). Accuracy of the automatic detection of R-waves was subsequently controlled by visual inspection to identify ectopic heart beats and time intervals confounded by artifacts. Following this preprocessing procedure, the number of heart beats for each of the time intervals of the HBT was determined and stored for further calculation of the interoceptive accuracy scores. Additionally, heart rate (HR) and root mean square of the successive differences (RMSSD) were calculated separately for the HBT (averaged across all time intervals), the emotional processing task, as well as the resting ECGs recorded prior to the experimental tasks (69). We calculated RMSSD of the normal-to-normal beat intervals (NN), while excluding each interval with an ectopic beat as well as the preceding and following RR interval, since these might be also distorted by the occurrence of ectopic beats (70). In general, RMSSD is considered to be a robust and statistically reliable HRV marker (71). It represents short-term HRV (72) and is used as a marker for vagally mediated HRV.

Statistical Analyses

Statistical analyses were carried out with SPSS v.25.0 (IBM Corp., USA). For all analyses statistical significance was set to $p < 0.05$.

Interoceptive Accuracy and Accuracy of Time Estimation

Interoceptive accuracy und TE accuracy scores were compared between experimental groups with independent samples *t*-tests. Additionally, we analyzed the effects of the physical challenge in a subsample of participants, for interoceptive accuracy and time estimation accuracy in two separate 2 × 2 mixed ANOVAs with

the independent factor "group" and the repeated measurement factor "time" (pre/post physical challenge).

Interoceptive Sensibility

To test group differences in IS, mean scores of all MAIA subscales were analyzed with multiple independent samples *t*-tests.

Interoceptive Awareness

Interoceptive awareness is defined as the correspondence between one's interoceptive accuracy, measured with an objective behavioral task, and IS that is the subjective evaluation of interoceptive abilities assessed *via* self-report measures. Previous studies investigating the link between behavioral measures of interoception (e.g., HBT) and MAIA subscales revealed associations only with the subscale "*Attention Regulation*" (73). Thus, it has been suggested that interoceptive accuracy measured by the HBT relates to more specific aspects of IS and not so much to general IS as assessed by the "*Noticing*" subscale. Since the HBT requires individual's ability to control and maintain attention toward bodily sensations, we assessed interoceptive awareness by computing Pearson's correlation coefficients between interoceptive accuracy scores and $IS_{attention\ regulation}$ scores across all participants in each experimental group (14, 74). To investigate group differences in interoceptive awareness, correlation coefficients in the IBD and HC group were standardized and compared between groups (75).

Emotional Processing

Differences in emotion processing between IBD and HC were analyzed with two separate 2 × 3 mixed-effects ANOVAs for the two dependent variables "valence" and "arousal" with the between-subject factor "group" and within factor "stimulus valence" (positive/ neutral/negative). Degrees of freedom were corrected using Greenhouse-Geisser estimate of sphericity. *Post-hoc* comparisons were done by sub-designs of ANOVA design and/or pairwise comparisons.

The Link Between Interoceptive Accuracy and Emotional Processing

To investigate whether greater interoceptive accuracy was associated with higher levels of experienced valence and arousal during emotional experience, two linear regression analyses across all participants were computed. Valence and arousal ratings averaged separately for the three types of stimuli valence constituted the dependent variables (DV), while interoceptive accuracy scores were used as independent variable (IV). Beyond these preregistered analyses, we computed two additional linear regressions to test whether superior IS was associated with changes in perceived valence and arousal of emotional stimuli. Since we hypothesized that alterations in emotional processing linked to interoceptive processes will be more pronounced for negative stimuli, mean valence and mean arousal ratings only for negative stimuli were included in the analyses.

The Role of ACE in Interoception, Emotional Processing and Their Association in IBD

The effect of childhood traumatization on interoceptive accuracy and IS was investigated using two linear regression analyses with CTQ scores (IV) and interoceptive accuracy and IS scores (DV), respectively. Furthermore, to investigate whether severity of childhood traumatization does influence emotional processing, linear regression models for valence and arousal ratings were computed separately. Finally, the modulating effect of ACE on the relationship between interoceptive accuracy and emotional processing was investigated using separate moderation analyses with interoceptive accuracy scores (IV) and valence and arousal ratings (DV), respectively. Again, beyond the preregistered statistical analyses, we computed two additional moderation models with IS (IV) and valence and arousal ratings (DV).

Heart Rate and Heart Rate Variability

HR and RMSSD were compared between groups with independent *t*-tests. The effects of the physical activation on HR and HRV parameters were analyzed with a variance analytical design including the independent factor "group" and the repeated measurement factor "time" (pre/post challenge) in the subgroup of participants who performed the short physical exercise. Finally, differences between baseline cardiac activity and physiological activation during the emotional processing were analyzed with a variance analytical design including the independent factor "group" and the repeated measurement factor "time" (baseline/task).

To control for multiple testing, we report the corresponding *p*-values adjusted according to Benjamini and Hochberg (76) and indicated this by a subscript (p_{FDR}).

RESULTS

Interoceptive Accuracy and Time Estimation Accuracy

Comparisons between IBD and HC revealed no differences between both groups either for the interoceptive accuracy scores or the TE scores (IACC $t_{67} = -0.432$, $p = 0.667$, TE $t_{67} = -0.047$, $p = 0.963$, see **Table 3**).

An analysis of the effect of the physical challenge in a subgroup of participants showed also no group differences for interoceptive accuracy either in general or depending on the challenge (main effect "group": $F_{1,46} = 0.108$, $p = 0.744$; "group" × "time": $F_{1,46} = 0.777$, $p = 0.383$). However, interoceptive accuracy after the physical challenge improved as non-significant trend (main effect "time": interoceptive accuracy: $F_{1,46} = 2.864$, $p = 0.097$). In contrast to interoceptive accuracy, HCs improved significantly in their TE performance after the physical challenge, whereas IBD patients did not show a significant difference (main effect "group": $F_{1,46} = 1.860$, $p = 0.179$; "group" × "time": $F_{1,46} = 4.428$, $p = 0.041$).

Interoceptive Sensibility

IBD patients reported a stronger tendency to distract themselves from unpleasant sensations ($IS_{not\text{-}distracting}$: $t_{66} = -3.500$, $p_{FDR} = 0.004$) and superior awareness of physical sensations associated with emotional states ($IS_{emotional\ awareness}$: $t_{66} = 3.504$, $p_{FDR} = 0.004$). For further details on MAIA subscales see **Table 3**.

TABLE 3 | Group differences in interoceptive accuracy, interoceptive sensibility and interoceptive awareness.

	IBD (M ± SD)		HC (M ± SD)		Test-statistics	*P*-value
Interoceptive accuracy						
IACC	0.65	±0.19	0.67	±0.21	−0.432[a]	0.667
TE accuracy	0.73	±0.14	0.73	±0.15	−0.047[a]	0.963
Interoceptive sensibility						
MAIA Noticing	2.61	±1.14	2.74	±1.03	−0.492[a]	0.625
MAIA Not distracting	2.20	±1.09	3.10	±0.83	−3.500[a]	0.004**
MAIA Not worrying	2.67	± 1.10	2.88	±0.79	−0.929[a]	0.356
MAIA Attention regulation	2.65	±0.89	2.41	±0.68	1.243[a]	0.218
MAIA Emotional awareness	3.47	±0.83	2.72	±0.92	3.504[a]	0.004**
MAIA Self-regulation	2.32	±1.03	1.95	±0.91	1.561[a]	0.123
MAIA Body listening	1.95	±1.16	1.76	±1.10	0.683[a]	0.497
MAIA Trusting	2.98	± 1.29	3.04	±1.05	−0.205[a]	0.839
Interoceptive awareness						
IAw	−0.317[b]		0.049[b]		−1.49[c]	0.069(*)

*IBD, inflammatory bowel diseases group; HC, healthy control group; IACC, interoceptive accuracy; MAIA, multidimensional assessment of interoceptive awareness; IAw, interoceptive awareness. *p < 0.05, **p < 0.01, [a]T-value, [b]r, [c]Z-value.*

TABLE 4 | Results of the analyses of variance for mean valence and arousal ratings with between-subject factor "group" (IBD/HC) and within-subjects factor "stimulus valence" (positive/neutral/negative).

Emotional processing task			
	F	***df*1/*df*2**	***P*-value**
Valence ratings			
Group	2.08	1/64	0.154
Stimulus valence	301.63	1/84	<0.001***
Group × stimulus valence	0.80	1/84	0.407
Arousal ratings			
Group	0.43	1/64	0.517
Stimulus valence	312.54	1/96	<0.001***
Group × stimulus valence	3.64	1/96	0.042*

*df, degrees of freedom; *p < 0.05, **p < 0.01.*

Interoceptive Awareness

Interoceptive accuracy and $IS_{attention\ regulation}$ scores showed a non-significant trend association in the IBD group but not in HC (all participants: $r_{68} = -0.151$, $p = 0.218$; IBD: $r_{33} = -0.317$, $p = 0.072$; HCs group: $r_{35} = 0.049$, $p = 0.779$). Interoceptive awareness differed between groups only as a non-significant trend ($Z = -1.49$, $p = 0.069$; **Table 3**).

Emotional Processing Task

Valence ratings did not differ between both groups, either in general or dependent on the stimulus valence (main effect "group": $F_{1,64} = 2.08$, $p = 0.154$; "group" × "stimulus valence": $F_{1,84} = 0.80$, $p = 0.407$) (**Table 4**).

Arousal ratings differed between groups depending on the stimulus valence ("group" × "stimulus valence": $F_{1,96} = 3.64$, $p = 0.042$; main effect "group": $F_{1,64} = 0.43$, $p = 0.517$). *Post-hoc* analyses revealed a significant interaction effect "group" × "stimulus valence" ($F_{1,64} = 5.329$, $p = 0.024$) with IBD patients exhibiting a greater difference in their perceived arousal between neutral and positive stimuli compared to HC (IBD: $M_{neutral} = 5.10 \pm 1.08$, $M_{positive} = 7.11 \pm 0.54$; HC: $M_{neutral} = 5.45 \pm 1.28$, $M_{positive} = 6.79 \pm 1.01$).

Interoception and Emotional Processing

Regression analyses revealed no significant associations between interoceptive accuracy and subjective valence or arousal ratings (all $p > 0.05$). Since only $IS_{emotional\ awareness}$ and $IS_{not\text{-}distracting}$ scores revealed significant group differences, only these subscales were used to investigate the link between IS and emotional processing. $IS_{emotional\ awareness}$ was a significant predictor of perceived valence of negative stimuli in the whole sample ($b = -0.390$, $p_{FDR} = 0.012$) with participants reporting greater emotional awareness perceiving negative stimuli as more negative compared to those with lower emotional awareness. Further analyses revealed that this association was significant only in the IBD group ($b = -0.493$, $p_{FDR} = 0.024$) but not in the HC group ($b = -0.293$, $p_{FDR} = 0.371$) (**Figure 3A**). Similarly, $IS_{emotional\ awareness}$ showed a significant association with perceived arousal of negative stimuli for all participants ($b = 0.357$, $p_{FDR} = 0.034$), with greater emotional awareness being associated with higher arousal. A non-significant trend for this association was found in the IBD group ($b = 0.477$, $p_{FDR} = 0.069$) but not in HC ($b = 0.235$, $p_{FDR} = 0.371$) (**Figure 3B**). $IS_{not\text{-}distracting}$ was not significantly associated with emotional processing (all $p > 0.05$).

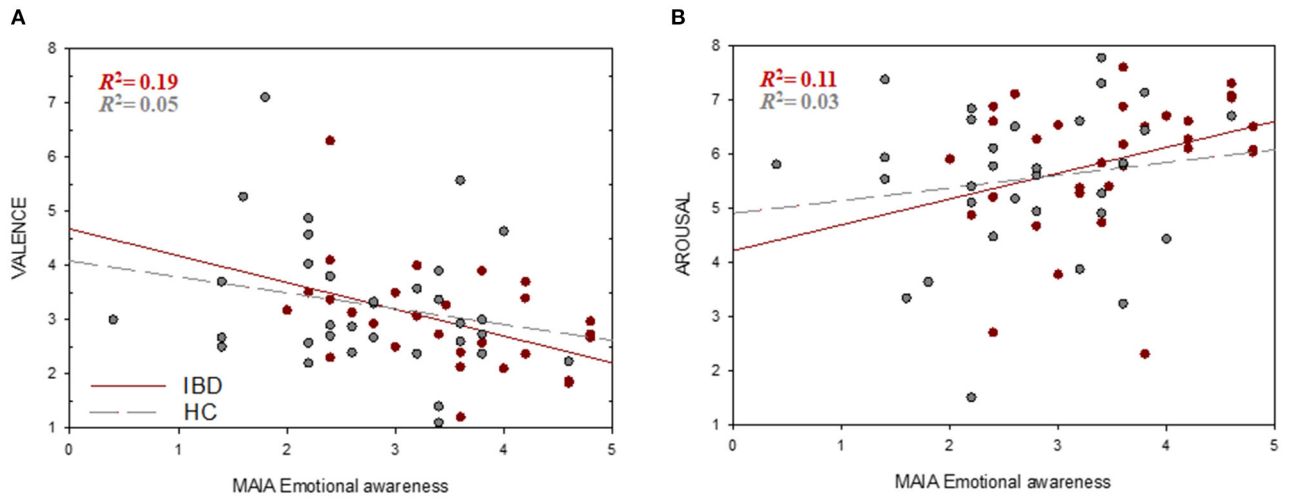

FIGURE 3 | Associations between interoceptive sensibility and emotional processing. Higher $IS_{emotional\ awareness}$ (MAIA) scores were associated with higher higher negative valence (1 = very unpleasant, 8 = very pleasant) **(A)** and arousal ratings (1 = low arousal, 8 = high arousal). **(B)** of negative stimuli.

Group Differences in Childhood Traumatization, Later Traumatic Experiences and PTSD Symptom Severity

There were no significant differences between both groups regarding the severity of ACEs measured with the CTQ. An equal number of IBD patients and HCs reported separation or death of a parent during their childhood (IBD: 32.3 %, HC: 26,5 %, χ^2 (1) = 0.263, p = 0.608). Both groups did not differ in the number of traumatic events experienced in later life (IBD: M = 1.52, SD = 1.56; HC: M = 1.11, SD = 1.30), however, the IBD group exhibited a higher level of PTSD symptoms compared to HC $t_{44} = 4.126$, $p < 0.001$. See **Table 2** for further details.

Childhood Traumatization and Interoception

Regression analyses revealed no significant associations between interoceptive accuracy and CTQ in the present sample (all $p > 0.05$). However, exploratory analysis showed that interoceptive accuracy after the physical challenge was lower in those participants with higher CTQ scores in the HC group ($r_{24} = -0.511$, $p_{FDR} = 0.022$), but not in the IBD group ($r_{24} = 0.070$, $p_{FDR} = 0.752$, comparison between groups: $Z = -2.06$, $p = 0.020$) (**Figure 4**). CTQ scores did not show any significant links either to IS or interoceptive awareness (all $p > 0.05$).

Childhood Traumatization and Emotional Processing

Linear regression analyses revealed no significant associations between CTQ scores and emotional processing (all $p > 0.05$).

The role of ACE in Interoception, Emotional Processing and Their Association

Moderation analyses showed no significant effects of CTQ scores on the link between interoceptive accuracy and emotional processing (all $p > 0.05$). However, CTQ severity significantly moderated the association between $IS_{emotional\ awareness}$ and valence ratings of negative stimuli ($R^2 = 0.22$, $F_{3,61} = 5.588$, $p = 0.002$). A significant interaction was found between $IS_{emotional\ awareness}$ and CTQ scores ($b = -0.05$, $p = 0.009$), indicating that severer traumatization strengthens the negative relationship between $IS_{emotional\ awareness}$ and valence intensity. Individuals with severe histories of ACE and higher IS rated negative stimuli as more negative compared to individuals with higher IS but no histories of childhood traumatization (**Figure 5A**).

For arousal ratings, analyses revealed a non-significant trend effect of CTQ on the association between $IS_{emotional\ awareness}$ and perceived arousal of negative stimuli ($R^2 = 0.12$, $F_{3,61} = 2.725$, $p = 0.052$). A significant interaction between $IS_{emotional\ awareness}$ and CTQ scores was found only for the highest CTQ severity ($b = 0.76$, $p = 0.007$) but not for the lower CTQ scores ($b = 0.28$, $p = 0.09$). These findings indicate that only severe ACE significantly amplified the positive relationship between $IS_{emotional\ awareness}$ and arousal, suggesting that individuals reporting higher levels of childhood traumatization and high IS, do experience negative stimuli as more arousing compared to individuals with high IS but no or low levels of childhood maltreatment (**Figure 5B**).

Heart Rate and Heart Rate Variability

Heartbeat Tracking Task

Mean HR during the HBT did not differ significantly between IBD and HC before the physical challenge ($t_{67} = 1.490$, $p = 0.141$). However, mean HR differed significantly before and after the physical challenge (main effect "time": $F_{1,46} = 5.372$, $p = 0.025$) and showed a non-significant trend for group differences (main effect "group": $F_{1,46} = 3.284$, $p = 0.076$; "time × "group": $F_{1,46} = 0.059$, $p = 0.809$). Thus, HR increased after the physical challenge in both groups, indicating that the implemented manipulation was successful.

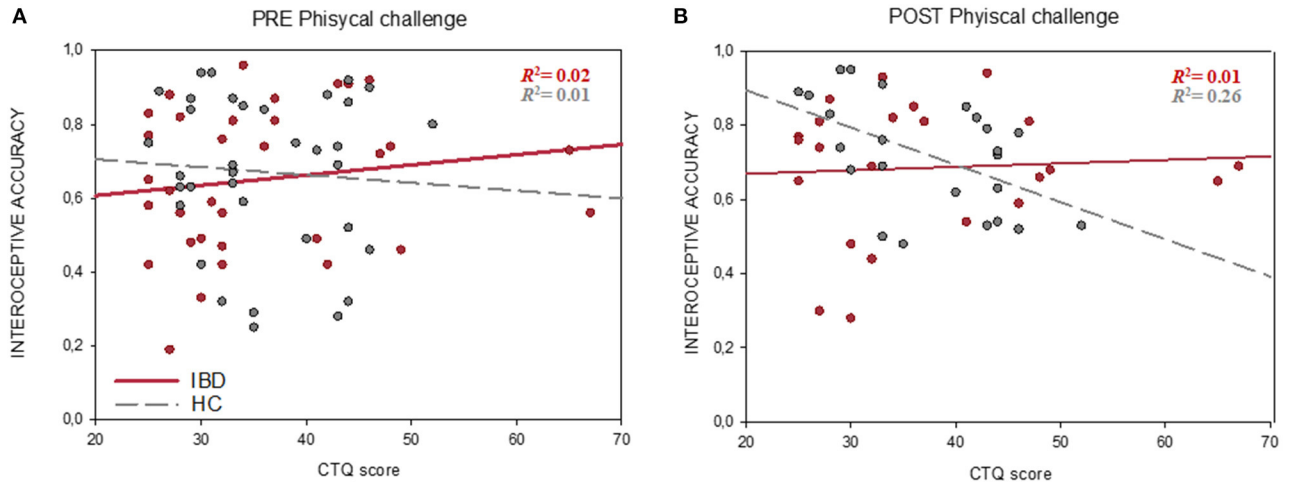

FIGURE 4 | Associations between Interoceptive accuracy (HBT) and childhood traumatization (CTQ score) before **(A)** and after the physical challenge **(B)**. In contrast to the IBD group (red line), HCs (gray dashed line) showed a significant negative correlation between interoceptive accuracy and CTQ scores after the physical challenge. the physical challenge was implemented only in a subsample of 48 participants. CTQ, childhood trauma questionnaire; HC, healthy controls group; IBD, inflammatory bowel diseases group.

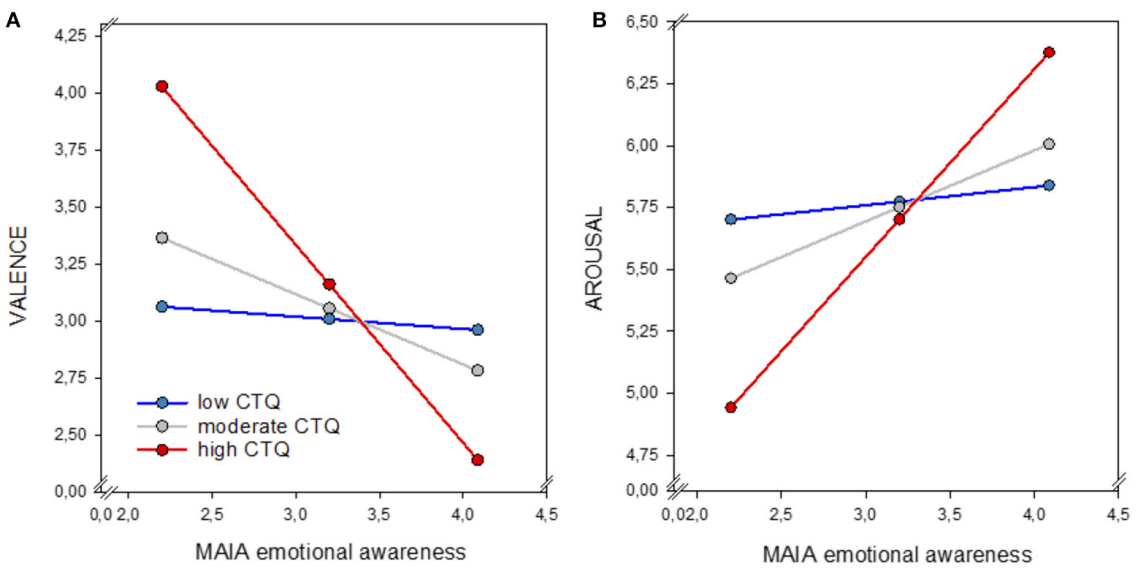

FIGURE 5 | Moderation effect of childhood traumatization (CTQ) on the link between $IS_{emotional\ awareness}$ (MAIA) and perceived valence (1 = very unpleasant, 8 = very pleasant) **(A)** and arousal (1 = low arousal, 8 = high arousal) **(B)** of negative stimuli. Participants reporting higher CTQ scores (red line) and high $IS_{emotional\ awareness}$ reported higher negative valence and arousal compared to individuals exhibiting high $IS_{emotional\ awareness}$ but moderate (gray line) or low (blue line) traumatization. IS, interoceptive sensibility; CTQ, childhood trauma questionnaire.

Mean RMSSD during the HBT did not differ significantly between both groups (t_{67} = 0.367, p = 0.714). However, mean RMSSD differed significantly before and after the physical challenge (main effect "time: $F_{1,46}$ = 18.10, p < 0.001) and differed between both groups only depending on the presence of physical challenge ("time × "group": $F_{1,46}$ = 9.66, p = 0.003; main effect "group": $F_{1,46}$ = 0.24, p = 0.625;). Both groups exhibited increased HRV after the physical challenge. In the IBD group, however, this increase was less strong compared to HC.

Emotional Processing Task

Due to technical problems, baseline ECG data of three participants could not be analyzed. Mean HR and RMSSD at baseline and during the emotional processing task did not differ

either in general or between both groups (all $p > 0.05$). For further details see **Supplementary Table 1**.

Childhood traumatization was not associated with alterations in cardiac activity in the whole sample (all $p > 0.05$). In IBD, higher CTQ scores were associated with higher HR at baseline ($r_{31} = 0.420$, $p = 0.019$). A non-significant trend association between mean RMSSD after the physical challenge and CTQ total score in the IBD group was found ($r_{23} = -0.376$, $p = 0.077$). No associations between cardiac activity and childhood traumatization could be found in HC. Because of the exploratory nature of these analyses, we did not correct for multiple comparisons (for more details see **Supplementary Table 1**.).

DISCUSSION

The present study investigated alterations of interoception and its role in emotion processing in IBD. This is the first study to assess interoceptive abilities as multidimensional construct implementing both behavioral and self-report methods. Therefore, we were able to investigate changes in different facets of interoception in IBD and to link these to emotion processing. Furthermore, associations between interoceptive abilities and emotion processing were investigated while taking childhood traumatization into account.

Interoceptive Accuracy

Our findings indicated no differences between IBD and HC in the objective ability to track and perceive internal bodily sensations. These results are in line with previous studies using the same experimental paradigm in somatoform disorders (77), fibromyalgia (78) and irritable bowel syndrome (24). Contrary to out hypothesis, IBD patients did not exhibit greater interoceptive accuracy of cardiac signals. One possible mechanism explaining this finding could be provided by current theories of somatization suggesting that the perception of bodily sensations is based on previously formed symptom-related memory structures (79, 80). Potentially, IBD patients might be more focused on disease-specific visceral signals, which in turn captures cognitive resources and might impede an attentional shift to other internal signals such as their heartbeats. However, future studies need to assess interoceptive accuracy of other internal sensations (e.g., gastric signals) in IBD compared to healthy individuals, in order to provide empirical evidence whether disease-specific bodily sensations might be perceived more accurately. We implemented a short physical challenge to investigate whether activation of the cardiovascular system might influence individuals' abilities to track their heartbeats differentially in healthy individuals and patients with IBD. Our results showed that both groups improved as a non-significant trend in their interoceptive accuracy after the short physical exercise, indicating that induction of increased sympathetic activity elicits increased interoceptive accuracy. To our knowledge, this is the first study to investigate interoception by implementing a physical challenge in adults. Indeed, after the short physical activation participants improved in their interoceptive accuracy, showing that it might be useful to investigate interoceptive abilities after induced physiological arousal.

Interoceptive Sensibility

Although both groups did not differ in their objective abilities to perceive visceral signals (heartbeats), our findings indicate that IBD patients do differ in their subjective interoceptive abilities regarding two main facets of IS: the tendency how to cope with unpleasant bodily sensations ($IS_{\text{not-distracting}}$) and their ability to be focused on the body when experiencing various emotions ($IS_{\text{emotional awareness}}$). Our results show that IBD patients exhibit a stronger tendency to use distraction as a coping mechanism when experiencing discomfort and physical pain. Coping strategies modulate the effects of psychological distress on illness experience in IBD (81). In line with our findings, previous research demonstrated that IBD patients often use self-distracting and avoidance strategies to cope with IBD symptoms (82). In general, distraction is the most common coping style for managing pain in chronic pain patients (83).

The current study expands existing findings on the association between emotional processing and interoception in IBD by showing a greater awareness of the connection between emotional states and bodily sensations in IBD patients. While the perception of visceral signals *per se* does not seem to be changed in remitted IBD patients, it is the appraisal of these sensations, which might be altered. When experiencing an emotion, IBD patients may appraise their bodily sensations differently from healthy individuals by putting greater emphasis on the perceived changes in the body, resulting in grater emotional awareness. Empirical findings from clinical and fundamental research have already demonstrated the physiological effects of gut microbiota on emotional processes, including emotion recognition. Tillisch et al. (84) could show a reduced midbrain connectivity activity and therefore altered activity in brain areas associated with vigilance to emotional stimuli in individuals after a 4-week therapy with probiotics (84). Alterations in gut microbiota, as frequently observed in IBD, might be linked to changes in emotion and sensory related brain regions (85), leading to changes in emotional awareness. Individuals with superior interoceptive abilities perceive emotions as more intense (86), which might be due to greater attention to emotion-related bodily changes and greater awareness of these mind-body associations. From a neurobiological perspective, the neural circuits involved in processing visceral information overlap with those involved in emotional processing (87, 88).

Interoception and Emotional Processing

Our results indicated no group differences in the perceived valence of emotional stimuli. However, when evaluating their subjectively experienced arousal, IBD patients exhibited a greater arousal increase when being presented with neutral compared to positive stimuli. Interoceptive accuracy was not related to emotional processing in the present study. In contrast, $IS_{\text{emotional awareness}}$ was associated with perceived valence and arousal of negative stimuli. Individuals exhibiting superior $IS_{\text{emotional awareness}}$ experienced negative stimuli with a higher intensity, accompanied by higher levels of perceived arousal. However, these associations could be found only in the IBD group but not in HC (**Figure 3**). Our findings indicate that only emotional awareness as part of individual's interoceptive

sensibility and not one's interoceptive accuracy influenced the perception of emotional stimuli. This pattern implies that altered processing of negative emotional content among IBD patients is not connected to changed perception of physiological stimuli but to their appraisal in the context of the emotional experience. These results could, therefore, indicate that the ability to identify and attribute physical sensations to certain emotional states (e.g., increased muscular tension and anger) might intensify patient's tendency to link bodily sensations to environmental triggers. In line with this interpretation, findings from fMRI studies also showed that individuals with high emotional awareness exhibit stronger emotion reactivity (89, 90). This might imply that IBD patients who are more aware of the physiological manifestations of emotions in the body may appraise these as more intense. Furthermore, neural correlates of emotional awareness include brain regions involved in the perception of both interoceptive signals and emotional cues (87, 91), suggesting that higher emotional awareness may be reflected by more efficient information exchange between these brain structures (92). It is conceivable that, although the perception of internal signals (heartbeats) did not seem to be changed, IBD patients might experience more differentiated bodily feelings during emotional experience as result of a changed neural functional connectivity (93). Since our results indicate that only the perception of negative stimuli was linked to emotional awareness, future studies need to investigate whether these effects can be explained by functional and structural changes in brain regions known to be relevant for the processing of negative emotions, visceral sensations, and interoceptive attention, such as the interior insula (91, 94).

The Role of Childhood Traumatization

In contrast to previous findings, the IBD sample in the current study did not report higher levels of ACE compared to HC. A recent study found a significant percentage of IBD patients to have at least one ACE, stressing the possibility that childhood trauma might influence the course of IBD shown by a higher use of health care resources (37). However, in other population-based studies the link between maltreatment during childhood and IBD later in life was found only for Ulcerative colitis, but not for Crohn's disease (4). One possible explanation why the prevalence of ACE was not increased in our IBD sample might be that patients reporting current and/or lifetime psychiatric disorders were not included in the study. Early life stress has been repeatedly linked to higher risk for developing mental health problems. Previous studies investigating the prevalence ACE and IBD took primarily lifetime major depression and generalized anxiety disorders into account (4), but no further psychopathologies. However, none of these studies managed to disentangle the effects of ACE on IBD as well as on anxiety or depression symptoms by now. Further studies are required to investigate whether the interplay between interoception, emotion processing and ACE in IBD patients is influenced by psychiatric co-morbidities.

To the best of our knowledge, this is the first study to investigate the role of childhood maltreatment in interoception, emotional processing and their association. Our findings revealed no associations between ACE and interoceptive accuracy in IBD. Interestingly, we observed that in HC, ACE was negatively related to interoceptive accuracy only after the physical challenge. The implemented physical exercise was used to induce an increase in participants' heart rate and thereby enhanced cardiac signals perception (95). Our findings could, therefore, reflect the long-term negative impact of childhood maltreatment on individual's abilities to perceive visceral signals under conditions of physiological activation. Chronic early life stress leads to altered physiological response to arousal and dysregulation of the brain-body signaling (38, 39). In line, various trauma-related disorders (e.g., PTSD) have been repeatedly linked to altered physiological reactions to external threat cues (96, 97). In this case, threat perception might lead to maladaptive coping mechanism such as suppression and denial of bodily sensations due to overwhelming physiological reactions. In line with this interpretation, physical detachment is often observed in early-traumatized individuals as coping mechanism under high-stress conditions. Our results are also in line with Schaan et al. (38) who found a negative relationship between early life stress and interoceptive abilities only after an acute psychological stressor has been induced. Our findings suggest, however, that a physical stressor is also an eligible method to affect interoceptive accuracy and might be a useful approach to reveal possible associations between interoception and childhood traumatization.

Adverse childhood experiences have been repeatedly linked to impairments in affective processing (98). However, studies investigating the role of childhood traumatization on the link between interoception and emotion processing are sparse. We observed that the association between $IS_{emotional\ awareness}$ and emotional processing of negative stimuli is moderated by severity of ACE independent of IBD diagnosis. This is a novel and interesting finding suggesting that among individuals with histories of childhood maltreatment, greater emotional awareness is associated with stronger intensity of negative affect and higher arousal to negative environmental stimuli. Previously, an attentional bias toward negative stimuli in individuals with ACE have been shown, indicating greater responsiveness to negative cues, heightened emotional response to possible threats and difficulties disengaging from negative emotional content (99). In the context of emotional experience, individuals with histories of childhood maltreatment might use their bodily signals in a more efficient way in order to track and recognize possible threats.

Finally, exploratory analyses of the data revealed higher PTSD symptoms severity including negative alterations in cognitions and mood, hyperarousal and reactivity in the IBD group. Some evidence indicates a higher risk for developing PTSD symptoms in IBD due to the challenges of the disease course most of the patients' experience (44). In summary, these findings emphasize the influence of early life adversity and higher frequency of posttraumatic stress symptoms in IBD. Since posttraumatic stress has been linked to worse IBD course through behavioral and physiological pathway, this might indicate a new possible target for intervention improvement (100).

LIMITATIONS

Finally, some limitations of the present study have to be addressed. First, although we aimed to investigate a bigger sample ($N = 120$), the final sample consisted of 69 participants. Thus, given the smaller sample size larger effect size was needed to detect significant effects. *Post-hoc* sensitivity analyses showed that our study was sensitive to detect effect sized of $d = 0.68$ with 80% power in contrast to $d = 0.52$ for the planned sample size of $N = 120$). Moreover, it should be mentioned that although all IBD patients were in clinical remission, some of them reported minor health problems (e.g., knee pain), whereas all healthy control participants did not declare any health related complaints. In line with other studies using this task, we found relatively poor mean interoceptive accuracy scores between 0.50 and 0.70 (77, 101). Thus, the observed variance in both groups was quite low. It should be emphasized that there is a considerable body of evidence from physiological studies supporting the construct and criterion validity of the HBT (95, 102, 103). Thus, the reported poor validity of interoceptive accuracy measures in some studies result to a large extent from insufficiently controlled experimental environments or non-standardized changes in participant's physiological reactions (e.g., changing body posture during the task) (104). Previous studies found a strong association between cardiac and gastric sensitivity suggesting the presence of a general sensitivity for interoceptive cues across the cardiac and gastric modalities (47, 48). Following these considerations, we decided to use the HBT as a measure of the general interoceptive abilities in IBD. However, a recent study by Ferentzi et al. (105) has suggested that different interoceptive accuracy tasks reveal significant associations only when belonging to the same sensory modality, indicating HBT as a not specific measure of gastrointestinal interoceptive accuracy. In contrast, Whitehead and Drescher (106) could show a moderate correlation between heartbeat perception and perception of gastric contractions, when using the Heartbeat discrimination task, indicating a generalized tendency to be aware of visceral signals. Since both cardiac and gastric signals are transmitted to the brain partially through the vagus nerve, it is conceivable that their perception is closely related. Furthermore, one may critically discuss whether the correspondence between the observed interoceptive accuracy during the heartbeat tracking task and the self-reported interoceptive sensibility indeed reflect the construct of interoceptive awareness (14). A recent model proposed by Murphy et al. (107, 108) stressed the need for a careful differentiation between individual's interoceptive accuracy and interoceptive attention. Accordingly, interoceptive awareness of one's interoceptive accuracy as a metacognitive construct should be assessed as the relationship between one's behavioral performance and the corresponding awareness of particularly this performance, for example, measured by ratings of the participants' confidence in the accuracy of their performance. Thus, in the current study the approach to estimate interoceptive awareness corresponds more closely to the concept of interoceptive attention as to interoceptive awareness when conceptualized as a metacognitive construct [see (107)]. In consequence, further studies are required to investigate whether IBD patients' interoceptive awareness assessed as confidence ratings on their HBT performance might be affected. Finally, it should be mentioned that the severity of ACE in the present sample was only low to moderate (60), which might be due to the exclusion of individuals reporting current or lifetime psychiatric diagnoses. IBD patients reporting moderate traumatization, but no histories of mental disorders might represent a subgroup of patients with a less severe IBD course or resilient individuals who exhibited an adaptive coping with the experiences of traumatization. This restricts the generalizability of our findings to IBD patients with comorbid mental disorders. Since the significance of childhood traumatization in IBD might be underestimated in the current sample, our findings on the influence of ACE in IBD need to be interpreted with caution.

CONCLUSIONS

In conclusion, IBD patients did not exhibit changes in the accuracy to perceive bodily signals such as their heartbeats. Our results demonstrate that the ability to attribute certain physiological sensations to emotional states intensifies the experience of negative emotions among IBD patients. As this population is quite prone to emotional distress and emotion dysregulation, future psychotherapeutic treatments should target patients' appraisals of physiological feedback during negative emotional states. Finally, the present findings point toward the important effect of early life stress on the interaction between mind and body, suggesting that individuals with histories of childhood traumatization might use their bodily sensations more efficiently in order to recognize negative emotional content and possible threats.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty Mannheim, Heidelberg University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KA, WR, and SL designed the study, wrote the protocol, and wrote the first draft of the manuscript. KA, TL, and WR recruited the sample. KA performed data collection and conducted all statistical analyses. SL and WR provided substantive and conceptual feedback on all drafts. All authors contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.680878/full#supplementary-material

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Sexuality in Persons With Hidradenitis Suppurativa: Factors Associated With Sexual Desire and Functioning Impairment

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Hidradenitis Suppurativa (HS) is a chronic skin disease involving intimate and sensitive areas and affecting physical and mental health. We investigated the prevalence of sexual desire and functioning impairment, and their associations with quality of life, anxiety, depression, minor psychiatric disorders (MPD), and clinical features (e.g., disease severity) in 77 patients with HS who completed self-report measures and answered to questions assessing socio-demographic characteristics, lifestyle habits, and hindered sexuality due to HS. The majority of patients reported hindered sexuality, and poor sexual functioning, while showing good levels of dyadic and solitary sexual desire. No associations were found between clinical severity and sexuality measures. Multivariate analyses showed significant associations of sexual outcome measures with alcohol consumption, low Body Mass Index, family history of HS, and severe skin symptoms. Moreover, we found that the presence of negative psychological factors (i.e., MPD, anxiety, poor mental status) increased the risk of sexual impairment. These findings underline the important role of psychological and sexual aspects in HS patients and suggest that physicians should consider the effect of disease burden on patients' sexual health.

Keywords: dermatology, acne inversa, sexual functioning, skin-related quality of life, anxiety, psychological distress, general health

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INTRODUCTION

Hidradenitis Suppurativa (HS) is a chronic, inflammatory, progressive, debilitating skin disease, characterized by painful, deep-seated, inflamed lesions, including nodules, sinus tracts, and malodourous abscesses (1). Literature reviews of previous studies (2, 3) suggested that HS causes a significant impairment of patients' quality of life (QoL) and that depression and anxiety are common comorbidities in individuals with HS. Moreover, people with HS reported high levels of alexithymia and psychological distress (4) as well as the worst quality of life among different skin conditions (5). Finally, due to the localization of lesions in sensitive and intimate body areas, HS may cause embarrassment and shame (5, 6) that hinder sexual activities (7).

Sexuality refers to "perceptions about one's body; the need to touch and connect with others, in both intimate and social settings; interest and ability to engage in sexual behaviors; communication of one's feelings and needs to others; and the ability to engage in satisfying sexual behaviors" (8).

Impairment in sexual functioning can cause different types of maladjustment, including frustration, anxiety, depression, and damaged relationships with partners (9). Most skin diseases may have negative effects on patients' self-perception, body image, and social relationships, causing impairment in sexual functioning (10, 11). The study of Sampogna et al. (12) found that about a quarter of dermatological patients reported sexual problems, with 66.7% of HS patients having the highest level of sexual impairment. This study also showed that sexual problems in the whole sample were strongly associated with depression, anxiety, and suicidal ideation, were generally more frequent in younger patients, and were positively correlated with clinical severity and itch.

Some studies (13, 14) investigated the role of HS in patients' sexual functioning, which "refers to the normal physiological and performance standards" including "sexual desire, sexual arousal, pain-free intercourse, and orgasm" (15). Recently, Cuenca-Barrales et al. (16) reviewed the scientific evidence on HS and sexual health showing that the prevalence of sexual dysfunction in HS patients ranged from 51 to 62% and that potential risk factors for sexual dysfunction were disease activity, symptoms and the absence of a stable relationship. The authors found that an increased frequency of anxiety and depression in HS patients could represent a vicious circle in which sexual functioning impairment can cause, and is consequence of, mood disorders (16).

To the best of our knowledge, little is known about HS patients' sexual desire, which is an important aspect of sexuality (15). According to a biopsychosocial approach, sexual desire can be defined as "the sum of the forces that lean us toward and push us away from sexual behavior" (17). Female Sexual Interest/Arousal Disorder is defined as "Lack of, or significantly reduced, sexual interest/arousal" (18), as manifested by at least three criteria, with a minimum duration of symptoms of 6 months that cause clinically significant distress in individuals. Instead, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) defines Male Hypoactive Sexual Desire Disorder as a "Persistently or recurrently deficient (or absent) sexual/erotic thoughts or fantasies and desire for sexual activity," with the same duration and impact as females (18). Spector, Carey and Steinberg (19) described sexual desire as the thoughts that may prompt individuals to search for or be open to sexual opportunities. These authors also proposed a multidimensional conceptualization of sexual desire, encompassing two domains: interest in dyadic sexual behavior (e.g., desired frequency of intercourse) and interest in individual sexual behavior (e.g., desired frequency of masturbation). The aim of this study was to investigate the prevalence of sexual desire and functioning impairment, and their relationships with QoL, anxiety, depression, psychological distress, and clinical features in patients with HS.

MATERIALS AND METHODS

Sample

Seventy-seven consecutive outpatients with HS, attending the Istituto Dermopatico dell'Immacolata (IDI-IRCCS, Italy) between January 2018 and February 2019, were enrolled at the dedicated HS outpatients' clinic and included in this cross-sectional study. Inclusion criteria were: (1) age 18 years or more; (2) a new diagnosis of HS, or attending the hospital for the first time; (3) history of at least 6 months of HS symptomatology; (4) written, informed consent. Exclusion criteria were: (1) presence of lesions associated with HS in absence of other criteria to fulfill the HS diagnosis; (2) presence of major diseases of the central nervous system; (3) presence of other dermatological diseases or medical comorbidities (e.g., hypertension, diabetes mellitus, or immune-mediated diseases); (4) current major psychiatric disorders; (5) denial of informed consent. The new diagnosis of HS, the history of previous symptoms, and the presence of HS lesions were made by a board-certified dermatologist. The presence of major medical diseases and psychiatric disorders was based on clinical judgment and retrospective assessments. The study was approved by the local Ethics Committee and was carried out in accordance with the 1964 Helsinki Declaration.

Measures

All participants completed a checklist assessing socio-demographic variables, smoking status ("never," "current," "ex-smokers" defined as those who have quit smoking for at least 6 months), alcohol consumption (yes/no), and measured height and weight to calculate Body Mass Index (BMI). Disease severity was assessed using the Hurley staging system (20), the Sartorius score (21), and the International HS Severity Scoring System (IHS4) (22). Pain experienced during the previous week was assessed with the Visual Analog Scale (range 0-10) (23). Other clinical information, including family history, age at onset, disease duration, and number and type of locations involved, was obtained from medical records.

Different measures were used to assess sexual functioning, sexual desire, and hindered sexuality after HS diagnosis. Sexual functioning was assessed using the 19-item Sexual Dysfunction Questionnaire (SDQ). Answers are given on 5-point scale (1: always; 5: never) and a score $\geq$45 indicates the presence of sexual dysfunction (24). A sample item is "I am satisfied with my sex life." Sexual desire was measured with the Sexual Desire Inventory-2 (SDI-2) (19). The questionnaire consists of 14 items, which are rated on a Likert scale, and of two subscales: dyadic sexual desire (items 1-9; maximum score 79) and solitary sexual desire (items 10-14; maximum score 44). Higher scores indicate greater sexual interest. Patients' hindered sexuality was measured using one question with dichotomous answer categories (yes/no): "Is your sexuality hindered by your Hidradenitis Suppurativa?."

Skin-related QoL was assessed with the Skindex-17 questionnaire (25), which measures symptoms and psychosocial aspects. Answers are given on a three-point scale (0: never; 1: rarely/sometimes; 2: often/always), with higher scores indicating a worst skin-related QoL. The 12-item General Health Questionnaire (GHQ-12) was used to assess symptoms of minor psychiatric disorders. Answers are given on a four-point scale. Individuals with scores of 4 or more based on the dichotomous scoring system (0-0-1-1) are defined as GHQ-cases (26). The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression symptoms (27). Both anxiety and

TABLE 1 | Socio-demographic and clinical characteristics of 77 patients with Hidradenitis Suppurativa.

	N† (%)
Sex	
Males	27 (35.1)
Females	50 (64.9)
Age, years	
Mean *(SD)*	33.4 (10.6)
Median (IQR)	31 (25-41)
Education level, years	
Low (≤8)	22 (28.6)
Medium (9-13)	34 (44.2)
High (>13)	21 (27.3)
BMI (kg/m^2)	
≤24.9	31 (40.8)
25-29.9	26 (34.2)
≥30	19 (25.0)
Smoking status	
Never smokers	14 (18.2)
Current smokers	54 (70.1)
Ex-smokers (at least 6 m)	9 (11.7)
Alcohol use	
No	49 (63.6)
Yes	28 (36.4)
Physical activity	
No	54 (70.1)
Yes	23 (29.9)
Age at onset	
<18	32 (41.6)
≥18	45 (58.4)
Disease duration, y	
Mean *(SD)*	11.2 (8.2)
Median (IQR)	10 (5-15)
Family history of HS	
No	68 (88.3)
Yes	9 (11.7)
Hurley stage	
I	25 (32.9)
II	45 (59.2)
III	6 (7.9)
Sartorius score	
0-49	44 (57.9)
50-99	20 (26.3)
≥100	12 (15.8)
IHS4	
Mild (≤3)	14 (18.4)
Moderate (4-10)	22 (29.0)
Severe (≥11)	40 (52.6)
Pain (VAS)	
Mean *(SD)*	5.3 (3.2)
Number of locations involved	
Mean *(SD)*	2.7 (1.5)
Involvement of:	
Groin	62 (81.6)
Axilla	50 (65.8)
Gluteal	32 (42.1)
Mammary region	15 (19.7)
Neck	10 (13.2)
Other‡	10 (13.2)

BMI, body mass index; HS, Hidradenitis Suppurativa; SD, Standard Deviation; IQR, Interquartile Range; IHS4, International HS Severity Score System; VAS, Visual Analog Scale.
† Totals vary because of missing values.
‡ back, sacred region, face.

depression subscales include seven items, each of which are rated on a four-point scale (from 0 to 3) with total scores ranging from 0 to 21. A cutoff of 8 on each subscale is used to identify borderline cases, while a cutoff of 11 is used for identifying clinically significant symptoms of both anxiety and depression. General health status was measured using the 36-Item Short Form Health Survey (SF-36) (28). It includes eight dimensions, which are combined to provide a Physical Component Summary (PCS) and a Mental Component Summary (MCS). Scores for each domain range from 0 to 100, with higher scores indicating better health status.

Statistical Analysis

The characteristics of HS patients were described as means and standard deviations (SD), medians and Interquartile Ranges (IQR) for continuous variables, and as absolute and relative frequencies for categorical variables. Since no cutoffs have been previously determined for the SDI-2, tertiles were calculated for each of the two subscales of the instrument. The lowest tertile (T1) was used as an indicator of low dyadic sexual desire (≤42) and low solitary sexual desire (≤2), respectively.

To explore potential factors associated with sexual dysfunction, we carried out uni- and multi-variate analyses for each of the four indices: sexual functioning (presence vs. absence), dyadic and solitary sexual desire (T1 vs. T2-T3), and hindered sexuality (yes vs. no). In the multivariate analysis we used four separate logistic regression models to estimate Odds Ratio and 95% Confidence Intervals, each for a single index as the outcome. Variables significantly associated with the outcomes in the univariate analysis ($p < 0.10$; see **Supplementary Tables 1a–c**) were included in the multivariate analyses. Starting with sex and age, the likelihood ratio test was used for a forward variable selection in the model. Statistical analyses were performed using STATA, release 15 (StataCorp LLC, College Station, TX).

RESULTS

Table 1 provides descriptive statistics on socio-demographic and clinical characteristics of the 77 HS patients. Participants had a

mean age of 33.4 years (SD = 10.6). The majority of HS patients were females (64.9%), were overweight or obese (59.2%), were current or ex-smokers (81.8%), did not exercise (70.1%), were classified as Hurley II e III (67.1%), and reported severe disease according to IHS4 (52.6%).

Table 2 described variables related to sexual health, skin-related QoL, health status, psychological distress, anxiety and depression. The majority of HS patients reported hindered sexuality and sexual dysfunction (61.8 and 60.8%, respectively). The mean values of dyadic and solitary sexual desire measured with the SDI-2 were 43.3 (SD = 16.5) and 8.9 (SD = 8.3), respectively. Our results showed that disease severity and clinical characteristics were not significantly associated with any sexuality measures (see **Supplementary Table 1b**).

We performed different multivariate models (**Table 3**), each adjusted for sex and age plus variables associated with each of the four outcomes in univariate analyses (see **Supplementary Tables 1a–c**). In the first model, we found that high GHQ scores, and low BMI increased risk of sexual dysfunction, whereas family history of HS decreased risk of it. In the second model, high GHQ scores increased risk of low dyadic sexual desire. In third model, we found that low BMI, and poor mental status increased risk of low solitary sexual desire, whereas alcohol consumption decreased risk of it. In the final model, severe skin symptoms and high anxiety scores increased risk of hindered sexuality due to HS.

TABLE 2 | Sexual health, quality of life, health status, psychological distress, anxiety and depression in 77 patients with Hidradenitis Suppurativa.

	N[†](%)
Hindered sexuality	
No	29 (38.2)
Yes	47 (61.8)
Sexual dysfunction (SDQ)	
Absence (≤44)	29 (39.2)
Presence (≥45)	45 (60.8)
Dyadic sexual desire (SDI-2)	
Mean *(SD)*	43.3 (16.5)
Medium/high (T2, T3)	45 (64.3)
Low (T1)[‡]	25 (35.7)
Solitary sexual desire (SDI-2)	
Mean *(SD)*	8.9 (8.3)
Medium/high (T2, T3)	44 (64.7)
Low (T1)[§]	24 (35.3)
Skindex-17 symptoms	
Not severe (0-49.9)	20 (27.8)
Severe (≥50.0)	52 (72.2)
Skindex-17 psychosocial	
Mild (≤20.82)	13 (18.1)
Moderate (20.83-37.5)	17 (23.6)
Severe (≥37.51)	42 (58.3)
MCS-36	
Mean *(SD)*	35.3 (10.0)
Median (IQR)	34.5 (27.7-43.2)
PCS-36	
Mean *(SD)*	40.9 (10.8)
Median (IQR)	43.3 (33.0-49.1)
GHQ-12	
0-3	38 (50.7)
≥4	37 (49.3)
HADS-Anxiety	
Normal	33 (46.5)
Borderline	10 (14.1)
Positive	28 (39.4)
HADS-depression	
Normal	46 (64.8)
Borderline	15 (21.1)
Positive	10 (14.1)

SDQ, Sexual Dysfunction Questionnaire; SDI, Sexual Desire Inventory; SD, Standard Deviation; T, Tertile; MCS, Mental Component Summary; PCS, Physical Component Summary; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale.

[†] Totals vary because of missing values.

[‡] T1 defined as "low dyadic sexual desire (≤42)".

[§] T1 defined as "low solitary sexual desire (≤2)".

DISCUSSION

In this study, we found a high frequency of hindered sexuality and sexual dysfunction, and a high prevalence of medium/high levels of both dyadic and solitary sexual desire in patients with HS. Previous studies focused especially on sexual functioning impairment. For example, Alavi et al. (29) found that HS patients reported higher sexual dysfunction, impairment in sexual life, and higher sexual distress (i.e., concerns about sexuality), compared to healthy controls. This study also showed that sexual dysfunction predicted a decline in skin-related quality of life in HS patients when controlling for the effects of disease severity (29). Janse et al. (13) found that sexual health was impaired in HS patients, also showing that late onset of HS was associated with poor sexual function, whereas other clinical features, including anogenital involvement, early onset of HS, disease severity, and disease activity, were associated with worse QoL. The association between sexual functioning impairment and disease severity is still controversial. Our results did not show a higher risk of sexual dysfunction associated with increasing disease severity. These findings are consistent with previous studies (13, 14, 16, 29). For example, Kurek et al. (14) found that HS patients had higher sexual dysfunction and sexual distress compared to matched control subjects, whereas severity of cutaneous alterations correlated neither with sexual dysfunctions nor with sexual distress. Because of its clinical manifestations, HS is a debilitating and painful skin disease, which typically involves intimate body areas and affects patients' physical, social, and sexual health. We hypothesize that HS compromise patients' sexual life regardless of disease severity.

The presence of negative psychological functioning increased the risk of worse sexuality in our sample. Indeed, patients with minor psychiatric disorders had an increased risk of having sexual dysfunction and low dyadic sexual desire, whereas

TABLE 3 | Multivariate analysis for factors associated with sexual dysfunction, dyadic sexual desire, solitary sexual desire, hindered sexuality (logistic regression models).

	Sexual dysfunction		Dyadic sexual desire		Solitary sexual desire		Hindered sexuality	
	OR (95%CI)[†]	*P*-value	OR (95%CI)[‡]	*P*-value	OR (95%CI)[§]	*P*-value	OR (95%CI)[¶]	*P*-value
Sex								
Females	1		1		1		1	
Males	0.87 (0.24-3.11)	0.828	0.79 (0.24-2.65)	0.706	0.52 (0.11-2.53)	0.418	0.50 (0.17-1.48)	0.211
Age								
<25.0	1		1		1		1	
25.0-39.9	1.78 (0.44-7.21)	0.422	1.91 (0.45-8.05)	0.381	0.42 (0.07-2.51)	0.338	0.79 (0.20-3.17)	0.745
≥40.0	9.19 (1.38-61.2)	0.022	7.37 (1.46-37.2)	0.016	3.98 (0.56-28.2)	0.166	0.68 (0.15-3.10)	0.620
BMI (kg/m2)								
≤24.9	3.96 (1.11-14.1)	0.033	…		6.27 (1.30-30.2)	0.022	…	
≥25.0	1				1			
Alcohol use								
No					1			
Yes	…		…		0.06 (0.01-0.43)	0.004	…	
Family history of HS								
No	1							
Yes	0.04 (0.005-0.43)	0.007	…		…		…	
GHQ-12								
0-3	1		1					
≥4	7.04 (1.93-25.7)	0.003	5.02 (1.50-16.8)	0.009	…		…	
MCS, tertiles								
Medium/high (T2, T3)					1			
Low (T1)[††]	…		…		8.54 (1.65-44.0)	0.010	…	
Skindex-17 symptoms								
Not severe (0-49.9)							1	
Severe (≥50.0)	…		…		…		3.67 (1.13-12.0)	0.031
HADS-Anxiety								
Negative							1	
Positive	…		…		…		4.40 (1.25-15.5)	0.021

HS, Hidradenitis Suppurativa; T, Tertile; OR, Odds Ratio; CI, Confidence Intervals; BMI, body mass index; GHQ, General Health Questionnaire; MCS, Mental Component Summary; HADS, Hospital Anxiety and Depression Scale.

[†]OR estimate the association of characteristics with presence of sexual dysfunction according to Sexual Dysfunction Questionnaire; ORs adjusted for sex, age, BMI, family history of HS and GHQ-12.

[‡]OR estimate the association of characteristics with low dyadic sexual desire according to Sexual Desire Inventory-2; ORs adjusted for sex, age and GHQ-12.

[§]OR estimate the association of characteristics with low solitary sexual desire according to Sexual Desire Inventory-2; ORs adjusted for sex, age, BMI, alcohol use and MCS tertiles.

[¶]OR estimate the association of characteristics with hindered sexuality; ORs adjusted for sex, age, Skindex-17 symptoms and HADS-Anxiety.

[††]T1 defined as "poor health status".

poor mental status increased the risk of low solitary sexual desire. Moreover, severe skin symptoms according to Skindex-17 and high anxiety were the only factors associated with an increased risk of hindered sexuality. Although previous literature reported associations between severe skin symptoms and both psychological distress (30) and quality of life (31), no previous studies examined the role these factors in negatively affecting sexuality in HS patients. Instead, Esmann and Jemec (7) suggested that severe skin symptoms may interfere with sexuality among HS patients. The authors found that some patients stopped their sexual life because of HS symptomatology and reported that their partners lost interest in them after HS lesions appearance. The latter study also found that HS patients were afraid of others' reaction (e.g., disgust) when they showed hidden parts of their body during sexual intercourse and they were embarrassed to explain their lesions.

Other factors decreased the risk of worse sexuality in our sample. For example, alcohol consumers among HS patients had a decreased risk of having low solitary sexual desire. Although previous research has examined the role of alcohol use in sexual behavior, little is known whether alcohol consumption is associated with sexual desire in dermatological patients. Commonly, alcohol use can influence individuals' sexual attitudes and behaviors, partly due to social disinhibition (32). Martin et al. (33) found that moderate alcohol use predicted a remission of low sexual desire among middle-aged and older men. Smith et al. (34) have shown that alcohol lowered inhibitions and increased the likelihood of engaging in sexual behaviors among women. We hypothesize that HS patients use

alcohol effects to cope with severe physical symptoms (e.g., pain, itching, smell) and this, in turn, may increase solitary sexual desire. Moreover, patients with a family history of HS had a decreased risk of having sexual dysfunction compared to patients without a family history of HS. This result seems to indicate that having a family history of HS may provide social support, which can buffer against embarrassment, shame, and stigmatization that characterize HS patients' experiences (5), especially for sexual activities. This could indicate that family support for HS patients can help these individuals to cope with the burden of the disease. Surprisingly, we found that patients with low BMI had an increased risk of having sexual dysfunction and lower solitary sexual desire in comparison to patients with high BMI. In the general population the links between sexual function and BMI are unclear. Our results differ from those of previous studies, in which obese and overweight individuals reported an increased risk of sexual dysfunction (35, 36). In contrast, Kadioglu et al. (37) did not find significant differences between obese female and healthy control groups for sexual functioning and desire. Although little is known about these associations in HS patients, Theut Riis et al. (38) found that, in HS patients with low BMI, an increase in BMI was a predictor of increased patient-reported severity. Although higher BMI is associated with low sexual desire in the general population, according to Theut Riis et al. (38) we hypothesize that, in our study, HS patients with low BMI perceived worst physical health due to HS lesions appearance, and this, in turn, may have implications for sexual functioning and desire.

This study has some limitations. First, the small sample size limits the generalizability of these findings. However, HS is a rare disease and it is difficult to collect enough data to obtain statistically significant observations. Second, the cross-sectional design prevents us from making causal interpretations. Third, our findings rely exclusively on self-report measures, which raises the possibility of common method variance problems. The use of a multi-method approach (e.g., self-report and psychophysiological measures) is needed to confirm and extend our findings.

Notwithstanding these limitations, our study is among the first to examine the relationship among sexual desire and functioning, and general health status in patients with HS. Our results suggested that HS patients could have many problems in sexual function, while reporting good levels of sexual interest and desire. In this context, we found that many psychological factors, including minor psychiatric disorders, anxiety, and poor mental status, could increase the disease burden, predisposing to a greater risk of sexual difficulties. Our findings underline the important role of psychological aspects in HS patients, according to previous conclusions (3), and suggest that physicians should consider the impact of HS on patients' sexual health during assessment and management of the disease. A multidisciplinary therapeutic approach is recommended: in addition to medical prescriptions, HS patients could improve their mental and sexual functioning through specific psychological treatments, such as Cognitive-Behavioral Therapy and Educational Interventions, Sex Therapy, and Rational Emotive Therapy, which have been shown to be effective in previous studies (39). Given the importance of many psychological variables in HS sexual health, dermatologists should also pay more attention to different aspects of distress and suffering, in order to prevent a worsening in sexual function and mental health.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico IDI-IRCCS. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RMQ and DA designed the study. RMQ, SM, FS, DA, and LI drafted the article. RMQ, LF, and RF administered the questionnaires and collected clinical data. SM and SF carried out the statistical analysis. All authors significantly contributed to the editing of manuscript, data interpretation, discussion, reviewed, and approved the final version for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.729104/full#supplementary-material

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The Effect of Yijinjing on the Cognitive Function of Patients With Chronic Schizophrenia

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Background: Patients with chronic schizophrenia present cognitive impairment, which affects their social function and prevents them from reintegrating into society. Yijinjing is a traditional Chinese aerobic exercise that has a putative psychosomatic effect on improving cognitive function.

Methods: From January to May 2021, 40 patients with chronic schizophrenia were recruited and randomly divided into a control group and a Yijinjing group. In the 12-week intervention, the patients in the control group received conventional treatment, whereas patients in the Yijinjing group performed Yijinjing exercise (40 min/session, twice a week) in addition to receiving conventional treatment. The Positive and Negative Syndrome Scale (PANSS), the Insight and Treatment Attitude Questionnaire (ITAQ), the Rosenberg Self-esteem Scale (SES), and the Mini Mental State Examination (MMSE) were used to measure clinical symptoms and cognitive function at 0, 6, and 12 weeks.

Results: The demographic information was not significantly different between groups. At baseline, the scores of all the scales were not statistically different between groups. After 12 weeks of intervention, compared to those at baseline, the scores of the negative scale ($t = 19.00$, $p < 0.0001$), general psychopathology scale ($t = 15.98$, $p < 0.0001$), and total score ($t = 15.47$, $p < 0.0001$) of the PANSS and SES ($t = 5.378$, $p < 0.0001$) had significantly decreased, and the scores of the ITAQ ($t = 7.984$, $p < 0.0001$) and MMSE ($t = 6.750$, $p < 0.0001$) had significantly increased in Yijinjing group; the score of the MMSE increased in the control group as well ($t = 2.491$, $p = 0.0222$). Compared to the respective scores in the control group, the negative scale score ($t = 2.953$, $p = 0.0054$) significantly decreased, and the ITAQ ($t = 3.043$, $p = 0.0042$) and MMSE ($t = 2.2.68$, $p = 0.0291$) scores significantly increased in the Yijinjing group after 12 weeks of intervention.

Conclusion: These results provide a preliminary indication that Yijinjing exercise had the potential to improve cognitive function and negative symptoms in patients with chronic schizophrenia. A larger-scale study to determine the trajectory of change in the longer term should be undertaken.

Keywords: aerobic exercise, cognitive function, psychosomatic medicine, Qigong, schizophrenia, traditional Chinese medicine, Yijinjing

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INTRODUCTION

Schizophrenia is a severe mental disorder that affects 1.13 million people worldwide, and the age-standardized incidence rate in China was 19.81 in 2017 (1, 2). The three core symptoms of schizophrenia are positive symptoms (e.g., hallucinations and delusions), negative symptoms (e.g., blunted affect and avolition), and cognitive impairment (e.g., memory impairment and processing speed inefficiency) (3). Antipsychotics are the first-line medications prescribed for schizophrenia; however, they are accompanied by many adverse effects, such as metabolic dysfunctions, obesity, or even cognitive impairment (4–6). Clinical studies have demonstrated that patients with chronic schizophrenia have a higher risk of metabolic syndromes and worse cognitive function than first-episode patients (7, 8). Self-awareness is a pivotal component of cognitive function, and patients with schizophrenia have severe cognitive dysfunction that is non-specific for this deficiency (9). Therefore, the health management of patients with chronic schizophrenia is a difficult task for psychiatrists and caregivers.

Aerobic exercise can fight metabolic syndrome in obese people and is beneficial to cognitive improvement in people with mental disorders (10, 11). In recent years, accumulating evidence has suggested that physical exercise and physical activity can help to prevent and treat schizophrenia or rehabilitate patients with the disorder (12, 13). Another meta-analysis showed that meditation-based mind–body interventions had potential efficacy in improving mental health, and no serious adverse effects were reported (14). Moreover, Chinese healthy policies encourage sports, especially traditional Chinese exercises, to play an active role in the prevention, treatment, and rehabilitation of chronic diseases (15). By the inspiration of the aforementioned methods and policies, we believed that the integration of exercise and medicine may exert a therapeutic effect on mental disorders.

Yijinjing, similar to Tai Chi or Baduanjin, is a traditional physical exercise in China. The origin of Yijinjing cannot be verified today; the legend states that the Yijinjing was developed based on the movements of the 12 animals by Bodhidharma. Although Yijinjing was invented as a martial art in the first place, it later became a daily exercise method for ordinary people. Literally speaking, the purpose of Yijinjing is to strengthen the flaccid and frail tendons and sinews; in Chinese, *yi* means "change," *jin* means "tendons and sinews," whereas *jing* means "methods." The five core rules of Yijinjing are quietness, slowness, extension, pause, and flexibility. It emphasizes the combination of symmetrical physical postures, meditative mind, and breathing techniques in a harmonious manner (16). Therefore, we hypothesized that Yijinjing integrated with the conventional treatment for schizophrenia may exert a psychosomatic effect in patients with cognitive impairment. To test our hypothesis, a randomized controlled trial was conducted by recruiting chronic schizophrenia patients with stable clinical symptoms and evaluating the improvement of cognitive function after 12 weeks of Yijinjing intervention.

MATERIALS AND METHODS

Study Design and Patients

In accordance with the principles in the Declaration of Helsinki, the study was approved by the ethics committee of Shanghai No. 1 Mental Health Center of Civil Administration (no. YJZXLL2021001) and registered in the Chinese Clinical Trial Registry (no. ChiCTR2100046078). The anonymized patient records were uploaded to the Clinical Trial Management Public Platform. All participants were inpatients from Shanghai No. 1 Mental Health Center of Civil Administration between January and May 2021 and signed the informed consent forms. The hospital is responsible for the rehabilitation of patients with mental disorders, and only for male patients who are unable to return to society and have to maintain therapy. The inclusion criteria were as follows: (a) met the diagnosis criteria of the 10th revision of the *International Classification of Diseases* (*ICD-10*) for schizophrenia, (b) stable mental symptoms, and (c) a disease course of at least 20 years. The exclusion criteria were as follows: (a) comorbidity of other mental disorders, (b) loss of hearing or eyesight, (c) severe cognitive function impairment, and (d) comorbidity of other diseases that did not fit this study, such as physical disabilities or brain lesions.

Data Collection

Demographic characteristics, including age, sex, course, hospitalization year, years of education, and medication information, were collected at baseline (0 weeks). The antipsychotic doses were converted to equivalent doses of chlorpromazine using the defined daily dose method recommended by the World Health Organization. At 0, 6, and 12 weeks, clinical symptoms were measured by the Positive and Negative Syndrome Scale (PANSS), insight was assessed by the Insight and Treatment Attitude Questionnaire (ITAQ), self-esteem was assessed by the Rosenberg Self-esteem Scale (SES), and global cognitive function was measured by the Mini Mental State Examination (MMSE). The PANSS is used for measuring symptom severity of patients with schizophrenia and recommended by *ICD-10*. The ITAQ, SES, and MMSE were used not only in patients with schizophrenia, but we also used them to interpret the relevant symptoms of the patients. All scales (Chinese versions) have been reported and validated previously (17–19). The scales were evaluated by three senior psychiatrists, and a consistency test was performed with the intraclass correlation coefficient before evaluation.

Yijinjing Exercise

The patients were randomly assigned to either the control group or the Yijinjing group in accordance with the random number table. The patients in the control group received conventional treatment (e.g., antipsychotic treatment and proper exercise), whereas patients in the Yijinjing group received Yijinjing training in addition to conventional treatment. The Yijinjing exercise was practiced 40 min/d (1 h away from a meal) twice a week for 12 weeks; in the meantime, the patients in the control group were staying in their room, taking a nap, or watching TV. The exercise consisted of four parts: (a) warm-up for 5 min, (b) static

TABLE 1 | Sociodemographic characteristics of patients with chronic schizophrenia.

Items	Control group	Yijinjing group	*t*	*P*
Sex (male)*	20 (100)	20 (100)		
Age (years)#	53.40 ± 7.04	53.00 ± 8.13	0.166	0.8688
Course (years)#	31.75 ± 5.31	31.10 ± 7.63	0.313	0.7562
Hospitalization (years)#	12.65 ± 6.48	14.15 ± 8.22	0.641	0.5254
Education (years)#	10.95 ± 2.24	9.80 ± 1.82	1.783	0.0826
Antipsychotics				
Aripiprazole*	1 (5)	3 (15)		
Chlorpromazine*	1 (5)	4 (20)		
Clozapine*	6 (30)	2 (10)		
Olanzapine*	3 (15)	1 (5)		
Quetiapine*	3 (15)	4 (20)		
Risperidone*	6 (30)	5 (25)		
Defined daily dose (g)#	352.50 ± 117.50	375.00 ± 121.90	0.594	0.5559

**Reported as n (%). #Reported as mean ± SD.*

exercise for 5 min (meditative mind and breathing practice), (c) Yijinjing exercise for 25 min, and (d) relaxation exercise for 5 min. The exercise was practiced indoors; an exercise coach guided the patients in every part. In the static exercise, the coach led the patients into a meditative state and taking abdominal breathing accompanied by soothing music. The whole set of Yijinjing exercises consisted of 12 postures and was described previously by Xue et al. (20). In the Yijinjing exercise, the patients followed the teaching video, the coach instructed all postures to every participant in the same sequence throughout the trial, and each posture was asked to be as standard as possible based on their ability. After the exercise, the patients were organized for experience exchange and discussion, and the patients were encouraged to practice by themselves every day.

Statistical Analysis

All of the data are presented as the mean ± SD. IBM SPSS Statistics software was used for data analysis. The Kolmogorov–Smirnov test was used to test for normality. For normally distributed data, intragroup differences were analyzed by paired *t*-tests, whereas intergroup differences were analyzed by *t*-tests. For data that were not normally distributed, group differences were examined using the Kruskal–Wallis test, followed by the Mann–Whitney *U*-test. $p < 0.05$ was considered statistically significant.

RESULTS

Background Information of Subjects

Forty patients with chronic schizophrenia who met the inclusion criteria and did not meet the exclusion criteria were invited, and all of them participated in our study with a response rate of 100%. As they were in stable clinical symptoms, they signed the informed consent forms by themselves. Generally, the participants were in middle to old age (range, 37–69 years), with a long course of schizophrenia (range, 20–43 years) and long-term hospitalization (range, 3–38 years). They were randomly divided into a control group ($n = 20$) and a Yijinjing group ($n = 20$), and none of them dropped out during the study. As shown in **Table 1**, age, sex, course, hospitalization year, years of education, and medication information between groups were not statistically different (all $p > 0.05$).

Scores of Scales in Different Groups

As shown in **Table 2**, all the scores of the scales were not statistically different between the control group and the Yijinjing group at baseline (all $p > 0.05$). After 6 weeks of intervention, the SES scores decreased ($t = 4.560$, $p = 0.0005$) and MMSE scores increased ($t = 3.684$, $p = 0.0016$) in the Yijinjing group compared to those at baseline. After 12 weeks of intervention, compared to those at baseline, the scores of the negative scale ($t = 19.00$, $p < 0.0001$), general psychopathology scale ($t = 15.98$, $p < 0.0001$), and total scores ($t = 15.47$, $p < 0.0001$) of the PANSS and SES ($t = 5.378$, $p < 0.0001$) had significantly decreased and the scores of the ITAQ ($t = 7.984$, $p < 0.0001$) and MMSE ($t = 6.750$, $p < 0.0001$) had significantly increased in the Yijinjing group; the score of the MMSE increased in the control group as well ($t = 2.491$, $p = 0.0222$). After 12 weeks of intervention, compared to the respective scores in the control group, the negative scale score ($t = 2.953$, $p = 0.0054$) significantly decreased, and the ITAQ ($t = 3.043$, $p = 0.0042$) and MMSE scores ($t = 2.2.68$, $p = 0.0291$) significantly increased in the Yijinjing group.

DISCUSSION

In China, primary mental health centers or community medical institutions are the main force for the rehabilitation of patients with chronic schizophrenia (21). Therefore, how and when patients with chronic schizophrenia can regain social function and return to society are primary concerns for doctors and nurses in those institutions. Previous studies have shown that Yijinjing can improve anxiety, depression, and sleep quality for college students (22). A recent clinical trial intended to use Yijinjing to improve the cognitive impairment in post-stroke

TABLE 2 | Scale scores of two groups in different time point (mean ± SD).

Scales	Control group ($n = 20$)			Yijinjing group ($n = 20$)		
	0	6	12	0	6	12
PANSS	67.80 ± 15.08	68.50 ± 14.77	66.40 ± 15.55	69.45 ± 13.57	67.70 ± 13.59	58.95 ± 12.39*
Positive scale	12.70 ± 6.11	12.40 ± 6.16	12.45 ± 6.59	12.65 ± 4.52	12.25 ± 4.42	12.10 ± 3.95
Negative scale	22.10 ± 4.80	22.80 ± 4.48	21.95 ± 4.76	24.35 ± 5.18	24.00 ± 5.33	17.70 ± 4.33*#
General psychopathology scale	33.00 ± 7.45	33.30 ± 7.59	32.00 ± 7.28	32.45 ± 6.83	31.45 ± 6.64	29.15 ± 6.56*
ITAQ	5.70 ± 5.09	5.65 ± 4.90	5.85 ± 5.17	7.90 ± 6.30	8.45 ± 5.98	11.35 ± 6.21*#
SES	19.60 ± 1.98	19.40 ± 2.23	19.40 ± 1.93	20.15 ± 1.56	19.15 ± 1.09*	18.85 ± 1.18*
MMSE	26.80 ± 2.39	27.25 ± 2.29	27.60 ± 2.50*	26.85 ± 2.16	27.35 ± 2.32*	29.00 ± 1.17*#

ITAQ, insight and treatment attitude questionnaire; MMSE, mini mental state examination; PANSS, positive and negative syndrome scale; SES, self-esteem scale.
**Vs. 0 weeks, $p < 0.05$. #Vs. control group, $p < 0.05$.*

patients; however, the result is still in progress (20). To the best of our knowledge, we are the first to introduce Yijinjing to schizophrenia patients, and we found that the integration of Yijinjing exercise and conventional treatment for schizophrenia can improve negative symptoms and cognitive function in patients with chronic schizophrenia.

To date, there are many interventions for schizophrenia patients with cognitive impairment, even some third-generation antipsychotics had promising efficacy on cognitive symptomatology associated with schizophrenia (23). The accumulative studies suggested that aerobic exercise seemed most beneficial to cognitive functioning in patients with schizophrenia (24, 25). A meta-analysis showed that aerobic exercise had significant positive effects on preventing age-related hippocampal deterioration, which may be the mechanism for improving cognitive impairment in patients with schizophrenia (26). The exercise type, intensity, and duration of aerobic exercise and the physiology and pathological state of the participant are worth considering (27, 28). Previous studies demonstrated that all intensities of exercise can improve the symptoms and cognitive function of schizophrenia, whereas moderate-intensity showed better benefits (29–31). Yijinjing is a moderate-intensity physical exercise, and the result is in line with previous research. A recent meta-analysis showed that global cognition can be protected by multicomponent exercise in mild cognitive impairment (MCI) patients. Another meta-analysis suggested that aerobic exercise at moderate intensity or above and a total training duration of >24 h can lead to a more pronounced effect on global cognition (32, 33). In our study, the total training duration of Yijinjing was 16 h. The possible explanation for the difference in total training duration was that we only recorded the time when they trained with the coach; perhaps, they practiced on their own in their spare time. Moreover, the integrated interventions targeting both neurocognition and social cognition may optimally improve functional outcomes in schizophrenia (34). The integration of neurocognitive interventions with Yijinjing may be more effective in improving cognitive function; however, it requires further investigation.

Previous studies indicate that traditional Chinese physical exercise (e.g., Tai Chi and Baduanjin) may improve cognitive function in elderly individuals and patients with MCI (35–37). On the other hand, meditation-based mind–body therapies also showed benefits to cognitive function and negative symptoms of schizophrenia (14, 38). Our randomized controlled trial is consistent with the previous studies. The results showed that the Yijinjing exercise can help antipsychotics to improve negative symptoms and schizophrenia symptoms (PANSS), insight (ITAQ), and global cognitive function (MMSE) in patients with chronic schizophrenia. Although the therapeutic mechanism of Yijinjing is still not clear, the advantages of Yijinjing may be as follows: first, unlike aerobic exercise (e.g., jogging or square dancing), Yijinjing exercise emphasizes the meditative and breathing practice, which may relax the mind and mood; second, unlike static exercise (e.g., meditation or Zen), Yijinjing strengthens the body and mind by active working; third, based on the theory of traditional Chinese medicine, Yijinjing can help to promote and circulate the qi and blood through the body. Therefore, Yijinjing exerts the therapeutic effect in a psychosomatic manner.

Given the preliminary nature of this study, the study has limitations that future studies can address. First, the sample size was small, and all the patients were male. Because of the particularity of our hospital, we are a primary mental health center and hospitalized only male patients. We attempted to minimize selection bias using a randomized experimental design, but only 40 patients who met the criteria participated in our study. Fortunately, none of them dropped out during the study. Second, the patients, psychiatrists, and exercise coach could not be blinded, which may have led to performance bias. Third, it is possible that the patients in the Yijinjing group benefited from positive features that are inherent to group-based exercises (e.g., social interactions and attention from exercise coaches). Fourth, as the average age of patients in our study was older than 50 years, and the MMSE is characterized by simplicity and ease of operation, the MMSE was chosen as the cognitive impairment measurement in this study. However, there are some specialized scales for cognitive measurement of patients with schizophrenia, such as the Brief Assessment of Cognition in Schizophrenia and MATRICS Consensus Cognitive Battery, and we may use those measurements in further study (39, 40). Fifth, patients with schizophrenia also have sleep problems such as sleep continuity

problems, sleep depth, and REM pressure alterations, which may increase the suicide rate (19, 41). In this study, we paid attention only to the benefits of cognitive functions brought by Yijinjing, while we neglected the adverse effects brought by insomnia, and we would factor in sleep quality in our further trials. In addition, exercise intervention has been reported to relieve antipsychotic-induced metabolic dysfunction (42); however, we did not investigate these aspects.

In conclusion, these results provide a preliminary indication that the integration of Yijinjing exercise and conventional treatment for schizophrenia contributes to the improvement of cognitive function in chronic schizophrenia patients and is sufficiently provocative to warrant further investigation. Thus, a larger-scale study to determine whether Yijinjing would result in improved multidimensional clinical measures of cognitive function should be undertaken in the longer term.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai No. 1 Mental Health Center of Civil Administration. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HG, CL, and J-HC designed the study. HG, R-PL, L-NJ, H-JQ, and QL collected data and performed clinical trial. CL, S-JT, and N-NL analyzed data. HG and CL wrote the main manuscript text. CL and J-HC administrated the study. All authors reviewed the manuscript.

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The Relationship of Food Addiction With Other Eating Pathologies and Impulsivity: A Case-Control Study

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The concept of food addiction (FA) has become central in recent years in understanding the psychological etiology of obesity. In this matched case-control study from Turkey, it was aimed to examine the prevalence of FA and related risk factors in four consecutive body mass index (BMI) categories. The case group consisted of pre-operative bariatric surgery patients with BMI over 35.0 kg/m^2 ($n = 40$) and the control group was composed of age- and gender- matching individuals from the other categories, namely obese ($n = 35$), overweight ($n = 40$), and normal weight ($n = 40$). The Yale Food Addiction Scale (YFAS) and a standardized clinical interview using the DSM-5 substance use disorders criteria adopted for FA, the Eating Disorder Examination Questionnaire (EDEQ) and the Barratt Impulsivity Scale (BIS-11) were used as assessment instruments. It was found that FA was significantly associated with more serious eating pathologies, more frequent weight-cycling and earlier onset of dieting, higher impulsivity, and higher BMI. Motor and total impulsivity scores showed a positive albeit week correlation with the severity of FA but no significant correlation with BMI, indicating a relationship between impulsivity and weight gain in some but not all individuals. The severity of FA predicted the increase in BMI. Our findings suggest that FA is associated with weight gain in a group of individuals, plausibly through impulsive overeating. Emphasis on FA and its clinical implications such as addiction-based treatments may improve outcomes in obesity and facilitate health promotion.

Keywords: body mass index, food addiction, obesity, eating disorders, impulsivity

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INTRODUCTION

Obesity is an escalating epidemic in wealthy countries as well as in developing countries and a major cause of preventable deaths worldwide (1, 2). According to a report published by the World Health Organization (WHO) in 2016, more than 1.9 billion adults were overweight (39% of the world population) and of these, over 650 million (13%) were obese (3). As reported in 2019, more than half of the population in 34 out of 36 OECD member countries is overweight and almost one in four people are obese (4). The low rate of success of treatments to prevent or reverse obesity and the significant rate of relapses indicate that obesity might not only be explained as a metabolic disorder but also as a behavioral alteration (5, 6). Recent clinical and neurobiological findings refer to an addictive process contributing to an elevated body mass index (BMI) (7, 8). Based on these, the concept of food addiction (FA), namely the idea that certain highly-processed and "hyperpalatable"

foods may have an addictive potential and that certain eating behaviors might be categorized as an addictive behavior was introduced (9–12). Furthermore, an assessment tool was developed based on the addiction criteria listed in the DSM-IV in 2009 (13).

Within a decade after the introduction of the concept, a growing number of clinical and neurobiological studies discussing FA have been published. Experiments with animals and neuroimaging studies in clinical and general populations have shown that individuals with FA demonstrate differences in the dopaminergic activation and functional connectivity of brain reward circuits, including subcortical regions such as amygdala, insula, nucleus accumbens, and ventral striatum (14–16), and some studies also indicate structural variations in reward circuit elements (17), as well as inhibited control of frontal circuits and executive functions such as planning and decision-making (18). A more detailed look reveals that especially processed foods with added sweeteners and fats, and those with high salt (sodium), fat, and sugar content which are calorie-dense have the greatest addictive potential (14, 19, 20), triggering reward mechanisms of the brain and resulting in a "conditioned hypereating" (21). Food addiction has been linked with not only changes in brain circuits but also with alterations in peripheral intestinal, immune, and metabolic mechanisms (20).

However, a well-agreed definition has not yet been established and there is no consensus on the details of this issue. While some authors strongly advocate for the impact of FA on the development of obesity (9, 10) some other experts find the concept unsupported (22), indicate that there is limited evidence (23), or evaluate it as a misnomer (24). Some researchers argue that this concept might lead to the overmedicalization of eating behaviors (25).

Food addiction has been criticized as lacking distinction from other eating disorders as a diagnosis (14, 23). Studies point to a high rate of overlap between FA and binge eating disorder (BED), which are both related to obesity, and in both of which there is an uncontrolled consumption of food and lack of delaying behavioral reactions to food-related stimuli (26, 27). In order to delineate the FA diagnosis from other eating pathologies, it is crucial to investigate factors associated with FA, such as personality factors including reward-sensitiveness and impulsivity which also contribute to the development of other addictions (28–30), in greater depth to establish a more comprehensive and solid model. Considering the changes in the understanding and evaluation of substance-use disorders in the DSM-5, it has become instructive to compare FA to recently updated diagnostic criteria as well (31). Further studies conducted in various settings are required to promote FA to a diagnostic category of universal validity.

In Turkey, the prevalence of obesity is sharply rising, for all genders, in adults and adolescents (32, 33). When compared with the WHO Europe Zone countries, the prevalence of obesity is slightly lower than the European average in men (21.5%), which is around the average in women (24.5%). However, studies assessing FA as a contributing factor to the development of obesity are relatively scarce (29, 34–37).

The aim of this study was to identify the prevalence of FA in a Turkish sample consisting of different BMI classes and to examine the relationship between FA and BMI, focusing on prominent risk factors in addiction including impulsivity. It was hypothesized that FA is related to higher BMI and more frequent dieting. Moreover, it was hypothesized that among other factors, impulsivity is independently associated with FA and the development of obesity.

MATERIALS AND METHODS

This study was designed using a matched case-control model. Considering the reported prevalence of FA in the clinical population (29, 38, 39), a sample size of 40 was calculated using a Raosoft sample size calculator, providing a confidence level of 95%, and a margin of error of 5% (40). Therefore, 40 consecutive morbidly obese patients with a BMI >35.0 kg/m^2 who were evaluated for bariatric surgery at the Marmara University Hospital between 2016 and 2017 who fulfilled the inclusion criteria were recruited as the case group. The control group consisted of age and gender-matched individuals from three other BMI categories, namely obese ($n = 35$), preobese/overweight ($n = 40$), and normal weight ($n = 40$), who were not seeking treatment. Ethical approval for the study was received from Marmara University School of Medicine Local Ethical Committee (Protocol Number 09.2015.244), in accordance with the Declaration of Helsinki. Participation was voluntary in all groups upon informed consent.

The inclusion criteria for the study were defined as being in the ages 18–65, being literate and complying with the instructions, and agreeing to participate in the study. The exclusion criteria were defined as having a severe decompensated medical condition such as acute myocardial infarction, severe respiratory and/or cardiac failure, cerebrovascular disease, cirrhosis, pregnancy (for women), and intellectual/cognitive disability that would not allow reading and understanding the informed consent and cooperating with the clinician for an interview.

A semi-structured interview was conducted to obtain sociodemographic data, clinical characteristics, and eating habits of the participants. The prevalence of eating disorders and subtypes was assessed using structured clinical interviews conducted by researchers based on the DSM-5 criteria. Eating disorder symptomatology was evaluated using the Turkish version of the Eating Disorder Examination Questionnaire (EDEQ) (41, 42). Food addiction diagnosis was assessed using the Turkish version of the Yale Food Addiction Scale (YFAS) (13, 38) and with the semi-structured clinical interview adopted by the researchers from DSM-5 substance use disorder criteria. Finally, impulsivity was assessed using the Turkish version of the Barratt Impulsivity Scale-11 (BIS-11) (43, 44).

Gender, employment, perceived income, and education were included as sociodemographic variables and assessed using descriptive statistics. Body mass index; accompanying medical disorders, current tobacco and alcohol use, dieting attempts,

TABLE 1 | Mean BMI and sociodemographic characteristics of participants.

	Normal (*n*:40)	**Preobese/Overweight (*n*:40)**	**Obese (*n* = 35)**	**Morbid obese (*n* = 40)**		***p***
BMI (mean ± SD)	22.13 ± 1.92	27.22 ± 1.27	32.74 ± 2.59	45.17 ± 4.92		<0.001*
Age (mean ± SD)	32.50 ± 6.34	36.10 ± 7.41	35.77 ± 6.39	36.05 ± 8.47		0.06†
	Min: 20	Min: 24	Min: 23	Min: 21		
	Max:46	Max:52	Max: 47	Max: 54		
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	χ^2	***p***
Gender						
Women	33 (82.5)	30 (75.0)	28 (80.0)	32 (80.0)	0.35	0.95
Men	7 (17.5)	10 (25.0)	7 (20.0)	8 (20.0)		
Education						
High School or below	21 (52.5)	26 (65.0)	20 (57.1)	25 (62.5)	1.54	0.67
Graduate or above	19 (47.5)	14 (35.0)	15 (42.9)	15 (37.5)		
Employment						
Currently employed	31 (77.5)	27 (67.5)	25 (71.4)	26 (65.0)	3.98	0.26
Currently unemployed	9 (22.2)	13 (32.5)	10 (28.6)	14 (35.0)		
Marital status						
Non-married	19 (47.5)	9 (22.5)	14 (40.0)	15 (37.5)	5.65	0.12
Married	21 (52.5)	31 (77.5)	21 (60.0)	25 (62.5)		
Perceived economic status						
Low	6 (15.0)	3 (7.5)	2 (5.7)	6 (15.0)	8.96	0.44
Low–Average	18 (45.0)	23 (57.5)	20 (57.1)	16 (40.0)		
High–Average	14 (35.0)	13 (32.5)	13 (37.1)	18 (45.0)		
High	2 (5.0)	1 (2.5)	0 (0.0)	0 (0.0)		

*Assessed with ANOVA, $F_{(3, 119)} = 372.17$, $p < 0.05$.

†Assessed with ANOVA, $F_{(3, 118)} = 2.51$, $p = 0.062$.

presence of eating disorders, and BIS-11 scores were assessed as independent variables. Chi-square tests were used for categorical variables. Normality distribution of continuous variables was assessed using the Shapiro-Wilk test and means were compared using Student's *t*-tests. Predicting factors of FA were assessed by logistic regression analyses in which FA diagnosis was the dependent variable and sociodemographic and clinical factors, impulsivity scores, and the presence of an eating disorder diagnosis were the independent variables. Statistical significance was set at p <0.05. To compare multiple groups, a statistical significance level of 0.0083 was accepted following Bonferroni correction ($k = 4$). SPSS 22.0 was used as a software program to compute the data.

RESULTS

Descriptive Characteristics of the Case and Control Groups

The case group, consisted of 40 individuals (32 women, 8 men) with a BMI over 35.0 kg/m^2 had a mean age of 36.05 ± 8.47 years. The control group of consecutive three BMI categories (normal, preobese, and obese) included individuals with a mean age of 32.50 ± 6.34, 36.10 ± 7.41, and 35.77 ± 6.39 years, respectively. Within the case group, 65.0% ($n = 26$) had a job at the time of the study and the majority were married ($n = 25$, 62.5%). The highest rate of employment (77.5%, $n = 31$) was among the normal BMI group, yet the difference between the groups did not differ significantly. The case and control groups did not differ significantly in terms of the assessed sociodemographic variables (**Table 1**).

The distribution of BMIs of participants in four BMI categories were normal. The mean BMIs of each group were as follows: 22.13 ± 1.92 kg/m^2 (18.80–25.00), 27.22 ± 1.27 kg/m^2 (25.20–29.80), 32.74 ± 2.59 kg/m^2 (30.0–38.05), 45.17 ± 4.92 kg/m^2 (37.80–58.90). Tobacco and alcohol use and family history were similar among the groups (**Table 2**), however, those with a BMI >30.0 kg/m^2 ($n = 75$) had a significantly higher rate (63.5%) of obesity in family history, when compared to the rest ($\chi^2 = 23.19$, $p < 0.01$). The morbidly obese group had a significantly higher rate of accompanying chronic medical disorders, namely diabetes, hypertension, and hyperlipidaemia (25, 20, and 10%, respectively).

Food Addiction Symptomatology

The different BMI groups differed significantly in terms of FA diagnosis by both instruments (**Table 3**). Food addiction was found to be more prevalent in the two groups with BMI >30 kg/m^2 (morbid obese, $n = 40$ and obese, $n = 35$) than in the normal ($n = 40$) and overweight ($n = 40$) individuals ($p < 0.01$), as measured by the YFAS (23.8 vs. 0.0%) and DSM-5 clinical interview (57.5 vs. 12.5%). In terms of severe FA as assessed by the

TABLE 2 | Clinical characteristics of participants.

	Normal (*n*:40)	Preobese/Overweight (*n*:40)	Obese (*n* = 35)	Morbid obese (*n* = 40)		
	n (%)	*n* (%)	*n* (%)	*n* (%)	χ^2	*p*
Tobacco use						
Yes	10 (25.0)	16 (40.0)	17 (48.6)	20 (50.0)	6.43	0.09
No	30 (75.0)	24 (60.0)	18 (51.4)	20 (50.0)		
Alcohol use						
Yes	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.5)	8.80	0.03
No	40 (100.0)	40 (100.0)	35 (100.0)	37 (92.5)		
Medical disorders						
Yes	6 (15.0)	12 (30.0)	13 (37.1)	28 (70.0)	27.45	<0.001
No	34 (85.0)	28 (70.0)	22 (62.9)	12 (30.0)		
Family history of chronic medical disorders						
Yes	27 (67.5)	30 (75.0)	30 (85.7)	36 (90.0)	7.53	0.06
No	13 (32.5)	10 (25.0)	5 (14.3)	4 (10.0)		
Family history of alcohol use disorders (AUD)						
Yes	9 (22.5)	8 (20.0)	6 (17.1)	5 (12.5)	1.49	0.69
No	31 (77.5)	32 (80.0)	29 (82.9)	35 (87.5)		
Family history of substance use disorders (SUD)						
Yes	0 (0.0)	1 (2.5)	2 (5.7)	2 (5.0)	2.50	0.48
No	40 (100.0)	39 (97.5)	33 (94.3)	38 (95.0)		
Family history of psychiatric disorders (other than AUD and SUD)						
Yes	11 (27.5)	10 (25.0)	8 (22.9)	7 (17.5)	1.22	0.75
No	29 (72.5)	30 (75.0)	27 (77.1)	33 (82.5)		

DSM-5 (having six or more symptoms), the obesity and morbid obesity group demonstrates 8.88 times higher prevalence than the normal and overweight groups (33.3 vs. 3.7%).

Food addiction diagnosis by both instruments was associated with a higher rate of chronic medical disorders ($\chi^2 = 7.0$, $p < 0.01$) and tobacco and alcohol use ($\chi^2 = 4.20$, $p = 0.04$; $\chi^2 = 5.41$, $p = 0.02$). Dieting and lifetime number of diet attempts were significantly higher in those with FA (11.22 ± 8.23; median 10) than in those without FA (6.89 ± 7.09; median 4) ($z = -2.03$, $p = 0.04$).

The most prevalent symptoms as assessed by the DSM-5 adopted clinical interview were (i) consumption of food in larger amounts or over a longer period than intended (71.3%), (ii) persistent desire or unsuccessful efforts to cut down or control (70.5%), and (iii) craving (45.1%); all indicating loss of control over food. Likewise, persistent desire or unsuccessful efforts to cut down or control (93.9%), tolerance (49.0%), and consumption despite persistent physical or psychological problems caused or exacerbated by it (46.9%) were the most frequently met criteria in YFAS assessments.

Food addiction severity, as defined by symptom count in both assessments, showed a significant correlation between YFAS (out of 7 criteria) and DSM-5 (out of 11 criteria). Greater FA severity correlated with increased BMI. Linear regression analysis showed that the severity of FA, measured as the DSM-5 symptom count predicted an increase in BMI [$F_{(1.153)} = 49.095$, $p < 0.01$, $R^2 = 0.243$]. The BIS-11 total and sub-scale scores did not significantly differ among BMI categories ($z = -1.19$, $p = 0.24$; $z = -1.27$, $p = 0.21$; $z = -0.76$, $p = 0.45$; $z = -0.79$, $p = 0.43$, respectively). Motor and total impulsivity scores showed a positive albeit weak correlation with the severity of FA (assessed by symptom count) but no significant correlation with BMI (**Table 4**).

Eating Disorder Symptomatology

The morbid obesity group had significantly higher rates of current BED (25.0%) and night eating syndrome (27.5%) diagnoses, as assessed by the DSM-5 criteria ($p < 0.001$). The total and sub-scale scores of the EDEQ were not normally distributed. A Kruskal-Wallis assessment revealed that the total and sub-scale scores of different BMI categories differed significantly, showing that higher BMI was associated with higher EDEQ scores. When the FA and non-FA groups were compared, FA was significantly associated with more severe eating symptomatology as assessed by EDEQ (**Table 5**).

Comparison of Food Addiction and Eating Disorders

When morbid obesity, FA, and BED diagnoses were examined together, although comorbidities were present, the majority of FA diagnoses (75%) did not meet the diagnostic criteria for BED. In the morbid obesity group, 22.5% had both FA and BED diagnoses. The comorbid group differed from the FA-only group with greater tolerance ($\chi^2 = 6.10$, $p = 0.01$), failure to fulfill major role obligations ($\chi^2 = 9.93$, $p < 0.01$), and higher attentional

TABLE 3 | Food addiction and eating disorders diagnoses and symptomatology and impulsivity in different BMI groups, as assessed by YFAS and DSM-5 clinical interviews, EDEQ, and BIS-11.

	Normal (*n*:40)	**Preobese/Overweight (*n*:40)**	**Obese (*n* = 35)**	**Morbid obese (*n* = 40)**		
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**	**χ^2**	***p***
YFAS assessment						
FA (–)	40 (100.0)	40 (100.0)	31 (91.2)	34 (85.0)	11.61	<0.001
FA (+)	0 (0.0)	0 (0.0)	3 (8.8)	6 (15.0)		
DSM-5 FA assessment						
FA (–)	35 (87.5)	35 (87.5)	19 (54.3)	10 (25.0)	48.82	<0.001
FA (+)	5 (12.5)	5 (12.5)	16 (45.7)	30 (75.0)		
Mild	1 (2.5)	2 (5.0)	4 (11.4)	6 (15.0)		
Moderate	2 (5.0)	2 (5.0)	3 (8.6)	8 (20.0)		
Severe	2 (5.0)	1 (2.5)	9 (25.7)	16 (40.0)		
DSM-5 eating disorders						
Not present	33 (82.5)	34 (85.0)	24 (68.5)	14 (35.0)	–	–
AN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	–
BN	1 (2.5)	0 (0.0)	0 (0.0)	1 (2.5)	1.90	0.59
BED	1 (2.5)	2 (5.0)	5 (14.0)	10 (25.0)	12.17	<0.001
Atypical AN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	–
Atypical BN	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.5)	2.18	0.54
Atypical BED	0 (0.0)	3 (7.5)	4 (11.4)	3 (7.5)	4.34	0.23
NES	5 (12.5)	1 (2.5)	1 (2.9)	11 (27.5)	15.72	<0.001
					χ^2 KW	***p***
EDEQ scores						
Total	0.65 ± 0.96	1.44 ± 1.01	2.03 ± 1.33	2.40 ± 1.10	48.20	<0.001
Restriction	0.63 ± 1.11	1.34 ± 1.17	1.76 ± 1.46	1.76 ± 1.16	29.30	<0.001
Food concerns	0.36 ± 0.75	0.61 ± 0.64	1.02 ± 1.01	1.31 ± 1.15	28.53	<0.001
Body concerns	0.91 ± 1.12	2.14 ± 1.49	2.93 ± 1.88	3.49 ± 1.70	46.40	<0.001
Weight concerns	0.74 ± 1.03	1.65 ± 1.24	2.41 ± 1.62	3.03 ± 1.38	57.71	<0.001
BIS-11 scores						
Total	59.12 ± 7.44	58.90 ± 8.86	58.32 ±10.20	61.28 ± 8.62	4.74	0.19
Non-planning	26.00 ± 4.63	25.85 ± 4.62	24.97 ± 4.61	26.87 ± 4.75	4.32	0.23
Motor impulsivity	19.22 ± 3.68	19.65 ± 3.68	19.35 ± 4.42	20.76 ± 4.11	3.60	0.31
Attentional imp.	13.90 ± 2.91	13.40 ± 3.24	13.50 ± 3.06	13.64 ± 2.88	1.19	0.76

impulsivity scores ($z = -2.08$, $p = 0.04$). On the other hand, the FA-only group differentiated from the comorbid FA and BED group, as they met the two following BED criteria significantly less frequently: (i) repetitive binge eating episodes and a sense of lack of control over eating during the episode, and (ii) feeling disgusted with oneself, depressed, or very guilty after overeating ($p = 0.02$, $p = 0.06$, respectively).

Finally, a logistic regression was performed to ascertain the effects of age, gender, sociodemographic characteristics, eating disorders and impulsivity on the likelihood that participants had FA. The logistic regression model was statistically significant, [$\chi^2_{(11)} = 33.46$, $p < 0.05$]. The model explained 45.7% (Nagelkerke R^2) of the variance in FA. Women were 6.7 times more likely to exhibit FA than men. The presence of BED (OR: 8.33 %95CI [1.96–22.42]; $p < 0.05$) and higher BIS-11 scores (OR = 1.09 %95CI [1.02–1.23]; $p = 0.03$) independently predicted the diagnosis of FA.

DISCUSSION

In this case-control study assessing the extent of and related factors with FA in different BMI categories, it was found that FA is associated with a higher BMI, an earlier onset of dieting and more frequent diet-weight gain cycles; as well as higher attentional and motor impulsivity. Moreover, the FA symptom count was positively correlated with BMI. Our findings suggest that FA might play an important role in obesity, through loss of control over food consumption in an addictive manner. Therefore, treating FA might be a useful approach in terms of weight loss.

TABLE 4 | Correlation of BMI, FA symptom count, and BIS-11 scores.

	DSM-5 symptom count	YFAS symptom count	BIS-11 non-planning	BIS-11 motor impulsivity	BIS-11 attentional impulsivity	BIS-11 Total
BMI	0.507*	0.561*	0.084	0.122	−0.019	0.085
DSM-5 symptom count	1	0.631*	0.006	0.191†	0.89	0.130
YFAS symptom count	0.631*	1	0.121	0.258*	0.125	0.223*
BIS-11 non-planning	0.006	0.121	1	0.341*	0.436*	0.822*
BIS-11 motor impulsivity	0.191*	0.258*	0.341*	1	0.322*	0.702*
BIS-11 attentional impulsivity	0.089	0.125	0.436*	0.322*	1	0.702*
BIS-11 total	0.130	0.223*	0.822*	0.702*	0.702*	1

*Spearman correlation, $p < 0.01$.
†$p < 0.05$.

TABLE 5 | Comparison of participants with and without food addiction as assessed by two instruments.

	DSM-5 Clinical Interview				YFAS			
	FA (+) ($n = 56$)	FA (–) ($n = 99$)	z*	p	FA (+) ($n = 9$)	FA (–) ($n = 145$)	z†	p
DSM-5 symptom count	5.27 ± 1.93	2.25 ± 1.89	−7.55	<0.01	5.33 ± 1.87	3.17 ± 2.34	−2.61	<0.01
YFAS symptom count	2.83 ± 1.34	1.42 ± 1.06	−6.47	<0.01	4.78 ± 1.30	1.75 ± 1.14	−4.88	<0.01
BIS-11 total	60.90 ± 9.55	58.56 ± 8.25	−1.73	0.83	62.56 ± 9.99	59.20 ± 8.70	−1.10	0.27
BIS-11 non-planning	26.14 ± 4.77	25.83 ± 4.64	−0.67	0.50	25.44 ± 4.33	25.98 ± 4.71	−0.09	0.93
BIS-11 motor impulsivity	20.98 ± 4.75	19.27 ± 3.36	−2.02	0.04	21.56 ± 3.54	25.98 ± 4.71	−1.53	0.13
BIS-11 attentional impulsivity	13.78 ± 2.99	13.45 ± 2.95	−0.69	0.49	15.56 ± 3.17	13.44 ± 2.91	−1.93	0.05
EDEQ total	2.43 ± 1.17	1.16 ± 1.07	−6.10	<0.01	3.07 ± 0.83	1.81 ± 1.50	−3.34	<0.01
EDEQ restriction	1.90 ± 1.33	1.06 ± 1.19	−4.36	<0.01	2.22 ± 1.22	1.30 ± 1.29	−2.28	<0.01
EDEQ eating concerns	1.33 ± 1.02	0.52 ± 0.78	−5.71	<0.01	1.91 ± 0.74	0.74 ± 0.92	−3.64	<0.01
EDEQ body shape concerns	3.52 ± 1.61	1.69 ± 1.60	−6.13	<0.01	4.26 ± 0.87	1.81 ± 1.50	−3.18	<0.01
EDEQ weight concerns	2.98 ± 1.43	1.35 ± 1.31	−6.30	<0.01	3.87 ± 0.83	1.52 ± 1.23	−3.51	<0.01

*Mann-Whitney U-tests were used as groups did not have a normal distribution.
†Mann-Whitney U-tests were used as groups did not have a normal distribution.

The Prevalence of FA Using DSM-IV and DSM-5 Approaches

The prevalence of FA in the morbid obesity group as assessed by YFAS (15.0%) is comparable with that in two studies in the field, in which 15 and 16.9% of bariatric surgery candidates were diagnosed with FA (45, 46). However, there are other studies conducted among individuals undergoing weight-loss surgery in which higher rates such as 21.1% (47), 25.8% (48), 41.7% (49), 53.7% (50), 57.8 (38) were found. This large variation might be due to the self-report nature of YFAS, which is less-objective than a standardized clinical evaluation and that our sample had a lower mean BMI than the aforementioned studies. It is stated that DSM-IV substance dependence diagnosis corresponds to severe substance use disorder of the DSM-5 (51). Given this, the prevalence of FA in the morbid obesity group appears to be 40.0%, implying that DSM-5 criteria might be more permissive in terms of determining FA, whereas YFAS might overlook some cases. Moreover, as YFAS, which is based on the DSM-IV substance dependence criteria does not include craving, which might contribute to lower than actual rates.

Our findings based on the DSM-5 adopted clinical interviews, especially the prevalence of FA in normal-weight and obese individuals, are similar to the findings of the studies conducted using the revised version of YFAS, YFAS 2.0 (52, 53). In accordance with the studies of Meule (54) and Hauck (53), it was found that there was a moderate level correlation between the FA symptom count and BMI ($\rho = 0.56$) and the FA prevalence was nine times higher in individuals with a BMI >30 kg/m^2 than in normal-overweight individuals.

Clinical Characteristics Related With FA

It was found that in the FA group, the dieting onset was earlier and diet-weight gain cycles were more frequent. This also supports that there might be an addictive, relapsing process behind in this subgroup of obese patients, as many other addictions also start during adolescence and early adulthood (55, 56). It is also true that eating pathologies tend to arise during this developmentally sensitive period (57).

Our findings reflect that the impulsivity scores of the case and control groups did not differ significantly from each

other. However, significantly higher attentional and motor impulsivity scores were found in the FA group than in the non-FA group, supporting our hypothesis. This might be related to impaired inhibitory control or the so-called negative urgency in these individuals toward specific food products. The findings can be interpreted as impulsivity not playing a direct role in weight gain but rather contributing to obesity in a subgroup of patients who present with FA. A similar mechanism has been implicated in other studies that explore impulsivity and FA. Higher attentional impulsivity (54, 58, 59), negative urgency (60), inability to delay rewards (61), and controlling impulses in negative mood states (62) were found to be related to FA. One study found that impulsivity persists after bariatric surgery (63), which may also be suggestive of impulsivity and FA as the reason behind unsuccessful weight loss outcomes. Neurocognitive studies also suggest deficits in inhibitory functions and dysfunctional frontostriatal circuits leading to eating pathologies and loss of control over food (14).

Tolerance, withdrawal, and craving constitute the most prominent symptoms of FA, whereas in eating disorders, including BED, weight, and body image related concerns are more critical. It was confirmed in several other studies that some FA patients did not meet the BED criteria and vice versa (64, 65). Although loss of control might be the intersecting symptom of the two diagnoses, it was found that BED is related to the binge eating episodes, that is, eating a substantially large amount of food in a very short time. However, in FA, one of the most important aspects of diagnosing substance use disorder the loss of control is observed throughout the day such as grazing, resulting in eating more than intended or planned and higher caloric intake, in a fashion like tobacco consumption. This finding is parallel to the interpretation of Gearhardt and Meule, who evaluated the concept in light of the DSM-5 (66).

As in our study, female gender was repeatedly found to be associated with FA in other studies (10, 60, 67, 68). It is known that women are more likely to self-medicate than men in the acquisition phase of addiction and show a more rapid escalation of use than men, whereas in general substance use disorders are much more common in men (69). The wide availability of hyperpalatable, high-calorie, and inexpensive food and the contextual and social factors that do not necessarily prevent women from consuming these drugs, contrary to that of illicit drugs, might explain why FA is more frequently observed in women than in men.

In our study, risky alcohol use in the morbid obesity group (7.5%) was higher than the general population rates of risky alcohol use reported in other studies from Turkey (70, 71). Higher rates of risky alcohol use might be interpreted as contributing to the development of obesity. This might also mean a predisposition to addiction in this group. Indeed, the higher rate of risky alcohol use in the FA group than in the non-FA group might be related to the cross-addiction phenomenon, which signifies addiction to two or more substances or behaviors, and is frequently observed in substance-related and addictive disorders (72–74).

Limitations and Strengths of the Study

Our study has some limitations. First, as the study used a cross-sectional method, our findings reflect associations between variables. More prospective and long-term studies, including those which investigate both clinical and neurobiological/hormonal/metabolic correlates of FA are required to better understand the causality. The case and the control groups were not compared for their diet characteristics and food environment which may also play a role in the development of FA. Also, for the classification of body weight, only BMI was used and bioimpedance analysis was not conducted, which would have enabled a more precise comparison, a method that needs to be considered for future studies. The second version of the YFAS, which is prepared in line with the newly established diagnostic criteria for substance use disorder in the DSM-5, was not used, as it had not been validated in Turkish at the time of the study (52). Nevertheless, the contemporary approach to addictive behaviors based on DSM-5 criteria was reflected by means of a clinical interview, which also enabled us to make a complementary evaluation in addition to the self-report assessment by the YFAS. In addition, the inclusion of consecutive BMI groups and comparison of FA-related features provide a more comprehensive understanding of this construct and contribute to the discussions in the field on the validity of FA, which we believe is a strength of this study.

To conclude, our findings support the view that a group of obesity patients demonstrate characteristics of addictive behaviors and FA contributes to the development of obesity, plausibly through impulsive but not-episodic over-eating. However, FA explains only part of the variance in BMI, which is in accordance with the multiple etiologies of obesity. Further neurobiological and clinical studies in different patient groups from different cultural profiles are necessary to address the universal validity of FA and specific treatments targeting this construct, such as brief interventions or other addiction-based treatments such as relapse prevention, which may help improve the treatment outcome in obesity and may facilitate health promotion.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Marmara University School of Medicine Local Ethical Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ES and YA designed the study and analyzed the data. ES and CÇ collected the data. ES wrote the initial draft. YA supervised the study. All authors commented on the revised version of the manuscript.

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Loneliness in Young Adults During the First Wave of COVID-19 Lockdown: Results From the Multicentric COMET Study

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The COVID-19 pandemic has affected the mental and physical health of the general population at any age, but it is expected to have a protracted and severe consequences for younger populations. The pandemic has had several consequences on mental health including anger and irritability, depressive symptoms and somatic complaints, insomnia, lack of motivation, and loneliness. In particular, loneliness and its related negative feelings are thought to be particularly pronounced during young adulthood because of the many social changes that young people deal with during this period of life. Therefore, it is essential to evaluate the type of impact of the pandemic on the mental health of young people and their levels of loneliness experienced during the first phase of the lockdown. Based on the largest Italian study on the effects of the COVID-19 pandemic on the mental health of general population, in this paper we aim to: (1) describe the levels of loneliness in a national sample of Italian young adults aged 18–34 years, during the first wave of lockdown in 2020; (2) evaluate the clinical and socio-demographic differences in young adults reporting low vs. high levels of loneliness; (3) assess the role of clinical symptomatology, coping strategies, levels of resilience, and duration of lockdown as possible predictors of loneliness. The final sample consists of 8,584 people, mainly female (72.6%), single, with a mean age of 26.4 (±4.4) years. The mean score at the UCLA was 47.5 (±13.6), with 27% ($N = 2,311$) of respondents exceeding the cut-off for high levels of loneliness. High levels of loneliness were predicted by the presence of avoidant coping

strategies, such as self-distraction (Beta coefficient, B = 0.369, 95% Confidence Interval, CI = 0.328–0.411), venting (B = 0.245, 95% CI = 0.197–0.293), denial (B = 0.110, 95% CI = 0.061–0.159), and emotional disengagement (B = 0.133, 95% CI = 0.080–0.185). Weeks of exposure to the pandemic were significantly associated with worsening of loneliness ($p < 0.000$). There is currently considerable interest in trying to reduce loneliness, both within the context of COVID-19 and more generally. Our results highlight that young people are at a higher risk of developing loneliness and suggest that more interventions and practical guidelines are needed.

Keywords: loneliness, trauma, pandemic, mental disorders, youth

INTRODUCTION

The COVID-19 pandemic is a "new" form of trauma affecting different groups of individuals, communities, cities, regions at the same time, with no possibility to identify and limit the "enemy" (1–3). Although the pandemic has affected the mental and physical health of the general population at any age (4–6), it is expected that this global crisis can have protracted and severe consequences for younger populations (7). In fact, the pandemic is posing multiple challenges to young people, through the disruption of daily educational, academic, professional, social, and family life (8, 9).

Due to the rapid spread of the coronavirus, several preventive measures, including physical distance, face masks, home quarantine, and lockdown restrictions have been implemented in order to contain the transmission and the contagion of other people (10, 11).

On March 8, 2020, the Italian Prime Minister announced the "stay at home" order and entered the first national lockdown in response to the COVID-19 pandemic. Based on previous experience with infectious disease outbreaks, quarantine, lockdown, and physical distancing are unpleasant experiences, involving separation from loved ones, uncertainty, and unemployment (12), increased mental distress and post-traumatic symptoms (13–15), anger and irritability (11, 16), depressive symptoms and somatic complaints (17, 18), insomnia (19, 20), suicidal ideation (21, 22), lack of motivation and loneliness (11, 16, 23, 24). In the general population, the adoption of different coping styles (25), the levels of resilience (26) and familiarity with mental disorders (27) have been identified as the most relevant moderators of the impact of the pandemic on mental health (2).

Loneliness is defined as a negative emotion related with the discrepancy between desired and existing relations, and it can be either emotional and social (28, 29). Emotional loneliness is described as a subjective experience resulting from the absence of a close bonding with a person, whereas social loneliness reflects an objective lack of contacts and social networks (30, 31).

Loneliness represents a major public health concern, since it is associated with an increased risk of depressive disorders, anxiety disorders, and suicidal ideation (32), as well as of cardiovascular disease, stroke, coronary heart disease (33, 34), cognitive decline (35), and increased all-cause mortality risk (36–38).

Loneliness and its related negative feelings are thought to be particularly pronounced during adolescence and young adulthood (39) because of the many social and personal changes that young people deal with during this period of life (40–43). Loneliness itself has been referred to as an epidemic, and there have been heightened concerns about its effects during the COVID-19 pandemic (8, 44–46). Therefore, it is essential to evaluate the type of impact of the pandemic and the levels of loneliness experienced by young people (47). By disentangling such complex relationship between pandemic and loneliness, it would be possible to develop *ad-hoc* preventive strategies targeting the young people (48–50), which are expected to be the most severely hit by the long-term consequences of the pandemic (51–53).

Based on the largest Italian study on the effects of the COVID-19 pandemic on the mental health of general population (27), in this paper we aim to: (1) describe the levels of loneliness in a national sample of Italian young adults aged 18–34 years, during the first wave of lockdown in 2020; (2) evaluate the clinical and socio-demographic differences in young adults reporting low vs. high levels of loneliness; (3) assess the role of clinical symptomatology, coping strategies, levels of resilience, and duration of lockdown as possible predictors of loneliness.

MATERIALS AND METHODS

The COvid Mental hEalth Trial (COMET) is a national trial coordinated by the University of Campania "Luigi Vanvitelli" (Naples) in collaboration with nine university sites: Università Politecnica delle Marche (Ancona), University of Ferrara, University of Milan Bicocca, University of Milan "Statale," University of Perugia, University of Pisa, Sapienza University of Rome, "Catholic" University of Rome, University of Trieste. The Center for Behavioral Sciences and Mental Health of the National Institute of Health in Rome has been involved in the study by supporting the dissemination and implementation of the project according to the clinical guidelines produced by the National Institute of Health for managing the effects of the COVID-19 pandemic. The COMET was conceived as a cross-sectional observational design using a snowball sampling method for the recruitment of the Italian general population. The full study protocol is available elsewhere (54).

The main outcome measure of the study is the DASS-21, evaluating the general distress on a tripartite model of psychopathology (55, 56). It consists of 21 items grouped in three subscales: depression, anxiety and stress.

The levels of loneliness have been evaluated by the UCLA scale short version, which includes 10 items rated on a 4-level Likert scale (57). Higher values indicate higher levels of loneliness. As reported by Morahan-Martin and Schumacher (58), participants in the highest 20% of responses were classified as "Lonely," compared with all other participants ("Non-lonely").

Respondents' socio-demographic (e.g., gender, age, geographical region, working, and housing condition, etc.) and clinical information (e.g., having a previous physical or mental disorder, using illicit drugs or medications, etc.) have been collected through *ad-hoc* schedules. Other validated and reliable questionnaires included in the study are: the General Health Questionnaire-12 items version (GHQ) (59); the Obsessive-Compulsive Inventory—Revised version (OCI-R) (60), the Insomnia Severity Index (ISI) (61), the Suicidal Ideation Attributes Scale (SIDAS) (62), the Severity-of-Acute-Stress-Symptoms-Adult scale (SASS) (63), the Impact of Event Scale—short version (IES) (64), the Connor-Davidson resilience scale (65), the brief-COPE (66), the short form of Post-Traumatic Growth Inventory (PTGI) (67), the Multidimensional Scale of Perceived Social Support (MSPPS) (68), and (only for healthcare professionals) the Maslach Burnout Inventory (MBI) (69). The present paper is based on a sub-analysis of the sample of young people. A previous survey promoted by the International Labor Organization in the UK, entitled "Youth and COVID-19," has selected participants aged 18–34 years and therefore the same age group has been considered in the present paper (70).

Ethics and Dissemination

This study is being conducted in accordance with globally accepted standards of good practice, in agreement with the Declaration of Helsinki and with local regulations.

The participants provided their written informed consent to participate in this study. The study has been approved by the Ethical Review Board of the University of Campania "L. Vanvitellii" (Protocol number:0007593/i).

Statistical Analysis

Descriptive statistics were performed in order to describe the socio-demographic and clinical characteristics of the sample. *T*-test for independent samples and Chi-square have been performed to test differences between "lonely" vs. "non-lonely" participants, as appropriate.

In order to identify possible predictors of the levels of loneliness, a multivariate linear regression model, weighted for the propensity score, was performed, including as independent variables: adaptive and maladaptive coping strategies, having been infected by the COVID-19, having a pre-existing mental disorder, being a healthcare professional. Furthermore, in order to evaluate the impact of the duration of lockdown and of other containment measures on the primary outcomes, the categorical variable "Week" was also entered in the regression models. The models were adjusted for the rate of new COVID-19 cases and of COVID-related mortality during the study period, as well as for several socio-demographic characteristics, such as gender, age, occupational status, having a physical comorbid condition, hours spent on Internet, health status, number of cohabiting people, satisfaction with one's own life, with cohabiting people, and with housing condition. All variables have been managed as reported in detail elsewhere (27).

Missing data have been handled using the multiple imputation approach. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 17.0 and STATA, version 15. For all analyses, the level of statistical significance was set at $p < 0.05$.

RESULTS

Global Sample

The final sample consists of 8,584 people, mainly female (72.6%, $N = 6,232$), single, with a mean age of 26.4 ($\pm$4.4). 58.2% of them ($N = 5,000$) have a university degree and 71.4% ($N = 6,131$) are single; 7.1% of respondents have lost their job or interrupted their studies during the pandemic.

The majority of participants reported to enjoy their living conditions (66.8%, $N = 5,732$) and to live with their co-habitants (70.5%, $N = 6,055$), while 24% of participants ($N = 2,094$) reported not to be satisfied with their own life. 5.4% ($N = 461$) participants reported to suffer from a mental disorder and 6.7% ($N = 573$) of a physical disorder.

The mean score at the UCLA was 47.5 ($\pm$13.6), with 27% ($N = 2,311$) of respondents exceeding the cut-off for high levels of loneliness (**Table 1**, **Figure 1**).

Differences in "Lonely" vs. "Non-lonely" Respondents

Participants from the "lonely" group reported a higher severity of depressive, anxiety, and stress-related symptoms (DASS-Depression: 13.8 $\pm$ 6.8; DASS-anxiety: 8.7 $\pm$ 7.0; DASS-stress:17.2 $\pm$ 6.1), compared to the "non-lonely" sample ($p < 0.0001$) (**Table 2**).

Moreover, 15.8% ($N = 365$) of the "lonely" sample scored above the threshold for clinical relevance of obsessive-compulsive symptomatology, with a global severity of obsessive–compulsive symptoms of 12.5 $\pm$ 8.7 at OCI-R, significantly higher than the "non-lonely" group ($p < 0.05$). Suicidal ideation was reported by 13.8% ($N = 318$) of the "lonely" group, with a mean score of 5.1 $\pm$ 7.1 at the SIDAS, compared to the 14.3% in the "not-lonely group" (4.7 $\pm$ 6.5).

The levels of resilience were significantly lower in participants from the "lonely" group, compared with the remaining sample ($p < 0.0001$).

People from the "lonely" group also reported to use maladaptive coping strategies very frequently. In particular, self-distraction was frequently used in 38% of cases (vs. 24% of cases in the "non-lonely" group, $p < 0.0001$), self-blame in 25% of cases (vs. 14.4%, $p < 0.0001$) and venting in 15.4% (vs. 8.4%, $p < 0.0001$). On the contrary, people from the "non-lonely"

TABLE 1 | Socio-demographic characteristics of the sample (N = 8,584).

	Global sample (N = 8,584)	Lonely (N = 2,311)	Not-lonely (N = 6,273)	P-value
Gender, female, % (N)	72.6 (6,232)	73.2 (1,691)	72.4 (4,541)	0.471
Age, M (SD)	26.4 (±4.4)	26.2 (4.4)	26.5 (4.4)	0.002
Age category				
18–29 ys	70.9 (6,088)	73 (1,686)	70.2 (4,402)	0.012
30–34 ys	29.1 (2,496)	27 (625)	29.8 (1,871)	
Marital status, single, yes, % (N)	71.4 (6,131)	72.3 (1,671)	71.1 (4,460)	0.346
Student, yes, % (N)	51.6 (4,429)	52.5 (3,293)	51 (3,201)	
Employed, yes, % (N)	51.6 (4,429)	52.5 (3,293)	49.2 (1,136)	
Lost job/interrupted educational activities, yes, % (N)	7.1 (606)	7.0 (162)	7.1 (444)	0.913
Any physical disorder, yes, % (N)	6.7 (573)	7.1 (165)	6.5 (408)	0.295
Any mental disorder, yes, % (N)	5.4 (461)	5.5 (126)	5.3 (335)	0.829
Educational level, university, yes, % (N)	58.2 (5,000)	55.2 (1,276)	59.4 (3,724)	0.013
Being infected by COVID, yes, % (N)	5.3 (453)	4,7 (109)	5,5 (344)	0.174
Severely hit region, yes, % (N)	28.6 (2,452)	28.2 (651)	28.7 (1,801)	0.628

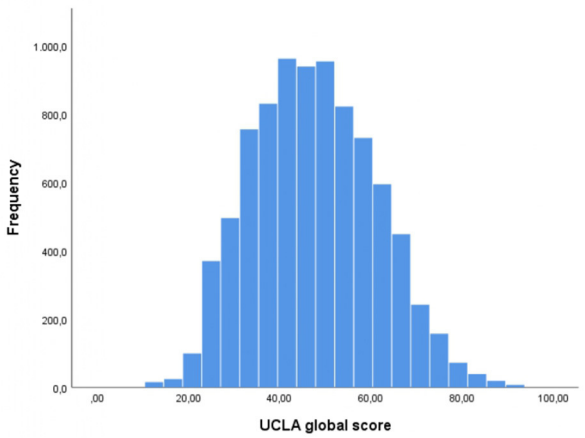

FIGURE 1 | Distribution of the levels of loneliness.

group more frequently used adaptive coping strategies, such as acceptance (47.7% of cases vs. 35.1%; $p < 0.0001$), planning (40.3 vs. 32%; $p < 0.0001$), and positive reframing (29% vs. 21.2%; $p < 0.0001$).

Predictors of Loneliness

According to the multivariate regression model, weighted for the propensity score, high levels of loneliness were predicted by the presence of avoidant coping strategies, such as self-distraction (Beta coefficient, B = 0.369, 95% Confidence Interval, 95% CI = 0.328–0.411), venting (B = 0.245, 95% CI = 0.197–0.293), denial (B = 0.110, 95% CI = 0.061–0.159), and emotional disengagement (B = 0.133, 95% CI = 0.080–0.185). Interestingly, the levels of loneliness were reduced by using adaptive coping strategies, such as search for information (B = −0.125, 95% CI = −0.184 to −0.066), planning (B = −0.106, 95% CI = −0.159 to −0.053) and positive reframing (B = −0.080, 95% CI= −0.127 to −0.034).

Weeks of exposure to the pandemic and to the related containment measures were significantly associated with worsening of loneliness, with Beta coefficient ranging from B = 0.4 (95% CI: 0.078–0.830) during the week April 16–22 to B = 0.323 (95% CI: 0.112–0.534) in the week April 30–May 4 ($p < 0.000$).

Being infected by COVID-19 and having a pre-existing mental or physical disorder did not impact on the levels of perceived loneliness, even after controlling for gender, age, living in the most severely affected areas, infection rate, and mortality rate for COVID-19 in Italy. We also found that the severity of depressive, anxiety or stress symptoms, of obsessive-compulsive symptoms, of insomnia, post-traumatic symptoms, and suicidal ideation did not have any influence on the levels of loneliness (**Table 3**).

Finally, high levels of post-traumatic growth, such as appreciation for life (B = 0.160, 95% CI = 0.102–0.219) were a significant protective factor for levels of loneliness (**Table 3**).

DISCUSSION

The COVID-19 pandemic represents an unprecedent traumatic event, which has completely disrupted the daily routine of the general population worldwide for more than a year now (71). The mental health of young adults has not been fully considered during the first weeks of the pandemic, although it was clear already from the beginning that young people would have been a group at higher risk of developing long-term physical, mental and social problems (72). In particular, the enforced physical isolation due to the public health containment measures can be associated with a subjective feeling of loneliness, which represent a specific dimension to be carefully monitored for the prevention of mental health problems (73). In many individuals, especially the younger ones, the lockdown and physical distancing can have increased the perception of social isolation. Although social isolation—defined as the absence of social interactions, contacts

TABLE 2 | Differences in clinical features between lonely and not-lonely participants.

	Global sample (*N* = 8,584)		Not-lonely (*N* = 6,273)		Lonely (*N* = 2,311)		*P*-value
	M	*SD*	*M*	*SD*	*M*	*SD*	
DASS stress	16.9	6.3	16.8	6.4	17.2	6.1	0.024
DASS anxiety	8.4	6.9	8.3	6.9	8.7	7.0	0.006
DASS depression	13.4	7.0	13.3	7.1	13.8	6.8	0.005
GHQ global score	17.4	3.3	17.3	3.2	17.4	3.2	0.288
OCI global score	12.0	8.7	11.8	8.7	12.5	8.7	0.001
SASS global score	7.1	5.3	7.0	5.3	7.5	5.4	0.001
Connor global score	31.3	10.4	32.5	10.2	27.9	10.3	0.000
ISI global score	7.2	5.4	7.1	5.4	7.4	5.3	0.517
IES intrusive	2.1	1.9	2.1	1.9	2.1	1.9	0.309
IES avoidance	2.4	1.9	2.4	1.9	2.3	1.9	0.084
IES hyperarousal	2.5	1.9	2.5	1.9	2.5	1.9	0.674
PTGI—relating to others	1.9	1.4	1.9	1.4	1.9	1.4	0.014
PTGI—new possibilities	1.8	1.3	1.9	1.3	1.7	1.3	0.000
PTGI—personal strenght	2.2	1.5	2.2	1.5	2.1	1.5	0.000
PTGI—spiritual help	1.2	1.2	1.2	1.3	1.2	1.2	0.249
PTGI—appreciation life	2.3	1.4	2.4	1.4	2.3	1.4	0.000
Support—family	21.1	6.8	21.9	6.4	19.0	7.3	0.000
Support—friends	20.4	6.6	21.1	6.3	18.7	7.0	0.000
Support—others	22.4	6.7	23.0	6.3	20.7	7.4	0.000
SIDAS global score	4.8	6.6	4.7	6.5	5.1	7.1	0.000
Suicidal ideation, yes, % (*N*)	14.2 (1,216)		14.3 (898)		13.8 (318)		0.534
Above OCI threshold, yes, % (*N*)	14.6 (1,249)		14.1 (884)		15.8 (365)		0.045

and relationships with others—is conceptually distinguished from loneliness—that is the feeling that one's social needs are not being met by the quantity or quality of one's social relationships, these two dimensions appear to be strongly interrelated, with physical and social isolation being a risk factor for becoming "lonely" (74).

During the ongoing health crisis, there have been calls to ascertain how the pandemic has affected loneliness to ensure that at-risk individuals receive all the necessary support. Therefore, in our study we decided to describe the levels of loneliness in a national sample of Italian adults, during the first wave of the lockdown in 2020, as one of the considered outcome measures.

In the sub-sample of young people aged 18–34 years, the levels of loneliness were quite high, being particularly severe in a third of cases. This is an expected finding, in line with those from other studies carried out in Europe, which highlighted that younger adults, women, people with low income, and those with mental health problems are more likely to be in the highest loneliness class relative to the lowest (75, 76). According to the COVID-19 Psychological Well-being study, people of younger age reported more severe levels of loneliness and were four to five times more likely to report loneliness, compared with older adults (77). In a sample of US young adults aged 18–35 years, the prevalence of loneliness was estimated at 43% (78). In this sample, results indicated a trend toward moderate levels of loneliness, with women reporting significantly more feelings of loneliness compared to men. In our sample, we did not find gender differences in the levels of loneliness, but this finding could be due to the overrepresentation of female population compared to male.

Furthermore, young people in the highest loneliness cluster reported a higher severity of depressive, anxiety and stress symptoms, of obsessive-compulsive symptomatology, and a high rate of suicidal ideation, even compared with the global COMET sample (27). As expected, people belonging to the group with highest rates of loneliness were those with more severe levels of psychiatric symptoms, confirming that loneliness is strongly associated with depression and other mental disorders both in old (79) and young adults (80, 81). Although loneliness has been traditionally linked with older adults (32, 82, 83), even young adults up to the age of 25 may experience high levels of loneliness (55, 84). These data confirm the hypothesis that loneliness can represent a useful dimension to be carefully monitored in routine clinical practice by healthcare professionals working with adolescents and young people (85, 86).

Another interesting finding is that adaptive coping strategies, such as planning and positive reframing, work as protective factors against loneliness. This is a relevant finding considering that coping strategies may easily change following specific psychosocial interventions, such as psychoeducation (87, 88) and problem-solving oriented interventions (89) or by improving the levels of resilience (25, 81, 90, 91).

Furthermore, we also found that the levels of loneliness tend to increase over time, being more severe in the last weeks of the lockdown, as confirmed in our regression models controlled for all respondents' socio-demographic characteristics. This finding

TABLE 3 | Predictors of the levels of loneliness.

	B	Sign.	95% Confidence Interval	
			Lower bound	Upper bound
Intercept	10,367	0.000	9,310	11,424
Being infected by COVID, yes	0.105	0.525	−0.220	0.431
Gender, female ref.	0.096	0.554	−0.223	0.416
Severely hit area, yes	0.097	0.173	−0.042	0.236
Pre-existing physical disorder, yes	−0.076	0.272	−0.210	0.059
Pre-existing mental disorder, yes	−0.106	0.393	−0.351	0.138
Time to exposure, ref. week March 30—April 8				
Week April 15–April 9	0.265	0.299	−0.235	0.765
Week April 16–April 22	0.454	0.018	0.078	0.830
Week April 23–April 29	0.198	0.246	−0.137	0.533
Week April 30–May 4	0.323	0.003	0.112	0.534
Quarantine	−0.211	0.043	−0.415	−0.006
Cases COVID	3,775	0.586	−9,830	0.000
Death COVID	0.001	0.157	0.000	0.002
Age, ref. cat. 18–29 ys (vs. 30–34 ys)	0.057	0.415	−0.079	0.192
Being student, yes	0.073	0.372	−0.087	0.232
Being employed, yes	−0.162	0.044	−0.004	−0.320
DASS anxiety	−0.002	0.695	−0.013	0.009
DASS depression	0.004	0.406	−0.006	0.015
DASS stress	0.002	0.689	−0.009	0.013
GHQ global score	−0.005	0.644	−0.024	0.015
OCI global score	0.007	0.121	−0.002	0.017
ISI global score	0.007	0.315	−0.006	0.020
IES global score	0.002	0.770	−0.010	0.014
SASS global score	−0.006	0.504	−0.022	0.011
Support from others	−0.038	0.000	−0.050	−0.027
Support from friends	−0.038	0.000	−0.050	−0.026
Support from family	−0.049	0.000	−0.060	0.038
Resilience levels	−0.034	0.000	−0.042	−0.027
COPE—Self-distraction	0.369	0.000	0.328	0.411
COPE- Active	−0.026	0.311	−0.075	0.024
COPE—Denial	0.110	0.000	0.061	0.159
COPE—substance use	0.121	0.000	0.065	0.177
COPE—emotional support	0.418	0.000	0.361	0.475
COPE—information	−0.125	0.000	−0.184	−0.066
COPE emotional Disengagement	0.133	0.000	0.080	0.185
COPE—venting	0.245	0.000	0.197	0.293
COPE—positive reframing	−0.080	0.001	−0.127	−0.034
COPE—planning	−0.106	0.000	−0.159	−0.053
COPE—humor	0.020	0.380	−0.024	0.064
COPE—acceptance	−0.036	0.157	−0.086	0.014
COPE—religion	−0.077	0.000	−0.116	−0.037
PTGI—relating to others	0.017	0.595	−0.047	0.082
PTGI—new possibilities	0.059	0.155	−0.022	0.140
PTG—personal strength	−0.065	0.063	−0.133	0.004
PTGI—spiritual help	−0.012	0.764	−0.093	0.068
PTGI—appreciation life	0.160	0.000	0.102	0.219

confirms the hypothesis that the duration of containment measures significantly influences mental health and well-being of the general population (27, 92, 93). The same trend in the levels of self-reported loneliness was reported by Bu et al. (76), who described a U-shaped trajectory in the levels of loneliness in the period June-November 2020, corresponding to the limitations

to social activities due to the lockdown policies (94). In fact, young people aged between 18 and 29 reported higher levels of loneliness, but with a decrease in loneliness in the first period of the pandemic, from March to May 2020 (76, 95–97).

In addition, being employed and being a student were associated with a lower risk of loneliness during the pandemic. This is consistent with Arnett's theory (98) that working and education status might potentially be signs of age-specific personal achievements (99). Moreover, school and workplace may also help young adults to increase their social network and to reduce social disconnection (100–102). Prolonged school closures, strict social isolation from peers, extended family, and community networks, economic shutdown, and the pandemic itself may have contributed to the mental health problems of many adolescents and young adults (103–105). Being confined to home leads to disturbances in sleep/wake cycles and physical exercise routines, and promotes the excessive use of technology (106–109). Further studies are needed in order to evaluate the long-term effects of these conditions on the development of full-blown mental health disorders (110, 111).

The present study has some limitations which are hereby acknowledged. First, the snowball sampling methodology could have led to a selection bias, with only those interested in the psychological consequences of the pandemic willing to participate (112). Second, the cross-sectional design of the survey prevents us to delineate any causal relationship between the selected variables. Third, several variables which could have had an impact on the levels of perceived loneliness, such number of contacts with peers (prior and during the pandemic), time spent with friends/peer, quality of social relationship, number of social activities in which they are usually involved, desire for social contact (113–115), the quality of family communication styles, and the individual acceptance and attitudes toward restrictive measures related to the pandemic, have not been collected in our study. Fourth, it is very difficult to disentangle the complex relationship between the exposure to COVID-19 pandemic and other contextual factors contributing to the levels of loneliness. In this study, the proxy measure selected is represented by the variable "weeks of lockdown," but it should be acknowledged that many other variables could have had an influence on the loneliness levels.

Finally, our sample cannot be considered fully generalizable of all young people because we could recruit only people aged 18 years or more.

Among its strengths, we should consider that this is one largest surveys carried out in Italy on the effects of the COVID-19 pandemic on the mental health and well-being of the general population. Moreover, given the large sample size, we could analyze differences and similarities between young and old people, but also between males and females (116). Finally, the large battery of used tests allowed us to test the effects of loneliness on several mental health dimensions and symptoms.

Overall, our findings suggest that the levels of loneliness during the weeks of the first strict lockdown were high in young adults. People using maladaptive coping strategies, such as self-blame or self-distraction, were at higher risk for reporting highest levels of loneliness. However, certain social factors such as having close friends, having strong perceived social support, having high levels of resilience and using adaptive coping strategies were protective factors. There is currently considerable interest in trying to reduce loneliness within society, both within the context of COVID-19 pandemic and more generally (117–121). Our results highlight that young people are at a higher risk of developing loneliness and suggest that more interventions and practical guidelines are needed.

DATA AVAILABILITY STATEMENT

The data presented in this study are available on request from the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the University of Campania L. Vanvitelli. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VG, GSam, and AF: conceptualization. ML and VV: methodology. GS: formal analysis. UA, CC, GSan, GC, MP, UV, BD, MBM, and FC: investigation. GS, VB, and GM: writing—original draft preparation. AF, UA, CC, GSan, MP, UV, BD, MBM, and FC: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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BRIEF RESEARCH REPORT
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Psychological Traits of Patients With Depression Comorbid With Chronic Pain: Are Complaint and Competitive Tendency Related to Pain?

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Background: Modern-Type Depression (MTD) is a category of depression that has been studied mainly in Japan; however, no study has attempted to determine its relation to chronic pain.

Aim: To determine possible associations between psychological traits related to MTD and the chronic pain of patients at psychiatric clinics.

Method: Two hundred and twenty-one first time patients who visited the psychiatric clinic at a Japanese university medical center or an associated clinic were enrolled. The Hamilton Depression Rating Scale was used to measure depressive symptoms. The 22-item Tarumi's Modern-Type Depression Trait Scale (TACS-22), Achievement Motive, and 20-item Toronto Alexithymia Scale were used to assess psychological traits related to depression and chronic pain. The clinical diagnosis of each patient was confirmed by use of the Structured Clinical Interview for DSM-IV Axis I Disorders, administered by experienced specialists. The medians of the psychological traits identified were compared between patients with or without chronic pain. Analysis was also done of patients with Major Depressive Disorder (MDD).

Result: Of the 221 patients, 139 had chronic pain. Patients with chronic pain had more severe depressive symptoms, Alexithymia, and high scores for the complaint trait of MTD. Seventy-three of the 221 patients met the criteria for MDD (53 had chronic pain). Patients with MDD comorbid with chronic pain had a higher competitive achievement score, severe depression, and difficulty identifying feelings.

Conclusion: Complaint and competitive traits were shown to be related to chronic pain in psychiatric settings. Further study will allow us to design multidimensional approach for patients suffering from depression.

Keywords: depression, chronic pain, personality traits, modern-type depression, alexithymia, TACS-22, achievement motive

INTRODUCTION

The global prevalence of depression is estimated at 3.76%, and the prevalence in Japan was reported to be 2.66% in 2019 (1). Similarly, chronic pain affects around 30.3% of the worldwide population (2) and 46.4% of Japanese older than 40 years (3). Depressed patients often complain of chronic pain, and vice versa (4, 5), and psychosocial factors are known to be common to depression and chronic pain (6, 7).

Alexithymia has been reported to be associated with both depression and chronic pain. In a recent meta-analysis, the degree of alexithymia was correlated with pain intensity, physical interference, depressive symptoms, and anxiety in a group of chronic pain patients (8). Economic factors and social isolation have also been reported to be prognostic of depression and chronic pain (9, 10).

Modern-type depression (MTD), an independent type of depression that is different from the conventional depression based on a melancholy temperament, has been widely reported in Japan (11–13). This condition is characterized by the occurrence of depressive symptoms mainly in a stressful workplace or school setting, then rapid disappearance once the patient leaves the stressful situation (14). A self-reporting questionnaire, the 22-item Tarumi's Modern-Type Depression Trait Scale (TACS-22), has been designed to assess the premorbid personality of patients with MTD, including three factors such as Avoidance of Social Roles, Complaint, and Low Self-Esteem (15). MTD is regarded as a gateway disorder to a type of pathological social withdrawal called hikikomori in Japan (11, 16–18).

Achievement motive (AM) is another instrument used in Japan to assess psychological traits related to depressive symptoms. It consists of two aspects of motivation: competitive and self-fulfillment. Those whose competitive achievement motive is high have been reported to have difficulty accepting social support and to have a tendency toward stronger depressive symptoms (19).

Studies have related the personality traits of MTD and AM to depressive symptoms, but their relation to chronic pain is unknown. Thus, to clarify which traits are related to chronic pain, we used the above inventories to investigate the interaction between depression and personality traits of patients with or without chronic pain. The patients were recruited from psychiatric clinics because we expected many of them to suffer from depression. The level of depression and confirmation of the diagnosis of the patient's base disease were assessed by semi-structured interviews done by experienced psychiatrists or psychologists.

METHODS

Data Collection

Patients who first visited the Mood Disorder/Hikikomori Clinic in the Department of Neuropsychiatry at Kyushu University Hospital or affiliated psychiatric institutes between July 2018 and February 2021 and who gave written consent were enrolled. Patients referred from other psychiatric medical institutions due to refractory symptoms and suspected of having a mood disorder were included. Patients who could not complete a face-to-face semi-structured interview and patients for whom detailed information about their pain was not available were excluded, leaving the data of 221 patients available for analysis.

This study was approved by the ethics committee of Kyushu University, Fukuoka, Japan. Participants agreed to join in the study after being informed that their anonymity would be maintained and that participation was voluntary.

Measures

The study was cross-sectional and done through the use of self-reporting questionnaires and a structured interview of all participants to examine psychological factors related to their depression and pain. The questionnaires were used to assess specific patient psychological traits, factors related to their disease, and clinical data including age, gender, location and duration of pain, socioeconomic status (smoking, alcohol consumption, marital status, education, employment etc.). Pain lasting more than 3 months was considered chronic. The following evaluations were done.

The Structured Clinical Interview for DSM-IV Axis I Disorders

The SCID (Japanese version) is a semi-structured psychiatric interview with established reliability that assesses if the patient has reached a diagnostic threshold according to the DSM-IV (20). All of the interviewers were psychiatrists or psychologists with extensive clinical experience and familiarity with SCID-I administration procedures.

The Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HDRS) is a structured interview that assesses the severity of depression (21). Answers to the Japanese version of the HDRS were assessed by trained psychiatrists or psychologists.

Patient Health Questionaire-9

The PHQ-9, this screening questionnaire is based on the diagnostic criteria of DSM-IV and consists of nine questions on depression in the preceding 2 weeks. It was used for assessment of depression severity (22). Answers are on a scale of 0–3, giving a maximum score of 27. A score of 20 or greater indicates severe depression. It can be administered in a short time and can be used to assess depression in primary care settings. The previously validated Japanese version was used (23).

The 22-Item Tarumi's Modern-Type Depression Trait Scale

TACS-22 is a self-reporting questionnaire that assesses the premorbid personality traits of MTD (15). The questionnaire consists of 22 items to be answered on a 5-point scale from 0 to 4. It has three subcategories: Avoidance of Social Roles, Complaint, and Low Self-Esteem.

The 20-Item Toronto Alexithymia Scale

TAS-20 is a 20 item self-reporting questionnaire that assesses Alexithymia-related personality traits (24). It consists of three subcategories: Difficulty identifying feelings (DIF), Difficulty

describing feelings (DDF), and Externally oriented thinking (EOT). The previously evaluated Japanese version was used (25).

Achievement Motive

AM is a self-reporting questionnaire that evaluates the strength of motivation to achieve a goal. It consists of 23 questions (26) and assesses two aspects: Self-fulfillment achievement motive and Competitive achievement motive (19).

Statistics

For the analysis, patients with pain lasting more than 3 months were placed in a chronic pain group (CP). All met the diagnostic criteria for major depression, and this group is referred to as MCP. Patients without pain (NP) were placed in a control group. All met the diagnostic criteria for major depression, and the group is referred to as MNP. The median values of each psychological scale measured were compared by Wilcoxon-Mann-Whitney test. Statistical analysis was done with R version 4.1.1. *P*-values of < 0.05 were considered to be statistically significant, and *P*-values of < 0.1 were considered as marginally significant.

RESULTS

The frequencies of the patients' primary disease for which the diagnostic threshold of the structured interview (SCID) was exceeded are summarized in **Figure 1**. Major depressive disorder (MDD, 73 patients) was the most common, followed by social phobia (27 patients) and somatoform disorders (15 patients). Twenty-eight patients met multiple diagnostic criteria. Descriptive statistics are shown in **Table 1**. Of the 221 patients enrolled, 139 had pain lasting more than 3 months (CP), 53 of whom had MDD (MCP).

A comparison of the median values of each psychological scale for CP ($n = 139$) and NP ($n = 82$) is shown in **Table 2A**. The median values of the severity of depression score on both PHQ-9 and HDRS were significantly higher in the CP group [PHQ9: 15 (CP)] vs. 10.5 (NP)/$p = 0.00002$, HDRS: 14 (CP) vs. 9 (NP), $p = 0.0000001$). The median TAS-20 score was also marginally higher in the CP group but was without significance [49 (CP) vs. 47 (NP)/$p = 0.0532$]. The median values were significantly high for Complaint of TACS-22 and DIF of TAS-20 [Complaint: 11 (CP) vs. 8.5 (NP)/$p = 0.0199$, DIF: 16 (CP) vs. 14 (NP)/$p = 0.0128$]. Although the median values for Low Self-esteem of TACS-22 were the same for CP and NP, the mean value was higher in CP [median: 16, mean 15.9 (CP) vs. 14.8 (NP)/$p = 0.0315$].

The median values of each psychological scale were compared for the patients of each group who reached the diagnostic threshold for major depression (**Table 2B**). Depressive symptoms were stronger in the MCP group ($n = 53$) than in the MNP group ($n = 20$) [HDRS: 19 (MCP) vs. 15 (MNP)/$p = 0.0111$]. The median TAS-20 score was also marginally higher in the MCP group, although it did not reach the level of significance [52 (MCP) vs. 48.5 (MNP)/$p = 0.0678$]. The median value of the MCP group was higher for the DIF of TAS-20 [19 (MCP) vs. 14 (MNP)/$p = 0.00211$]. In addition, the competitive achievement motive of the AM inventory was higher in the MCP group [45 (MCP) vs. 40 (MNP)/$p = 0.0163$].

DISCUSSION

In our study to clarify the psychological characteristics of psychiatric outpatients with or without pain, patients with pain lasting more than 3 months showed more depressive symptoms and a tendency toward Alexithymia. This tendency was also observed in patients who met the diagnostic criteria for major depression. For all patients analyzed, personality traits related to MTD were stronger in the group with chronic pain, but there was no significant difference when only patients with major depression were included. The competitive achievement motive "aiming to beat or overcome others to be appreciated by others or society" did not differ between patients with or without chronic pain, but in the group with major depression and chronic pain the score was higher than for those without chronic pain.

The results showing that depressive symptoms were stronger in the group with chronic pain are consistent with the results of previous studies (4). Our study was unique in that we focused on personality traits. No significant difference in the total score of TACS or AM was seen for patients with or without chronic pain, but there was a significant difference in some of the subscales. The complaint item of the TACS-22 is a factor related to relationships with others and responsibility, and the competitive achievement motive is a factor related to gaining an advantage in comparison with others. These are important factors related to the development of social isolation. This is consistent with the results of a previous study (6) showing that depression partially mediates the relation between social isolation and pain interference. Sadly, the COVID-19 pandemic has increased loneliness and caused more severe social isolation (27). Increases in the incidence and intensity of pain and the prevalence of chronic pain have been reported in Japan (28). With the increased social isolation due to the pandemic, pain may become more prevalent among depressed patients.

The clinical manifestations, response to pharmacotherapy or psychotherapy, staging, and functioning of patients with depression are widely varied, and the development of personalized treatment modalities is necessary (29). To optimize treatment, multidimensional evaluation of depression is crucial (30). MTD is an exciting new concept of depression (11, 13, 14). Our findings will contribute to the development of multidimensional evaluation regimens related to specific personality traits.

Limitations

Because this was an exploratory pilot study, its findings are limited. First, we did not assess the cause of chronic pain because the study was done in a psychiatric clinical setting with patients whose chief complaints were not pain. The sample size of MDD patients was relatively small, which limited the statistical analysis and does not allow us to draw conclusive findings. In addition, we did not use multiple test correction to avoid the risk of false negatives: the purpose of this study was to do a wide-ranging analysis of psychological

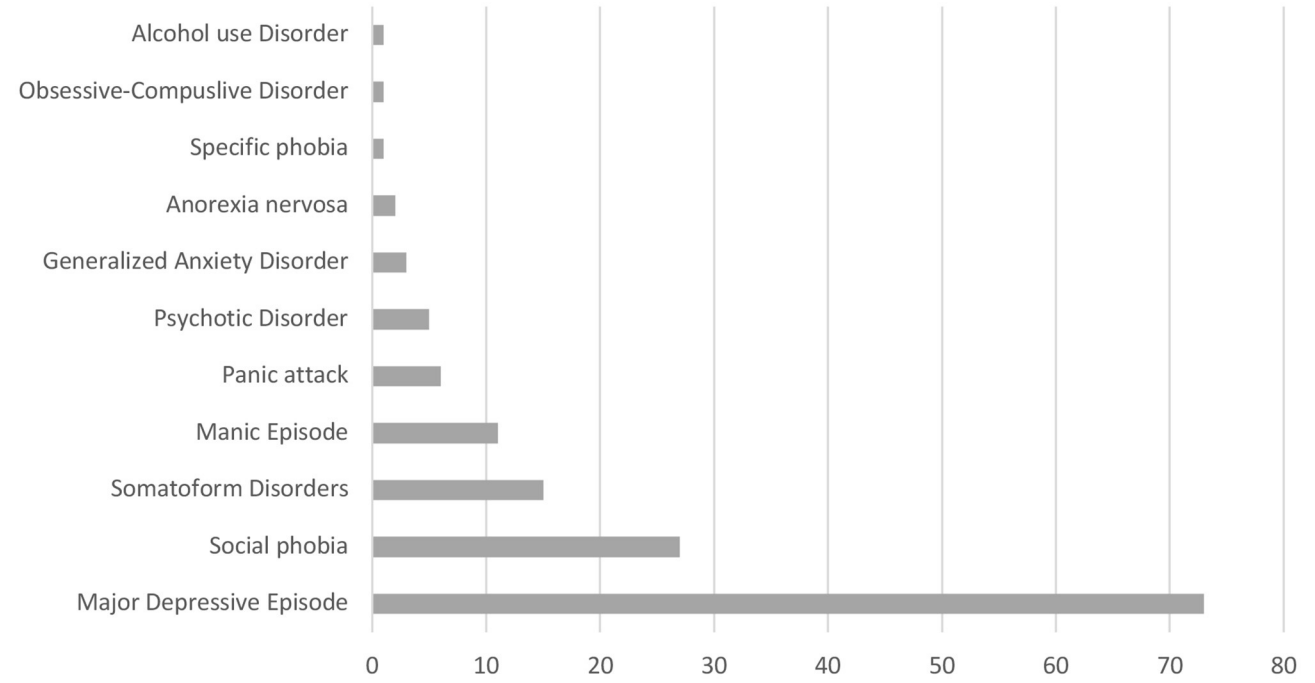

FIGURE 1 | Frequency of psychiatric diagnosis based on DSM-IV.

TABLE 1 | Demographic characteristics.

		All ($n = 221$)	Major depression ($n = 73$)	No-Major depression ($n = 148$)
With chronic pain (%)		139 (63%)	53 (73%)	86 (58%)
Age (mean ± SD years old)		33.8 ± 12.2	35.6 ± 12.0	32.9 ± 12.2
Sex (female)		117 (53%)	44 (60%)	73 (49%)
Current smoker (%)		41 (19%)	18 (24%)	23 (16%)
Alcohol drinking	Not at all (%)	132 (60%)	46 (62%)	86 (59%)
	<3 times a week (%)	65 (29%)	20 (27%)	45 (31%)
	More than 4 times a week (%)	24 (11%)	8 (11%)	16 (11%)
Martial status	Single (%)	130 (59%)	36 (49%)	94 (64%)
	Married (%)	69 (31%)	30 (41%)	38 (26%)
	Divorced or bereaved (%)	14 (6%)	5 (7%)	9 (6%)
Education	Secondary (%)	95 (43%)	27 (36%)	68 (46%)
	Higher vocational or Universities (%)	119 (54%)	34 (46%)	62 (42%)
Paid employment (%)		104 (47%)	38 (51%)	66(45%)
Antidepressant use (%)		31 (14%)	13 (18%)	18 (12%)
Living alone (%)		40 (18%)	14 (19%)	26 (18%)

TABLE 2A | Comparison of medians ($n = 221$).

Measurement		CP (patients with chronic pain) ($n = 139$) (SD)	NP (patients without chronic pain) ($n = 82$) (SD)	*P*
HDRS		14 (7.1)***	9 (6.1)	<0.001
PHQ-9		15 (6.7)***	10.5 (7.0)	<0.001
TACS-22	Total	50 (12.3)	47 (11.6)	0.15
	Avoidance of social roles	23 (6.3)	23.5 (6.8)	0.95
	Low self-esteem	16 (4.5)*	16 (4.1)	0.03
	Complaint	11 (5.5)*	8.5 (4.6)	0.02
Achievement motive	Total	109 (17.3)	105 (18.6)	0.93
	Self-fulfillment	64 (11.2)	63 (11.5)	0.71
	Competitive	45 (10.3)	44 (10.9)	0.61
TAS-20	Total	49 (9.7)	47 (9.4)	0.05
	Difficulty identifying feelings	16 (6.1)*	14 (6.3)	0.01
	Difficulty describing feelings	12 (3.1)	12 (3.0)	0.68
	Externally oriented thinking	21 (4.1)	21 (3.8)	0.90

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. CP, patients with chronic pain; NP, patients without chronic pain; SD, standard deviation; HDRS, Hamilton Depression Rating Scale; PHQ-9, Patient Health Questionaire-9; TACS-22, The 22-item Tarumi's Modern-Type Depression Trait Scale; TAS-20, the 20-item Toronto Alexithymia Scale.*

TABLE 2B | Comparison of medians of the MDD Patients ($n = 73$).

Measurement		MCP (MDD patients with chronic pain) ($n = 53$) (SD)	MNP (MDD patients without chronic pain) ($n = 20$) (SD)	*P*
HDRS		19 (6.3)*	15 (3.9)	0.01
PHQ-9		19 (3.7)	17 (5.3)	0.06
TACS-22	Total	52 (11.0)	52 (7.8)	0.50
	Avoidance of social roles	24 (5.9)	23.5 (5.8)	0.88
	Low self-esteem	18 (3.6)	17.5 (3.6)	0.77
	Complaint	12 (5.0)	9 (3.6)	0.11
Achievement motive	Total	109 (15.7)	102 (16.4)	0.06
	Self-fulfillment	64 (9.4)	61 (11.6)	0.26
	Competitive	45 (9.8)*	40 (8.8)	0.02
TAS-20	Total	52 (9.1)	48.5 (6.1)	0.07
	Difficulty identifying feelings	19 (5.3)*	14 (4.2)	0.002
	Difficulty describing feelings	13 (2.8)	13 (2.0)	0.46
	Externally oriented thinking	20 (4.1)	21 (3.3)	0.22

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. MCP, MDD patients with chronic pain; MNP, MDD patients without chronic pain; SD, standard deviation; TACS-22, The 22-item Tarumi's Modern-Type Depression Trait Scale; TAS-20, the 20-item Toronto Alexithymia Scale.*

traits as an exploratory pilot study as the basis for future validation studies. Despite the small sample size, we have found useful, statistically significant data. With the psychological trait candidates we were able to identify, follow-up studies with greater sample size will be able to be done to verify our preliminary findings.

CONCLUSION

We found that psychiatric patients with chronic pain tend to have MTD-related psychological traits, notably "complaint to others." Interestingly, patients with MDD who have chronic pain have a stronger tendency to be motivated by competitive aims than those without chronic pain. Our findings show that a complaining and competitive personality are related to chronic pain and depression, both of which are related to maintaining healthy relationships with others. MTD is known to be related to severe social isolation, hikikomori (17, 31), and further studies need to be done to clarify the interactions between chronic pain, depression, MTD, and hikikomori.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by Ethics Committee of Kyushu University, Fukuoka, Japan. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TK initially designed the study, oversaw data analysis, participated in data interpretation, and writing of the manuscript. RK participated in study design and statistical analyses. KF conducted the statistical analyses, the literature searches, and wrote the manuscript. MH, TM, and KM participated in data interpretation and writing of the manuscript. TN and NS reviewed the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Uric Acid Potential Role in Systemic Inflammation and Negative Symptoms After Acute Antipsychotic Treatment in Schizophrenia

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Uric acid (UA) has been shown to have neuroprotective or neurotoxic properties, in relation to specific tissues and diseases that have been studied. Previous studies provided contradictory results on the role of UA in schizophrenia as a neurodegenerative disorder. The aim of this brief report was an additional analysis of UA sera levels in different phases of schizophrenia. Here, 86 patients with first-episode psychosis (FEP) vs. 45 patients with schizophrenia in relapse (SC in relapse) vs. 35 healthy control subjects (HC) were studied before and 1 month after antipsychotic therapy. Further, we aimed to explore the possible correlation of UA with scores presenting clinical features and with serum concentrations of the proinflammatory cytokines interleukin (IL)-6 and IL-17. When comparing the data between all three groups, we did not find significant differences in UA levels, either before or after the applied therapy. Also, comparing sera concentrations of UA in every single group, the analysis did not reveal statistically significant differences between FEP patients, but statistically, a significant difference was found in SC in relapse before and after treatment (334.71 ± 116.84 vs. 289.37 ± 109.15 μmol/L, $p = 0.05$). Uric acid serum levels correlated with negative sub-score ($p = 0.001$, $r = 0.306$), general sub-score ($p = 0.015$, $r = 0.236$), and total PANSS score ($p = 0.009$, $r = 0.3$) after 1 month of therapy. We have established a statistically significant positive correlation between serum concentrations of UA and IL-6 in exacerbation ($p = 0.01$, $r = 0.220$) and with IL-17 after treatment and in the stabilization of psychosis ($p = 0.01$, $r = 0.34$), suggesting potential cascades in different phases of schizophrenia that potentiate inflammation.

Keywords: uric acid, schizophrenia, cytokines, interleukin-6, interleukin-17

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INTRODUCTION

Uric acid (UA) is the final oxidation product of the adenine- and guanine-based purine catabolic pathway and is considered as a risk factor of numerous pathological conditions (1). Homeostatic imbalance of purine catabolism has been associated with various psychiatric disorders, such as depression (2, 3), schizophrenia (4), and bipolar disorder (5). It has been postulated that UA

may exert both neuroprotective and/or neurotoxic effects in the brain tissue (6), by modulating oxidation processes and inflammatory response, which could be of particular interest in the pathophysiology of schizophrenia. In a recent review paper, Morris and Maes (7) detailed that the immune-inflammatory response is associated with increased nitro-oxidative stress through the activation and involvement of macrophages, dendritic cells, neutrophils, T cells, B cells, and natural killer cells, is associated with increased nitro-oxidative stress. These redox-associated mechanisms modulated the production of pro- vs. anti-inflammatory cytokines.

Increased levels of UA in the initial phase may reflect an attempt to counteract oxidative stress, suggesting its neuroprotective role (8), whereas the sustained increase in UA may also be considered a marker of oxidative stress (4), and could lead to a systemic inflammatory response (4). Uric acid is thought to have strong proinflammatory activity by triggering interleukin (IL)-1β-mediated inflammation via activation of the nucleotide oligomerization domain-like receptor protein (NLRP) 3 inflammasome, a multimolecular complex that plays a central role in many pathological inflammatory conditions (9, 10). In neuroprogressive disorders, UA may act as an alarmin, leading to NLRP3 inflammasome activation, and internalized UA may increase nuclear factor-κB activity as well as oxidative, nitrosative, and inflammatory stress (7). Elevated UA levels correlate positively with several pro-inflammatory markers such as C-reactive protein and white blood cells count (11), IL-6, IL-17, tumor necrosis factor-alpha (TNF-α) (11). The role of IL-6 has also been discussed in the etiopathogenesis of schizophrenia in terms of treatment-resistant schizophrenia being associated with increased IL-6 serum levels, an association between higher IL-6 levels and cognitive decline, that was established, and a decrease in serum levels of IL-6 following antipsychotic therapy (12). Recently, we have observed that the predomination of type 17 immune response facilitates the progression of inflammation and could be involved in the regulation of cognition (13).

The relationship between altered UA levels and schizophrenia remains unclear, and studies have yielded conflicting results. A significant decrease in plasma UA levels was observed in the first episode of schizophrenia (14), and a meta-analysis confirmed reduced UA levels in patients with first-episode psychosis (FEP) (15). Previous studies also revealed that schizophrenia patients had lower UA levels compared to healthy control (HC) subjects (4, 16), whereas several studies reported higher UA levels in schizophrenia patients compared with HCs (17, 18). However, it is still not known whether the reduction in UA levels occurs early in the course of the illness and whether it is independent of treatment or illness progression. This study aimed to examine whether serum levels of UA are altered in drug naïve patients with FEP and in patients with schizophrenia in relapse (SC in relapse) and compared them with levels measured in HC subjects. A secondary aim was to assess the effects of acute treatment on UA serum levels after 1 month. Finally, we aimed to explore the correlations between UA and the cytokines IL-6 and IL-17 and to further test whether altered UA serum levels are associated with specific clinical features of schizophrenia.

MATERIALS AND METHODS

Subjects

This study represents an additional analysis of the database from our previous cytokine studies in different phases of schizophrenia (19, 20). Briefly, patients were enrolled in Psychiatric Clinic, Clinical Center Kragujevac, and the Special Hospital for Psychiatric Diseases "Dr. Laza Lazarevic," Belgrade. We examined 86 drug-naive patients with FEP, 45 patients with SC in relapse who were already treated with antipsychotics, and 35 HC subjects. The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) (21) was used to determine the diagnoses. The psychopathological status of psychotic patients was assessed by trained physicians using the Positive and Negative Syndrome Scale (PANSS) (22). Exclusion criteria included acute or chronic medical conditions, acute infections, recent surgical procedures, alcohol or drug abuse, any illness that is immune-and redox-mediated, allergies or autoimmune disorders, ongoing anti-inflammatory or antiviral treatment, and treatment with medications that can influence UA levels (vitamin C, diuretics, epinephrine, levodopa, methyldopa, acetylsalicylic acid, and azathioprine). The research project was approved by two ethics committees of these institutions and was conducted in compliance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to any study procedure.

Laboratory Measurements

A somatic examination was performed, and vital signs were measured on admission. Patients' blood samples were collected at least 8 h before the administration of antipsychotic therapy during the current psychotic episode. The control group consisted of HC subjects matched to the patients by gender and age with patients and recruited at a blood donation in the Service supply of blood and blood products, of Clinical Center Kragujevac. Serum UA levels were determined using a hematology analyzer, ABX MICROS 60-OT (UK). The reference values for UA were in the following range: 154–428 μmol/L. Serum cytokine levels were measured using conventional enzyme-linked immunosorbent assay (ELISA) kits (R & D Systems Minneapolis, MN for IL-17 and IL-6, according to the manufacturer's instructions). Immunological measurements were performed at the Center for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac. The acute effects of treatment on UA serum levels were assessed after 4 weeks, since the first 2–4 weeks of antipsychotic treatment are crucial for a substantial reduction of positive symptoms (23).

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, Illinois, USA). Numerical values are reported as mean, standard deviation (SD), and standard error (SE). The normal distribution of the data was tested using Shapiro–Wilk and the Kolmogorov–Smirnov test. A Paired Sample test and the Wilcoxon test were used to compare the

TABLE 1 | Demographic and clinical characteristics of the sample.

Parameters	FEP	SC in relapse	Controls	
	***n* = 86**	***n* = 45**	***n* = 35**	
Age (years, mean ± SD)	33.64 ± 8.84	35.95 ± 11.40	36.63 ± 8.73	
Sex (male/female)	36/50	17/28	22/13	
Mean duration of illness (mean ± SD)	0.28 ± 1.93	7.31 ± 6.30	NA	
Positive and Negative Syndrome Scale (PANSS) (mean ± SD):				
	Day 0	**Day 30**	**Day 0**	**Day 30**
Total score	100.96 ± 14.76	56.22 ± 21.01**	104.39 ± 18.88	65.82 ± 21.45**,***
Positive symptoms	25.49 ± 5.74	12.36 ± 5.37**	25.97 ± 6.50	18.35 ± 24.3***
Negative symptoms	22.08 ± 5.78	13.15 ± 5.86**	24.09 ± 8.27*	16.82 ± 7.59**,***
General psychopathology	53.40 ± 7.13	30.71 ± 11.00**	54.55 ± 8.24	34.76 ± 10.82**,***

*Kruskal–Wallis test, statistically significant difference between two groups at the baseline ($p = 0.006$).
**Paired sample test, statistically significant difference between two measurements ($p < 0.005$).
***Kruskal–Wallis test, statistically significant difference between two groups after antipsychotic therapy ($p = 0.05$).

TABLE 2 | Comparison of serum uric acid levels between groups.

Parameter	FEP	SC in relapse	HC	*p*
Uric acid				
Before treatment (mean ± SD)	339.04 ± 175.97	334.71 ± 116.84	332.60 ± 83.71	0.663
After treatment (mean ± SD)	304.01 ± 113.06	289.37 ± 109.15	332.60 ± 83.71	0.349
Uric acid				
	Before treatment (mean ± SD)	**After treatment (mean ± SD)**		***p***
FEP	339.04 ± 175.97	304.01 ± 113.06		0.207
SC in relapse	334.71 ± 116.84	289.37 ± 109.15		0.050*

FEP, first-episode psychosis; SC in relapse, schizophrenia in relapse; HC, healthy controls.
**Wilcoxon test, statistical significance $p < 0.05$.*

clinical parameters in the same group before and after therapy. We used the Mann–Whitney test for non-parametric variables to assess mean differences between two groups of patients. A Kruskal–Wallis test was used to assess differences in serum UA levels between three groups (FEP, SC in relapse, and HC). We examined the correlations between serum UA and cytokines, as well as the relationship between serum UA levels and PANSS scores, positive, negative, and general psychopathology sub-scores using Pearson's or Spearman's correlation. Multiple regression analysis was used to assess the significant demographic and clinical predictors of serum UA levels and PANSS scores. A *p*-value of 0.05 was considered to be statistically significant.

RESULTS

From our previous study database (19, 20), only patients with successful UA sampling were included. Sample characteristics were as expected in terms of phase of the disease and applied therapy (see **Table 1** for details).

When comparing data between all three groups of FEP, SC in relapse and HC subjects (339.04 ± 175.97 vs. 334.71 ± 116.84 vs. 332.60 ± 83.71 μmol/L, $p = 0.663$) and after applied therapy (304.01 ± 113.06 vs. 289.37 ± 109.15 vs. 332.60 ± 83.71 μmol/L, $p = 0.349$), we did not detect statistically significant differences in UA values before therapy. When comparing serum UA levels in each group, the analysis did not reveal statistically significant differences between FEP patients (339.04 ± 175.97 vs. 304.01 ± 113.06 μmol/L, $p = 0.207$), but statistically, a significant difference was found in SC in relapse, before and after treatment (334.71 ± 116.84 vs. 289.37 ± 109.15 μmol/L, $p = 0.05$). We also analyzed serum UA levels between FEP and SC in the relapse group before treatment (339.04 ± 175.97 vs. 334.71 ± 116.84 μmol/L, $p = 0.611$), and after treatment (304.01 ± 113.06 vs. 289.37 ± 109.15 μmol/L, $p = 0.349$), and no statistically significant differences were observed (presented in **Table 2**).

We found a significant correlation between UA serum levels with negative sub-score ($p = 0.001$, $r = 0.306$), general sub-score ($p = 0.015$, $r = 0.236$), and total PANSS score ($p = 0.009$, $r = 0.3$) after 1 month of therapy in both patient groups, while a correlation between serum UA levels and positive sub-score was not significant ($p = 0.128$, $r = 0.149$) (**Figure 1**). In addition, we found a statistically significant, but weak positive correlation between serum concentrations of UA and IL-6 in exacerbation ($p = 0.01$, $r = 0.220$) and with IL-17 after treatment and in the stabilization of psychosis ($p = 0.01$, $r = 0.34$) (**Table 3**).

Multiple regression analysis indicated that sex [$F_{(3/108)} = 8.027$, $p < 0.001$, $R^2 = 0.187$, Adjusted $R = 0.163$] was a significant predictor of serum UA levels, with female gender implicating an increase in UA. Uric acid serum levels [$F_{(4/101)}$

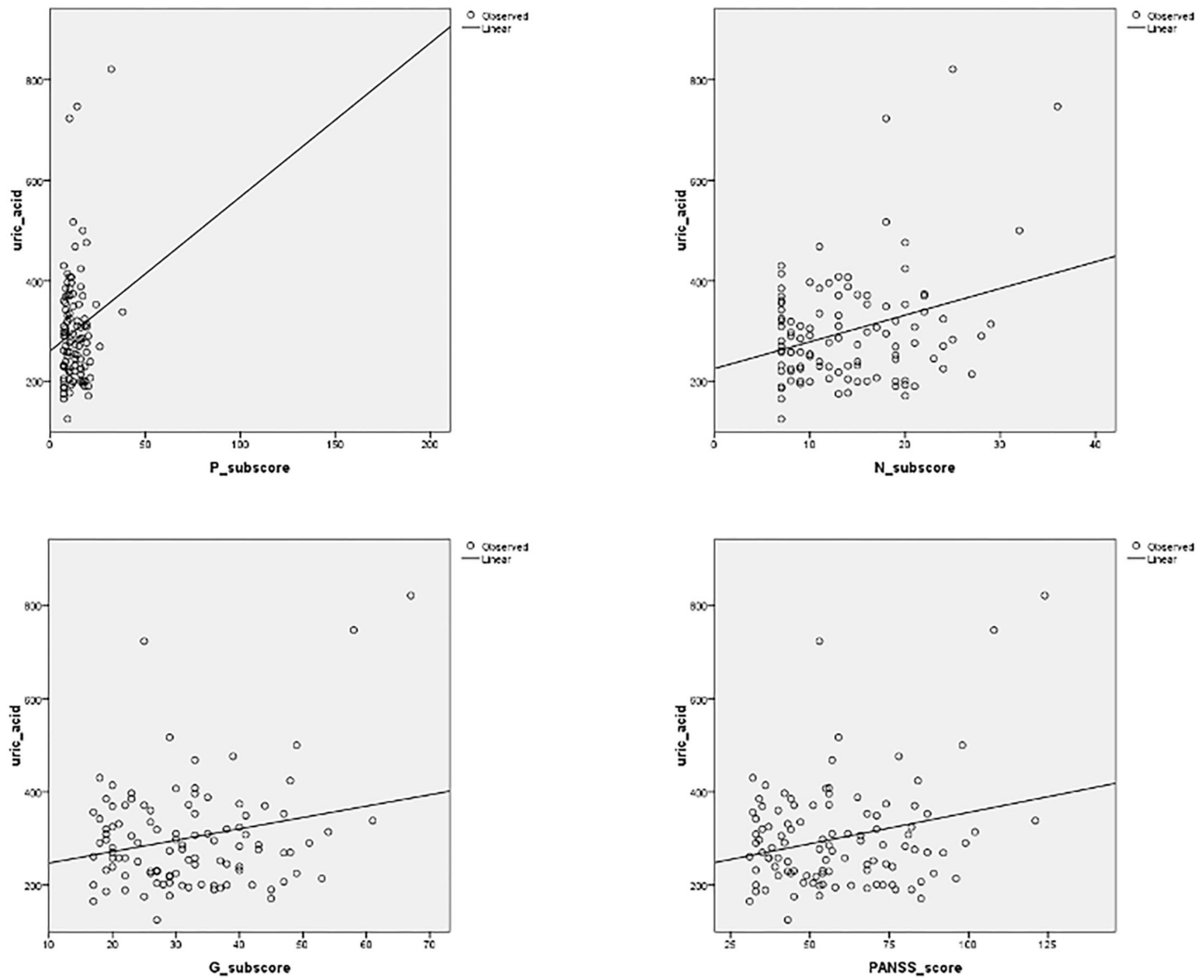

FIGURE 1 | Correlation between serum uric acid (UA) levels and positive, negative (N), and general (G) sub-scores, and total PANSS (Positive and Negative Syndrome Scale) score, after 1 month of antipsychotic treatment. Significant correlation was established between UA serum levels with negative sub-score ($p = 0.001$, $r = 0.306$), general sub-score ($p = 0.015$, $r = 0.236$), and total PANSS score ($p = 0.009$, $r = 0.3$) after 1 month of therapy.

TABLE 3 | Positive correlation of UA with IL-6 serum levels before, and with IL-17 serum levels after acute treatment.

Serum concentration (pg/ml)	Uric acid	
	Spearman's rho	*p*
IL-6	0.220	0.01*
IL-17	0.340	0.01*

*Spearman's correlation, statistical significance $p < 0.05$.

$= 2.192$, $p = 0.013$, $R^2 = 0.080$, Adjusted $R = 0.043$] and IL-17 serum levels after treatment in all psychotic patients [$F_{(1/48)} = 5.027$, $p = 0.030$, $R^2 = 0.097$, Adjusted $R = 0.077$] are significant predictors for PANSS score (presented in **Table 4**).

DISCUSSION

In the new tendency to publish negative results, we must emphasize that we did not find statistically significant differences in serum UA levels between patients with FEP, SC in relapse, and HC subjects, neither before nor after the applied therapy. We pointed out that patients with schizophrenia had higher UA serum levels in exacerbation than in the stable phase of this psychosis. There is a significant correlation between UA serum levels and negative, general sub-score, and the total PANSS score in the stabilization phase. A statistically significant positive correlation was observed between serum concentrations of UA and IL-6 in exacerbation, and with IL-17 after treatment and in the stabilization of psychosis. Our findings suggest that in a stable phase of the illness, serum levels of UA and IL-17 are significant predictors for PANSS scores.

TABLE 4 | Results of multiple regression analysis with serum UA levels and total PANSS score in all psychotic patients after therapy as dependent variables and demographic and clinical data as explanatory variables.

Dependent variables	Explanatory variables	*B*	*SE*	*β*	*T*	*P*
UA levels	Sex	72.671	15.657	0.410	4.641	<0.001*
PANSS score	UA	0.052	0.020	0.268	2.534	0.013*
	IL-17	0.155	0.069	0.311	2.242	0.030*

UA, uric acid; PANSS, Positive and Negative Syndrome Scale; IL-17, Interleukin-17.
**Statistically significant $p < 0.05$.*

Firstly, we would like to discuss phase specificities of oxidative and inflammatory stress in schizophrenia. Plasma UA levels were significantly lower in patients with FEP, but not in patients with bipolar or depressive disorder (14). In contrast to our findings, a recent meta-analysis that included 17 studies revealed that UA levels were decreased in subjects with a first psychotic episode (24). In a study by Yao et al. (25), symptom severity was measured with the Bunney-Hamburg Global Rating Scale, and a significant inverse relationship was found between plasma UA levels and psychosis scores. Previous studies showed that patients with schizophrenia had lower UA levels compared to HCs (4, 16). Other studies found no differences in UA levels in schizophrenia patients when comparing the acute and remission phases of the illness (26). In contrast, several studies reported higher levels of UA in patients when compared with HCs (17, 18). Our results are consistent with the most recent meta-analysis from 2020, which found no significant difference in UA levels between patients with schizophrenia and HCs, regardless of the use of the antipsychotics (24). To date, it is still not clear whether serum UA levels should be considered in schizophrenia onset or as an outcome of disease progression. Complex analyses of the data from genome-wide association studies within the Global Urate Genetics Consortium and the Psychiatric Genomics Consortium revealed no causal role of serum UA concentrations in schizophrenia, suggesting that low UA levels may be a consequence of schizophrenia onset and are more appropriate for diagnostic purposes or treatment monitoring (27). We examined serum UA levels in different phases of schizophrenia and found no significant difference between FEP and SC in relapse patients, nor 1 month after applied therapy in FEP. Our findings can be explained by the short duration of the disease, so we could not address possible further increases in UA serum levels in chronic schizophrenia. In patients with prolonged schizophrenia, UA levels could be initially elevated in the proinflammatory milieu during exacerbation and secondarily decrease due to the antipsychotic effect. It should be kept in mind that UA disturbances may not only be a consequence of the disease itself and aforementioned antipsychotics, but also could be a consequence of smoking (28), metabolic abnormalities such as weight gain, abdominal obesity, dyslipidemia (29, 30), hypertension (31), or insulin resistance (32).

Antipsychotics could increase the levels of UA (33). In a study designed as an on-off-on haloperidol treatment for schizophrenia, significantly lower plasma UA levels were found in male patients compared to HC subjects, and these levels decreased further after haloperidol was discontinued (25). Hyperuricemia was found to be associated with treatment with olanzapine and clozapine (34). There was no difference in plasma UA levels in patients with first-episode schizophrenia and in patients with chronic schizophrenia treated with risperidone for 6 months (35). In unmedicated patients with schizophrenia before and after 8 weeks of risperidone monotherapy, 20 marker metabolites were identified that helped distinguish between patients before and after treatment, and among them, myo-inositol, UA, and tryptophan showed the highest combined classification performance (36). In this sample, decreased serum levels of UA were normalized after risperidone treatment in responders, but not in non-responders. The uricosuric pharmacology of the antipsychotic drug and the resulting decrease in UA levels should be considered (37). Our previous publication discussed this issue of dose and type of oral antipsychotic medication in this study (20). The diversity of antipsychotic treatment hampered a more thorough analysis of the specific antipsychotic impact on UA serum levels.

In addition, the immune response seems to be modulated through UA impact. We found a statistically significant positive correlation between serum concentrations of UA and IL-6 in exacerbation and with IL-17 after treatment and in the stabilization of psychosis. Interleukin-17 is a pro-inflammatory cytokine produced mainly by Th17 cells and Type3 innate lymphoid cells when stimulated by cytokines such as IL-6 or IL-1, stimulating the production of cytokines and chemokines, and facilitating inflammation (38). An increase in Th17 cells has been reported in patients with neurodegenerative diseases (39, 40) and has also been postulated in schizophrenia. Interleukin-17 can induce blood-brain barrier disruption via a mechanism that depends on the production of reactive oxygen species, suggesting that IL-17 could exacerbate neurodegeneration through oxidative damage to lipids, proteins, and deoxyribonucleic acid (41). A recent randomized, double-blind, placebo-controlled pilot study showed a positive correlation between UA serum levels and IL-6, IL-17, and TNF-α, suggesting that xanthine oxidase inhibitors reduce levels of serum UA but also of these cytokines in patients with gout (42). It is already known that IL-6 is a key factor for Th17 differentiation and subsequent IL-17 production, and in turn, innate immunocytes respond to IL-17 by releasing IL-6. The IL-6/IL-17 axis functions as positive feedback that should be much more thoroughly explored in schizophrenia.

Yao et al. discussed the previously established links between UA and intelligence and reported the data from their research on the association between low levels of UA and greater impairment in sensory processing tasks (43). In a more recent study that included first-episode drug-free schizophrenia patients, no correlation was found between UA serum levels and scores representing cognitive functioning (44). However, we observed a weak correlation between UA serum levels and negative and general sub-scores and PANSS total score after 1 month of treatment. Coleman described the autistic child with marked hyperuricemia and also on antisocial, aggressive, or hyperactive behavior commonly observed in patients with

excessive UA production (45). It has been shown that in patients with Parkinson's disease, IL-6 correlates positively with motor symptoms severity, while IL-17 correlates with non-motor symptoms, specifically mood and cognition scores, with a negative correlation reported between IL-17 and cognitive deterioration (46). Therefore, this could be similar to the changes observed in schizophrenia: excitability could be related to IL-6 and UA, and negative and cognitive symptoms might be mediated by IL-17 and UA interactions.

When examining whether these cascades might be of clinical benefit in patients with Parkinson's disease, lower UA levels seem to imply a higher risk of transition to mild cognitive impairment (47). In contrast, after adjusting for age, sex, and smoking habits, the authors found and presented significantly higher levels of UA in the stable phase of schizophrenia than in HC subjects, suggesting higher oxidative stress and greater inflammation in patients with poorer outcomes (48).

This study reflects the naturalistic sampling in real clinical practice, in a specific timeframe. The diagnosis could be made only after a longer prodromal phase of the disease, sometimes to avoid stigmatization of these patients and due to inadequate family support. The limitation of this study is also that the data do not allow extrapolation in the chronic patients and required further research of a much longer duration of the illness. In addition, the fact that the decrease in FEP patients was not statistically significant could be a by-product of the higher variance in the FEP group, which also requires a larger sample size.

Our results indicate a possible detrimental effect of elevated serum UA levels in certain phases of schizophrenia. No significant differences in UA levels were observed in the initial phase of the illness, but it has been shown by others that repeated acute relapses might be followed by increased UA levels in patients with a longer duration of illness. Uric acid serum levels could be associated with IL-6 elevation in exacerbation, once more showing IL-6 as a crossroads in the pathophysiology of schizophrenia. These results could be explained by the fact that a different type of immune response is activated in schizophrenia than in other neurodegenerative diseases. For example, multiple sclerosis predominates type 1 immune response, while in schizophrenia type 2 immune response overweights and type-17 immune response could be related to cognitive decline. It could be considered that the type of immune response influences the further role of UA and whether it exhibits pro/antioxidant or pro/anti-inflammatory effects. Also, it is important to consider the lower serum levels of UA after therapy in patients with chronic schizophrenia, and that this potential further elevation of UA may contribute to residual symptomatology and poorer therapeutical response. Uric acid can be considered as a marker of the disease course in the later disease cascades.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study involving human participants, was reviewed and approved by the Ethics Committee of the Clinical Centre Kragujevac and the Special Hospital for Psychiatric Diseases "Dr. Laza Lazarevic", Belgrade, and was conducted in compliance with the ethical principles. Informed consent was obtained from all patients before any study procedures began.

AUTHOR CONTRIBUTIONS

MB and the team of trained psychiatrists have selected the patients, performed the psychological assessment, and sampling. MB has conceptualized the manuscript together with KV. KV and MB did the statistical analysis. KV designed figures and tables. MB and SJ wrote about the psychiatric aspects of this topic. KV and NM wrote about the role of UA. IJ and NA did the cytokine measurements and wrote about immunological aspects. MB prepared an integral version of the manuscript. All authors contributed equally to the content of this manuscript and approved the final version of the manuscript.

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