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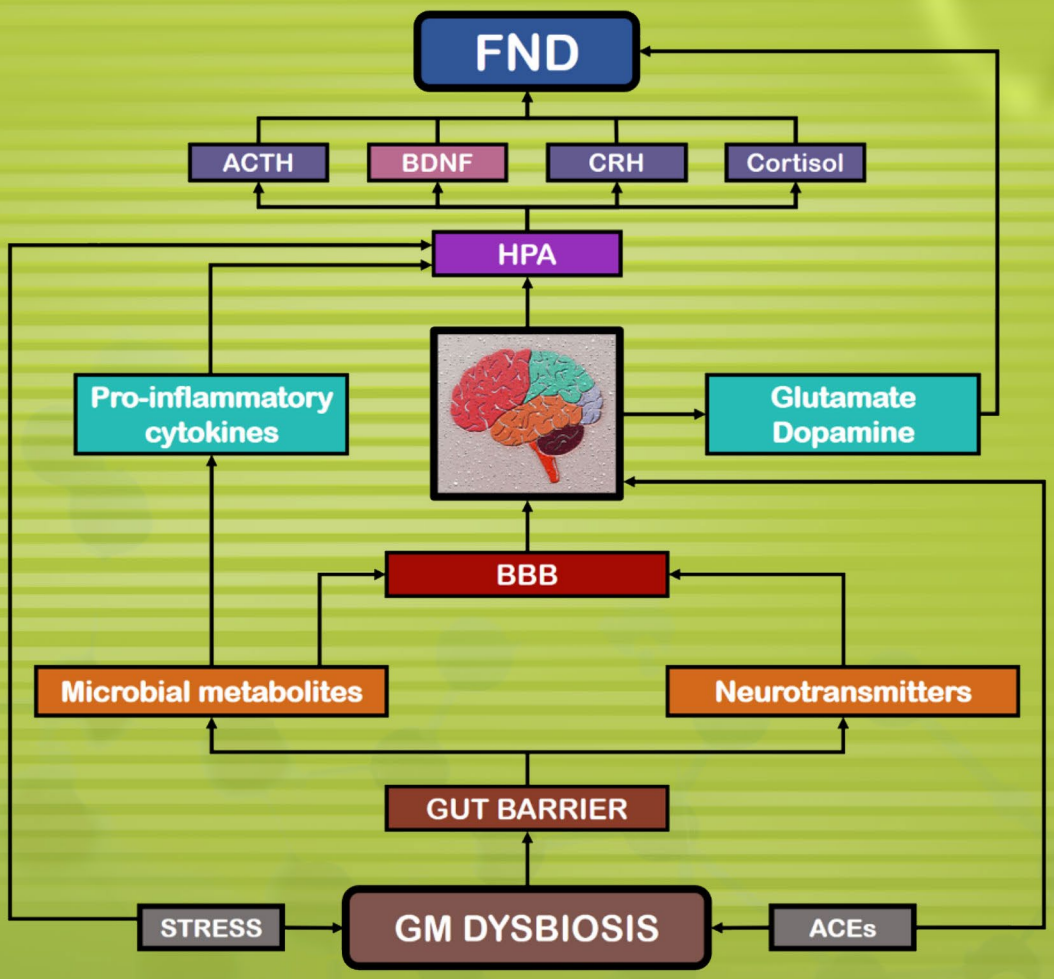

Functional neurological disorder and gut microbiome: Casual or causal relationship?

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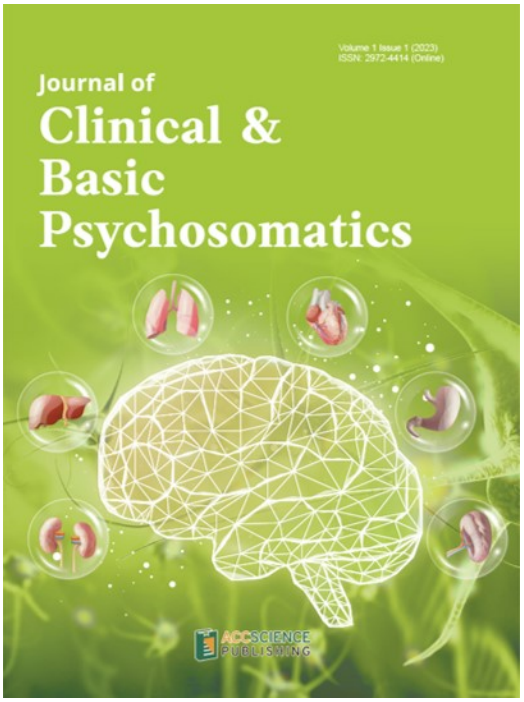

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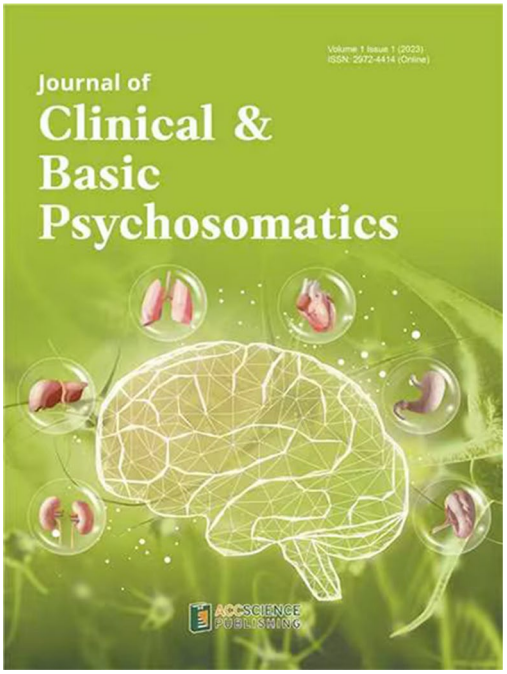

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REVIEW ARTICLE

Functional neurological disorder and gut microbiome: Casual or causal relationship?

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Abstract

Functional neurological disorder (FND), or conversion disorder, is a psychosomatic condition that affects the voluntary motor and/or sensory functions of the patient. Its origin is not yet fully understood, but the main risk factors related to this disorder include exposure to recent psychological stressors and previous experience of aversive episodes during childhood, such as abuse, family dysfunction, and neglect. The symptoms of FND result from complex interactions involving the central nervous system and also the endocrine and immune systems. In this work, we hypothesized the relationship between the gut microbiome and the pathophysiology of FND because both share several common features, such as the effects of neurotransmitters, the hippocampal expression of brain-derived neurotrophic factor, and the inflammatory responses. Based on these common aspects, we suggested that stress, gut microbiome, and inflammation factors induce chronic and systemic inflammation of the brain causing neurological disorders, including FND. More specific studies are warranted to validate the casual or causal relationship between FND and the gut microbiome.

Keywords: Functional neurological disorder; Conversion disorder; Gut microbiome; Neurotransmitters; Microbial metabolites; Neuroinflammation

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1. Introduction

Psychosomatic disorders affect both body and mind, and these conditions are mainly characterized by physical symptoms that result from psychological causes such as stress, anxiety, and depression.[1] In the past decades, there has been a rapid increase in the prevalence rates of psychosomatic disorders as a result of the swiftly changing modern lifestyle of people, as well as due to long-standing emotional, social, and occupational stress.[2] Historically, the term "psychosomatic" was first used by the German psychiatrist Johann Christian August Heinroth in 1818,[3] while the term "psychosomatic medicine" was introduced by Felix Deutsch in 1922.[4] Sigmund Freud systematically studied the now-famous case of "Anna O," who suffered from what was then called hysteria.[5,6] Explaining the mechanisms of the psychosomatic disorder of alexithymia, Nemiah *et al.* stated in 1976 that emotional reactions occur in two dimensions: psychological and vegetative states.[7]

Functional neurological disorder (FND), or conversion disorder, is a psychosomatic condition affecting the voluntary motor or sensory function of the patient,[8] in which

its symptomatology cannot be explained by any other psychological or physiological condition.[9] The main symptoms of FND include abnormal movements, aphasia, blindness, deafness, dizziness, localized anesthesia, muscle weakness, paralysis, pseudoseizures, psychogenic non-epileptic seizures, speech difficulties, and tremors.[10,11]

The origin of this disorder is not yet fully understood, although several predisposing, precipitating, and perpetuating factors have been reported as possible consequences of its etiology.[12] However, there is an association between the development of FND and the life event stressors during childhood that lead to trauma.[13,14] It is well known that trauma affects salience, emotion processing, and sensorimotor circuitry in the brain.[15] On the other hand, event stressors may be caused by external stimuli, physiological illnesses, or psychological pressures, and regarding these states, there is comorbidity with other neuropsychiatric disorders, including anxiety, dissociative disorders, post-traumatic stress disorder, and depression.[16,17]

FND symptoms result from complex interactions involving the central nervous system (CNS), endocrine, and immune systems. Especially, the hypothalamic-pituitary-adrenal (HPA) axis plays a crucial role, as its dysfunction is influenced by prolonged psychological stress.[18] As a result, stress hormones, such as cortisol, can have detrimental effects on immune function, inflammation, and overall balance within the organism.[19]

There are studies that have investigated the effects of psychological stress on the gut microbiome.[20] In addition, the gut microbiome influences brain function and behavior through the gut-brain axis, and its dysbiosis can potentially lead to the development of various psychological and psychiatric disorders.[21] Therefore, in this work, we hypothesized the relationship between the gut microbiome and the pathophysiology of FND because gut microbiome dysbiosis and FND share several common features, such as the effects of neurotransmitters,[22] the hippocampal expression of brain-derived neurotrophic factor (BDNF),[23] and inflammatory responses.[24]

2. Pathophysiology of FND

Frequent manifestations of FND include functional seizures (also known as dissociative or psychogenic non-epileptic seizures), functional movement disorders (FMDs) (paresis), somatosensory or visual symptoms, and speech disorders.[12] Brain differences (gray matter and basal ganglia volumes) have been found in FND individuals compared to healthy controls.[25] FND individuals show increased connectivity between the insula, motor, and parietal areas[26] and abnormalities in agency and limbic networks.[27] In recent decades, new hypotheses on the pathophysiology of these disorders have been formulated based on the integration of psychology and neurobiology, taking into account the neuropsychobiological factors that contribute to the development and maintenance of FND.[28,29]

Few studies have placed the focus on the molecular basis of FND. The current evidence highlights the presence of altered levels of the neurotransmitter glutamate in the limbic system and in the cerebrospinal fluid of patients with FMD, a specific subtype of FND.[30,31] In addition, another neurotrophin, the BDNF, is involved in the development, survival, maintenance, and plasticity of neurons, and has been related to the pathophysiology of FND,[32] as patients with epileptic and psychogenic non-epileptic seizures have decreased serum BDNF levels.[33] More recently, Demartini *et al.*[34] reported lower blood levels of glutamate, BDNF, and dopamine in FMD patients compared to healthy controls and concluded that glutamatergic and dopaminergic dysfunction may be involved in the pathophysiology of FMD.

Another factor that may contribute to the pathophysiology of FND is oxidative stress, which provokes damage in the brain through the production of reactive oxygen species (ROS).[35] Oxygen derivatives and peroxides have been implicated in the harmful mechanisms of several neuropsychiatric disorders, such as anxiety, depression, and schizophrenia.[36] However, various markers of oxidative stress, including ROS, 8-isoprostane, thiols, and nitrite derivatives, have not yet been evaluated in FND.[37,38]

The potentiality that inflammation plays a role within the pathophysiology of FND may provide feedback regarding how trauma and stressful events during childhood adversely affect the adult's health.[39] It is well known that stress provokes inflammation,[40,41] mainly by causing an imbalance in the homeostatic mechanisms, ultimately leading to the release of glucocorticoids through the HPA axis,[42] and there is a hyperarousal stress state in the FND motor-related symptoms.[43]

3. Microbial neurotransmitters and metabolites

Gut microbes regulate several host functions and behavior through chemical interactions with the CNS, including both "direct" and "indirect" communication.[44] Microorganisms have the ability to produce various neurotransmitters, such as acetylcholine, dopamine, gamma-aminobutyric acid, norepinephrine, and serotonin (Table 1), which can stimulate host production of other neuroactive compounds that regulate gut-brain signaling.[45] Therefore, dysbiosis

Table 1. Microbial production of neurotransmitters[21,46,47]

Neurotransmitters	Precursors	Gut microbiota producers
Acetylcholine	Choline	*Bacillus, Escherichia, Lactobacillus,* and *Staphylococcus*
Dopamine	Tyrosine, L-DOPA	*Bacillus, Escherichia, Serratia,* and *Staphylococcus*
GABA	Acetate	*Bacteroides, Bifidobacterium, Escherichia, Eubacterium, Lactobacillus, Parabacteroides,* and *Pseudomonas*
Glutamate	Acetate	*Bacteroides, Brevibacterium, Campylobacter, Corynebacterium,* and *Lactobacillus*
Histamine	Histidine	*Klebsiella*
Noradrenaline or norepinephrine	Tyrosine	*Bacillus, Escherichia,* and *Saccharomyces*
Phenylethylamine	Phenylalanine	*Staphylococcus*
Serotonin	5-hydroxytryptophan, tryptophan	*Candida, Clostridium, Enterococcus, Escherichia, Lactobacillus, Staphylococcus,* and *Streptococcus*
Tryptamine	Tryptophan	*Clostridium, Ruminococcus,* and *Staphylococcus*
Tyramine	Tyrosine	*Providencia* and *Staphylococcus*

of the gut microbiome may disrupt neurotransmitter synthesis and lead to mental disorders.[46,47]

Short-chain fatty acids (SCFAs), including acetate, butyrate, and propionate, are metabolic lipids produced by gut microbes through the fermentation of dietary fiber. The major gut bacterial producers of SCFAs are listed in Table 2.[48-50] SCFAs have the ability to influence the host energy balance, hormones, and metabolism, regulating the epigenetics, immune system, and neuroplasticity within the CNS, and they also constitute an important gut-brain signaling pathway through the vagus nerve.[51] Other microbial metabolites, such as alpha-tocopherol, indole, p-aminobenzoate, secondary bile acids, and tyramine, affect the production and secretion of serotonin by the enteroendocrine cells.[52] The mechanism underlying the production of gut hormones acts through the activation of G protein-coupled receptors by the SCFAs within the colon, which enhance the liberation of peptide YY and glucagon-like peptide 1 from enteroendocrine L-cells.[53,54] These hormones in turn can affect mood, memory, and learning processes, increasing neuroplasticity and neuroprotection in the hippocampus,[55] and reducing beta-amyloid plaques and microglial activation.[56] In addition, ghrelin, leptin, and insulin are other metabolic hormones influenced by SCFAs that affect brain function.[45]

Microbial enzymatic processes can produce the neurotoxins D-lactic acid and ammonium compounds, and other neuroactive metabolites, such as amino acids (tryptophan and tyramine), lipopolysaccharide (LPS), long-chain fatty acids, trimethylamine-N-oxide, and polysaccharide A, which induce peripheral immune cell migration into the brain and cause neuroinflammation,[44] although it is complicated to directly assess to what extent microbial metabolism affects CNS activity.[57]

4. Gut microbiome dysbiosis and neuroinflammation

The gut microbiome can modulate host immune activity by regulating the production of pro-inflammatory cytokines, which afterward influence the HPA axis to release corticotrophin-releasing hormone, adrenocorticotropic hormone, and cortisol.[58] The HPA axis is modulated by diverse stressors such as microbial infection and psychological stress; the toll-like receptors (TLRs) recognize pathogenic microorganisms or adverse conditions leading to an activation of the nuclear factor kappa B pathway, cytokine production, and ultimately HPA response.[59] Besides, the HPA response mediated by stress can also be regulated by serotonin neurotransmission.[60]

Regarding neuroinflammation, several clinical studies have demonstrated reduced diversity and dysbiosis of the gut microbiome. Nevertheless, it is still unclear whether it is dysbiosis that actively modulates inflammatory processes within the CNS, or whether it is only due to an effect of neuroinflammation itself.[61] It has been demonstrated that dysbiosis increases the permeability of the gut epithelial barrier, exposing the host to greater levels of microbial metabolites and to an increased quantity of cell wall components, such as bacterial extracellular vesicles (BEVs), lipoteichoic acids (LTA), LPS, and various peptidoglycan (PG), which could exert a significant impact on the pathogenesis of neurological diseases.

LPS and LTA can interact with several TLRs expressed by human neurons, and this ligand-receptor interaction triggers the production of inflammatory substances, such as ROS, which can mediate microglial activation.[62] In addition, neuronal death by caspase-3-dependent apoptosis is promoted by pro-inflammatory cytokines liberated in

Table 2. SCFAs and their corresponding bacterial producers[48-50]

SCFAs	Bacterial phyla	Bacterial genera
Acetate (C2)	Actinomycetota	*Bifidobacterium*
	Bacillota	*Acetobacterium* *Blautia* *Clostridium* *Eubacterium* *Ruminococcus* *Streptococcus* *Thermoanaerobacter*
	Bacteroidota	*Bacteroides* *Prevotella*
	Verrucomicrobiota	*Akkermansia*
Propionate (C3)	Actinomycetota	*Propionibacterium*
	Bacillota	*Anaerostipes* *Coprococcus* *Dialister* *Eubacterium* *Faecalibacterium* *Megasphaera* *Phascolarctobacterium* *Roseburia* *Veillonella*
	Bacteroidota	*Bacteroides*
	Pseudomonadota	*Salmonella*
Butyrate (C4)	Bacillota	*Acidaminococcus* *Anaerostipes* *Clostridium* *Coprococcus* *Eubacterium* *Faecalibacterium* *Peptostreptococcus* *Roseburia*
	Fusobacteriota	*Fusobacterium*

Abbreviation: SCFAs: Short-chain fatty acids.

response to LPS, LTA, and PG.[63] Neurons in certain brain areas, such as the cerebellum, hippocampus, and prefrontal cortex, express elevated levels of PG recognition protein 2 (PGLYRP2), which enables them to identify and discern muropeptides emanating from both Gram-positive and Gram-negative bacteria.[64] PGLYRP2 connects to the bacterial cell wall to cleave the stem peptide, leading to the generation of pro-inflammatory cytokines (interleukin-1β, interleukin-6, and tumor necrosis factor).[65]

Interestingly, there is an alternative direct communication network between bacteria and their host that involves the liberation of bacterial-derived functional molecules through BEVs.[66] The BEVs (exosomes and microvesicles) are enriched in lipids, nucleic acids, metabolites, proteins, and virulence factors, and they are released by both pathogenic and symbiotic bacteria, although their content may differ according to the bacterial species and the growth conditions. BEVs play a pivotal role in bacterial adaptation, communication, and virulence, but recent evidence also suggests a pathophysiological role of BEVs in the interactions involving bacteria among themselves and bacteria with their host.[67,68] Moreover, BEVs have been shown to activate innate immune cells, such as dendritic cells, macrophages, and microglia, as well as adaptive immune T and B cells in distant organs at the time BEVs are administered into the systemic circulation,[69] in addition to propagating inflammation in CNS tissues.[70] Once in the brain, BEVs possess the ability to directly alter neurological function and induce pathological variations.[71] Activation of astrocytes and microglia by virulence factors such as LPS, PG, and proteins provided by BEVs induces the release of inflammatory chemokines and cytokines.[72]

The gut microbiome can also alter the cytokines through the microbial metabolites by commanding the dynamics of pro- and anti-inflammatory T cells. This leads to changes in TLR signaling,[73] to the induction and proliferation of Treg cells and TH17 cells,[74] and to the dampening of intestinal epithelial cell responses.[75] The proposed role of the microbiome in regulating inflammatory cytokine concentrations makes the microbiome a critical factor in dictating the dynamics related to the immune response.

5. Conclusion

Psychosomatic medicine studies the interactions of biological, psychological, and social factors that regulate the balance between health and disease, emphasizing the holistic nature of human health and recognizing that cognitive and emotional states can significantly influence physical outcomes and vice versa. This illustrates the complex yet close interaction between mind and body, which is notably modulated by different intrinsic mechanisms, such as the autonomic nervous system, the HPA, and the immune responses. Moreover, the interplay between genetic predispositions and environmental stressors is a critical aspect that offers insights into personalized approaches to prevention and treatment. For instance, individuals with genetic vulnerability to certain mental health conditions may suffer exacerbated symptoms when exposed to major life stressors. This understanding has led to the development of interventions that address both biological and psychosocial constituents, such as cognitive-behavioral therapy combined with pharmacological treatment and lifestyle modifications. In this regard, the progress in neuroimaging and psychophysiological assessments (*e.g.*, functional magnetic resonance imaging and positron emission tomography scans) have allowed researchers to observe

brain activity in real-time, facilitating the identification of the specific neural correlates of psychosomatic symptoms. Besides, other kinds of psychophysiological evaluations, including measures of heart rate variability and galvanic skin response, provide additional data on how the body reacts to stress and emotional stimuli. In fact, advances in scientific methods have been widely applied in the study of psychosomatic disorders, facilitating the exploration of their underlying causal mechanisms and the examination of correlations between brain function and clinical manifestations.[76]

FND, a psychosomatic disorder, has a multifactorial etiology, and the main risk factors for this disorder in adults comprise the exposition to psychological stressors as well as the previous experience of aversive episodes during childhood, while in children, the risk factors include abuse, bullying victimization, family dysfunction, neglect, and perceived peer pressure.[77,78] FND often co-occurs with other psychological conditions, such as anxiety, depression, and post-traumatic stress disorder, as well as cluster B personality traits.[79] FND is also related to other functional somatic disorders, including chronic pain and irritable bowel syndrome, which suggest the overlapping risk factors or mechanisms shared by their comorbidities.[80]

Undoubtedly, FND is a very peculiar health condition that presents an important challenge for both the clinical and social ambits due to the lack of a clear understanding of its etiology and pathophysiology. The absence of an identifiable neurological cause complicates its diagnosis and treatment; this uncertainty not only makes clinical approaches difficult but also perpetuates the stigma associated with mental disorders since the symptoms of individuals suffering from FND may be mistakenly perceived as feigned or illusory. In social terms, this deeply affects individuals who suffer from this disorder, who often face barriers in seeking support and understanding, thereby negatively impacting their quality of life. Thus, recognizing these implications and promoting a multidisciplinary approach are pivotal. In this respect, the study of the gut microbiota of patients with FND could constitute a promising way to address this disorder, as well as the administration of psychobiotics as a treatment could improve the related symptoms and comorbid health conditions. Psychobiotics, including probiotics, prebiotics, synbiotics, postbiotics, and parabiotics, are used to treat various neuropsychiatric and psychological disorders. Their mechanisms of action involve immunomodulation, modifying the HPA axis, synthesizing neurotransmitters, regulating BDNF, interacting with the vagus nerve, maintaining or improving intestinal barrier function, suppressing microbial pathogens, and configuring neural networks. These effects are partly mediated by the secretion of SCFAs, which regulate metabolic processes such as intestinal homeostasis, energy acquisition, colonocyte activity, immune system performance, and other physiological functions.[81] Despite significant advancements in understanding the role of psychobiotics in treating mental disorders, several questions remain unanswered, including how factors such as diet, genotype, sex, and age influence their effects, whether psychobiotics alter gut microbiota architecture, if their effects are short term or long term, their potential side effects on the CNS, the factors that modulate their impact, and how they interact with psychotropic agents. On the other hand, a promising therapeutic intervention that could be considered to address FND symptoms is fecal microbiota transplantation, which involves introducing fecal matter from a healthy donor into the recipient's intestinal tract to restore the microbiota. Fecal microbiota transplantation has shown effectiveness in treating recurrent *Clostridioides difficile* infections and is recognized as a viable option for various inflammatory and mental diseases.[82]

In summary, gut microbes influence both the enteric and CNS through the production of microbial metabolites and neurotransmitters. In addition, the human microbiome is involved in neuroinflammation processes. Thus, changes in the microbiome, particularly that of the human gut, may exert a subtle impact on the cognitive and behavioral levels of individuals, as well as on their brain health.[83] The variations in the activity of diverse brain areas in response to modifications in the microbiome point that the human microbiota and its associated products are crucial determinants for neuronal coordination, an aspect involved in the pathophysiology of FDN. Therefore, based on these common aspects, we postulated that stress, gut microbiome, and inflammation factors may alter the integrity of the two pivotal barriers within the gut microbiota-brain axis – the gut barrier and the blood–brain barrier – inducing chronic and systemic inflammation of the brain, and causing neurological disorders, including FND.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Stigma in maintenance hemodialysis patients: A cross-sectional study

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Abstract

This study aimed to explore stigma and its predictors among patients undergoing maintenance hemodialysis. We utilized corresponding scales to measure both stigma and quality of life, and examining their correlations. Clinical and laboratory data were obtained through self-reported scales and medical records, screening for possible predictors associated with stigma. We recruited 115 patients in this study, with an average age of 52.14 ± 11.84 years. The level of stigma indicated correlations with all modules of the SF-36 scale. Specifically, bodily pain, general health, vitality, social functioning, role-emotional, and mental health modules had significant relationships with stigma ($P < 0.05$). Internalized stigma was significantly related to uremic pruritus and the duration of hemodialysis ($P < 0.05$). Enacted stigma revealed a significant relationship with uremic pruritus, the Beck Depression Inventory score, and the Beck Anxiety Inventory score ($P < 0.05$). Overall, stigma appears to exert negative impacts on the quality of life of patients undergoing incident hemodialysis. The occurrence of internalized stigma may be related to uremic pruritus and the duration of hemodialysis, while enacted stigma may be associated with uremic pruritus, depression, and anxiety.

Keywords: Maintenance hemodialysis; Stigma; Quality of life; Internalized stigma; Enacted stigma

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1. Introduction

Stigma was initially defined as "the situation of an individual who is disqualified from full social acceptance".[1(preface)] Unfriendly attitudes, such as stereotypes, prejudice, and discrimination held by others, have adverse consequences for people with stigmatizing conditions.[2,3] Importantly, stigma exacerbates the physical and mental health challenges of people already suffering from chronic illnesses.[4] Kurzban and Leary[5] specifically found that individuals with illness have worse prospects and could not offer physical, social, emotional, and economic value to others. This conceptualization suggests that stigma should be prevalent and similar among patients with different chronic illnesses. Stigma can lead to adverse consequences, such as social isolation and a lack of social support, which can become a very powerful stressor and further cause more adverse psychosomatic reactions.[5]

There are approximately 3 million patients with end-stage renal disease (ESRD) worldwide undergoing maintenance hemodialysis. They belong to a special population of chronic illness patients, and their management should follow the biopsychosocial

medical model. Hemodialysis can save the lives of those suffering from ESRD, but the therapy itself also brings psychological and symptom burdens that impair the quality of life and prognosis.[6,7] Presently, there are few reports on stigma in patients with ESRD. The present study aims to understand the situation of stigma in patients undergoing hemodialysis and explore the effect of stigma on their quality of life. Furthermore, we attempt to identify possible predictors associated with the occurrence of stigma in these patients. This may help nephrologists develop strategies to alleviate this psychological condition and improve their quality of life.

2. Methods

2.1. Participants

All maintenance hemodialysis patients registered at the Blood Purification Center of Jinshan Hospital, affiliated with Fudan University, in January 2023 were regarded as candidates. Inclusion criteria were as follows: (i) patients with ESRD undergoing hemodialysis for at least 3 months; (ii) willingness to participate in the study and sign an informed consent; and (iii) ability to read. Patients experiencing severe acute complications were excluded from this study. This study adhered strictly to the principles outlined in the Declaration of Helsinki (2013) (approval no. JIEC2022-S83).

2.2. Data collection and definitions

We collected data using medical records and self-reported questionnaires, which included: (i) Epidemiological information: age, gender, household location, marital status, children's status, living arrangements (alone or with others), education level, occupations, religious belief, etc.; (ii) clinical information: primary diseases, duration of dialysis, blood pressure, status of kidney transplantation candidacy, types of daily oral medications (e.g., antihypertensives, furosemide, sodium bicarbonate), Charlson comorbidity index (CCI),[8] dysfunction of vascular access, residual urine volume, presence of uremic pruritus, and restless legs syndrome; (iii) lifestyle information: smoking and drinking habits, engagement in social and recreational activities, and commuting time to dialysis facilities; and (iv) recent laboratory data: hemoglobin (Hb), calcium (Ca), phosphorus (P), parathyroid hormone (PTH), albumin (Alb), prealbumin (preAlb), triglyceride (TG), total cholesterol (Chol), and dialysis adequacy indicators (Kt/V and urea reduction ratio [URR]).

2.3. Evaluation of stigma

The Stigma Scale for Chronic Illness (SSCI), comprising 24 items, was utilized to assess the level of stigma in patients undergoing incident dialysis. The scale is divided into two modules: internalized stigma and enacted stigma.[9] Internalized stigmas includes 13 items regarding self-perception (e.g., embarrassment and self-blame). Enacted stigma includes 11 items regarding the unkind attitude of others toward the patients (e.g., avoiding and discrimination). The Likert rating system is used to score 1 – 5 points based on the options of "no," "rarely," "sometimes," "often," and "always," with a total score of 24 – 120 points. A higher score represents a higher degree of stigma. The SSCI instrument has satisfactory content validity and internal consistency and is considered a generic tool to measure stigma in different chronic illnesses.[10]

2.4. Evaluation of depression and anxiety

The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were used to evaluate the degree of depression and anxiety.[11-13] Both the BDI and BAI contain 21 questions, which are effective in diagnosing depression and anxiety in many studies, especially in patients with chronic somatic diseases.[14,15] Each question has four options: 0 – 3. The cumulative score range of all items is 0 – 63. A higher score represents more severe symptoms.

2.5. Measurement of quality of life

We utilized the medical outcomes study 36-item short-form health survey (SF-36) to measure the quality of life. The scale consists of eight modules: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Each module has a score range of 0 – 100. A higher score represents a higher level of quality of life.[16]

2.6. Statistical analysis

Quantitative data were expressed as mean ± standard deviation (SD), while categorical data were expressed as frequency and percentage (*n*; %). Pearson correlation analysis was employed to examine the correlation between stigma and quality of life. Multiple linear regression analysis was used to identify the predicted factors associated with internalized stigma and enacted stigma, respectively. We adopted the SPSS software version 23.0 to analyze the data, with statistical significance set at $P < 0.05$.

3. Results

After screening, 115 patients were enrolled in this study, with an average age of 52.14 ± 11.84 years and 74 (64.35%) being male. Most patients were married (n = 84; 73.04%) and had children (n = 103; 89.57%). The average duration of hemodialysis was 89.73 ± 64.79 months. The average value of the CCI was 3.13 ± 1.75, and 13.91% of patients were awaiting transplantation. The average scores for BDI and BAI were 18.11 ± 12.15 and 9.41 ± 9.85, respectively (Table 1).

Table 1. Epidemiological, lifestyle, clinical information, and recent laboratory examinations

Variables	Mean±SD/*n* (%)
Age (years)	52.14±11.84
Gender	
Male	74 (64.35)
Female	41 (5.65)
Household location	
Local	101 (87.83)
Non-local	14 (12.17)
Marital status	
Married (cohabition)	84 (73.04)
Single	31 (26.96)
Raising children	
Yes	103 (89.57)
No	12 (10.43)
Living alone	
Yes	14 (12.17)
No	101 (87.83)
Education status	
Primary school or below	8 (6.96)
Junior middle school	46 (40)
Senior middle school	39 (33.91)
University or above	22 (19.13)
Unemployment	
Yes	52 (45.22)
No	63 (54.78)
Religious beliefs	
Yes	16 (13.91)
No	99 (86.09)
Primary diseases	
Glomerulonephritis	74 (64.35)
Diabetic nephropathy	18 (15.65)
Renal vascular disease	7 (6.09)
Others	16 (13.91)
Duration of hemodialysis (months)	89.73±64.79
Systolic pressure (mmHg)	
<140 mmHg	35 (30.43)
140 – 159 mmHg	60 (52.17)
160 – 179 mmHg	20 (17.40)
≥180 mmHg	0 (0.00)
Diastolic pressure (mmHg)	
<90 mmHg	64 (55.65)
90 – 99 mmHg	41 (35.65)
100 – 109 mmHg	5 (4.35)
≥110 mmHg	5 (4.35)
Types of daily oral medications	
<5	41 (35.65)
5 – 10	60 (52.18)
>10	14 (12.17)
Residual urine volume (mL/24 h)	
>1000	5 (4.35)
500 – 1000	12 (10.43)
100 – 500	26 (22.61)
<100	72 (62.61)
Uremic pruritus	
Yes	48 (41.74)
No	67 (58.26)
Restless legs syndrome	
Yes	30 (26.09)
No	85 (73.91)
Waiting for kidney transplantation	
Yes	16 (13.91)
No	99 (86.09)
Charlson comorbidity index (CCI)	3.13±1.75
Vascular access failure during the past 12 months	
Yes	16 (13.91)
No	99 (86.09)
Smoking	
Yes	30 (26.09)
No	85 (73.91)
Alcohol	
Yes	13 (11.30)
No	102 (88.70)
Social activities	
Yes	19 (16.52)
No	96 (83.48)
Recreational activities	
Yes	65 (56.53)
No	50 (43.47)
Travel time to dialysis facilities (min)	
<30	55 (47.83)
30 – 60	22 (19.13)
>60	38 (33.04)
Hemoglobin (g/L)	108.68±16.96
Serum calcium (mmol/L)	2.33±0.30

(Cont'd...)

Table 1. ***(Continued)***

Variables	Mean±SD/*n* (%)
Serum phosphorus (mmol/L)	2.12±0.68
Parathyroid hormone (pg/mL)	342.39±290.38
Albumin (g/L)	38.41±2.93
Prealbumin (g/L)	321.92±66.28
Triglyceride (mmol/L)	1.99±1.57
Cholesterol (mmol/L)	3.74±1.20
Dialysis adequacy indicators	
Kt/V	1.27±0.25
URR	68.13±7.09
BDI	18.11±12.15
BAI	9.41±9.85

Note: Data are presented as mean±standard deviation (SD) or *n* (%).
Abbreviations: BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; URR: Urea reduction ratio.

The average score of the SSCI was 43.09 ± 14.95. Within the SSCI, the scores for internalized stigma and enacted stigma were 25.91 ± 9.26 and 17.19 ± 6.72, respectively (Table 2). Correlation analysis indicated that the total score of the SSCI was negatively related to all modules of the SF-36. Specifically, bodily pain, general health, vitality, social functioning, role-emotional, and mental health revealed significant relationships ($P < 0.05$) (Table 3).

Multivariate linear regression analysis revealed that internalized stigma was significantly associated with uremic pruritus (β = 4.113; 95% confidence interval [CI]: 1.723 – 6.503; $P = 0.001$) and duration of hemodialysis (β = −0.018; 95% CI: -0.001 – (−0.036); $P = 0.042$) (Table 4). Enacted stigma was significantly associated with uremic pruritus (β = 2.941; 95% CI: 0.626 – 5.256; $P = 0.013$), BDI score (β = 0.153; 95% CI: 0.051 – 0.255; $P = 0.004$), and BAI score (β = 0.149; 95% CI: 0.024 – 0.274; $P = 0.020$) (Table 5).

4. Discussion

Stigma is a common phenomenon concomitant with different chronic illnesses, disabilities, and contagious diseases, causing much distress to those who are stigmatized.[17,18] Moreover, stigma poses indirect but adverse implications for public health efforts aimed at combating the diseases or conditions concerned.[19] The consequences for the affected patients may manifest as psychological stress, social isolation, and an increased risk of disability and disease progression.[20,21] Enacted stigma affects self-perception and anticipation of discrimination, while internalized stigma involves internalizing negative stereotypes, resulting in low self-esteem and behavioral futility.[22] For ESRD patients, losing renal function and depending on hemodialysis for survival becomes a focal point of stigma.

The quality of life of maintenance hemodialysis patients is also a field that nephrologists should actively pay attention to. Our findings suggested that stigma is negatively correlated with all modules of quality of life in maintenance hemodialysis patients. Beyond physical suffering, these

Table 2. Stigma scores in MHD patients

Variables	Values (mean±SD)
Stigma (total)	43.09±14.95
Internalized stigma	25.91±9.26
Enacted stigma	17.19±6.72

Abbreviations: MHD: Maintenance hemodialysis; SD: Standard deviation.

Table 3. Correlation between the total score of stigma and each domain of the short-form health survey (SF-36)

Domains	*r*	*P*
Physical functioning	−0.078	0.406
Role-physical	−0.140	0.134
Bodily pain	−0.212	0.023*
General health	−0.232	0.012*
Vitality	−0.231	0.013*
Social functioning	−0.319	0.000*
Role-emotional	−0.308	0.001*
Mental health	−0.332	0.000*

Note: *$P<0.05$.

Table 4. Factors associated with internalized stigma in MHD patients

Variables	β	95% CI	*t*	*P*
Uremic pruritus	4.113	1.723 – 6.503	3.413	0.001*
Duration of hemodialysis	−0.018	−0.001 – −0.036	2.060	0.042*

Note: *$P<0.05$.
Abbreviations: CI: Confidence interval; MHD: Maintenance hemodialysis; SD: Standard deviation.

Table 5. Factors associated with enacted stigma in MHD patients

Variables	β	95% CI	*t*	*P*
Uremic pruritus	2.941	0.626 – 5.256	2.521	0.013*
BDI	0.153	0.051 – 0.255	2.986	0.004*
BAI	0.149	0.024 – 0.274	2.374	0.020*

Note: *$P<0.05$.
Abbreviations: BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CI: Confidence interval; MHD: Maintenance hemodialysis; SD: Standard deviation.

patients face significant life changes such as economic burdens, interpersonal relationships, and modifications in social and family status. A review suggested that stigma affects marriage, interpersonal relationships, mobility, employment, access to treatment and care, education, leisure activities, and social and religious participation,[23] all of which contribute to a diminished quality of life.

Uremic pruritus is a common and distressing symptom in patients with ESRD, affecting up to 46% of hemodialysis patients.[24,25] Moreover, it is associated with multiple health-related complications and is independently associated with mortality.[26] Our study suggested that uremic pruritus was associated with both internalized and enacted stigma in hemodialysis patients. Uremic pruritus, which is a chronic stressor, can significantly impact one's mental well-being and may contribute to the experience of stigma. On the other hand, systemic inflammation is a common characteristic of brain and kidney lesions in ESRD patients, making it quite reasonable to hypothesize that inflammatory mediators may contribute to the cross-talk between the kidneys and brain.[27] Systemic inflammations may be a common pathogenesis of uremic pruritus and neuropsychiatric disorders, which is probably associated with stigma. The well-identified role of cytokines in mediating peripheral and central nervous system communication reinforces this hypothesis.[28]

Our study suggested that internalized stigma was negatively associated with the duration of hemodialysis. For patients with ESRD, the initiation of dialysis itself can be regarded as an acute stressor that produces a series of psychosocial reactions, which may manifest as emotional, cognitive, and behavioral disturbances. Higher BDI scores were noted in patients at the initiation of hemodialysis.[29,30] However, individuals may gradually adapt to this stressor through adaptive coping strategies, leading to an alleviation of adverse psychological reactions over time. Therefore, a methodological, thorough, and comprehensive evaluation should be conducted before the initiation of hemodialysis, and psychological conditions should be identified and addressed as soon as possible.[31]

Previous findings on neurological and psychiatric disorders suggested that depression and anxiety are related to stigma.[32,33] Our study also found that depression and anxiety are related to enacted stigma. Enacted stigma involves experiences of prejudice, discrimination, and stereotyping directed at individuals by others. In essence, it still belongs to an individual's subjective perception, influenced by one's cognitive and emotional patterns. Aaron Beck[x], the founder of cognitive therapy, believes that patients with depression and anxiety have negative cognitive and emotional patterns. These patterns influence how individuals receive, filter, edit, and process information obtained from objective environments. Such negative cognition and emotion may distort information from others, leading to misunderstanding others' attitudes as prejudice or discrimination.

There are several limitations to our study. First, there is currently no established norm or standard value for assessing stigma specifically related to ESRD, so a quantitative comparison could not be conducted. Second, although the various scales we used have been proven to be very effective, they may not capture stigma as comprehensively as a structured clinical interview. Therefore, clinical trials with larger, multi-center samples and more refined psychological assessments are warranted in the future.

5. Conclusion

Stigma is prevalent among maintenance hemodialysis patients, significantly impairing their quality of life. Internalized stigma appears to be associated with uremic pruritus and duration of hemodialysis, whereas enacted stigma correlates with uremic pruritus, depression, and anxiety. Therefore, timely identification and effective intervention by nephrologists are crucial for enhancing the quality of life among patients undergoing maintenance hemodialysis.

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Conflict of interest

The authors have no potential conflicts of interest to disclose.

Author contributions

Conceptualization: All authors
Formal analysis: All authors
Investigation: Wei Ye
Methodology: Wei Ye
Writing-original draft: Wei Ye
Writing-review & editing: Wei Ye

Ethics approval and consent to participate

This study was conducted in compliance with local regulations and the revised established principles of the Declaration of Helsinki (2013). The Medical Ethics Committee of Jinshan Hospital affiliated with Fudan University (approval no.: JIEC2022-S83) approved the

study, and written informed consent to the investigation was obtained from all participants.

Consent for publication

Not applicable.

Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL RESEARCH ARTICLE

Exploring the role of genetic factors in personality disorders among women with heroin dependence

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Abstract

Heroin dependence is a severe psychiatric issue that often coexists with mood disorders and personality disorders, which further compound the complexity and severity of the dependence. The utilization of genetic factors in predicting psychiatric disorders has made notable advancements. We enrolled female patients diagnosed with heroin dependence ($n = 263$) and assessed individuals with paranoid personality disorder, depressive personality disorder, antisocial personality disorder, and schizoid personality disorder based on the DSM-IV criteria. Our objective was to examine the single nucleotide polymorphisms (SNPs; rs174696, rs174699, rs4680, rs4818, rs737866, rs933271, rs12953076b, and rs44458044b) and their association with personality. We discovered a significant association of antisocial personality disorder with rs1544325, rs4680, and rs4818 ($P < 0.05$). Additionally, hallucinogen use was associated with rs3792738 ($P < 0.05$), rs10062367 ($P < 0.05$), and rs1875999 ($P < 0.01$). However, we did not observe a relationship between the SNPs and schizoid personality disorder, paranoid personality disorder, or depressive personality disorder. Heroin dependence is linked to specific personality disorders, particularly antisocial personality disorder. The influence of genetic factors could have a significant impact on the emergence of personality alterations linked to the consumption of heroin.

Keywords: Heroin dependence; Heroin dependence treatment; Drug addiction; Psychotic disorder; Personality disorder; Hallucinogen use; Antisocial personality disorder

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1. Introduction

The abuse or dependence on heroin is a widespread and frequently encountered issue,[1] and it associated with negative mood states,[2] cardiovascular problems,[3] poor oral health,[4] cognitive impairment,[5] accelerated aging,[6] impulsivity,[7] experimentally-induced aggressiveness,[8] and impaired behavior.[9] The health-related quality of life is negatively impacted in Asian individuals who use heroin and report experiencing psychopathological symptoms.[10]

The consumption of heroin can potentially lead to alterations in one's personality, while individuals with specific personality traits such as positive urgency[11] may be inclined to engage in heroin use. Individuals possessing positive urgency may have a higher likelihood

of engaging in heroin use, which could potentially result in alterations to their personality. The clinical manifestation of addiction primarily revolves around mood and impulse-control dysregulation[12] while heroin dependence has a negative effect on impulse control.[13] People with specific personality characteristics, such as a tendency for risk-taking behaviors, may demonstrate a predisposition towards heroin use. For instance, a prior study[14] indicated that antisocial personality disorder was the only domain where a cumulative risk was observed for heroin overdose. Antisocial personality disorder is frequently identified as the predominant comorbid diagnosis among individuals with substance abuse issues.[15,16] Furthermore, it is crucial to emphasize that an individual's personality traits may influence their preference for a particular drug. A previous study[17] has identified a specific externalizing dimension that distinguishes heroin users from those who use alcohol, marijuana, and cocaine. This suggests that certain personality traits may be associated with a higher likelihood of choosing heroin over other substances. Nevertheless, it remains uncertain which specific personality traits have an impact on the preference for heroin over other substances. Furthermore, the use of heroin may be linked to several personality disorders, such as schizoid, depressive, and paranoid personalities. Schizoid and depressive personality disorders have been found to be associated with feelings of loneliness, and individuals experiencing loneliness may turn to drug use as a way to cope with its impact. Drugs can temporarily alleviate negative emotions, provide a sense of euphoria, or serve as a distraction from feelings of loneliness. However, using drugs as a coping mechanism for loneliness is problematic and can lead to a vicious cycle. Drug use can exacerbate symptoms of depression and anxiety, impair social functioning, and further isolate individuals from supportive relationships. It can also lead to the development of substance use disorders, which can further worsen their overall well-being.

Moreover, previous research findings have demonstrated that combining personality traits with demographic information enables the prediction of drug consumption.[18] However, the relationship between specific personality disorders and heroin abuse remains uncertain, as does the association between genetic factors and heroin abuse. While the influence of genetics on personality variations is well recognized, our understanding of the precise mechanisms involved is limited.[19] Moreover, the identification of common genetic associations among co-occurring addiction disorders in this patient population has the potential to open up new avenues for treatment. This could involve pinpointing specific gene biomarkers in individuals with genetic susceptibility.[20] A prior investigation[21] explored the potential links between the dopamine D2 receptor and characteristics of individuals with heroin dependence. In comparison to control subjects, the individuals with heroin dependence exhibited elevated scores for personality traits related to novelty seeking and harm avoidance. In addition, a variation in the gene responsible for producing catechol-O-methyltransferase (*COMT*) has been demonstrated to impact human executive cognition and the functioning of the prefrontal cortex and this influence is likely due to its effect on prefrontal dopamine signaling.[22] Moreover, the *COMT* gene can play a role in personality traits.[23] Certain variations (polymorphisms) of the *COMT* gene can result in different levels of enzyme activity, leading to variations in dopamine regulation.

Collectively, our goal was to investigate single nucleotide polymorphisms (SNPs) of *COMT* and those related to stress, as well as their relationship with personality disorders among women with heroin dependence.

2. Methods

The study protocol was authorized by the review boards at the Shanghai Mental Health Center (SHMC), School of Medicine, Shanghai Jiao Tong University. The research adhered to the principles outlined in the Declaration of Helsinki. All patients gave their informed consent, prior to participating in the study. Furthermore, meticulous records were kept to document the number of interviews conducted with each patient for precise record-keeping. The frequency of employment is depicted in Figure 1.

2.1. Measures

2.1.1. Demographic information and heroin use

The demographic information collected encompassed age, gender, education (categorized as completion of

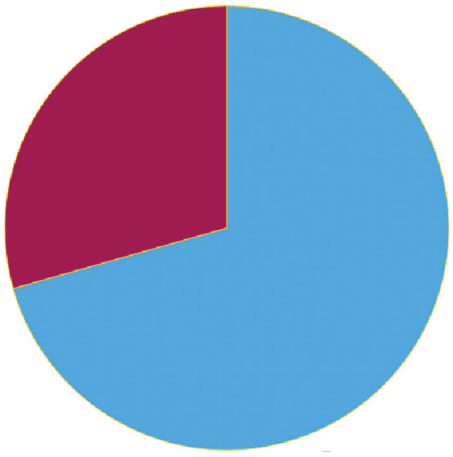

Figure 1. Distribution of employment status among study subjects. Blue part denotes unemployed (n = 185, 70.3%), whereas as red part represents employed (n = 77, 29.3%)

secondary school or not), marital status (married or not), and employment status (employed or unemployed). Participants in this study were individuals who met the definition of drug dependence, which refer to individuals who have relapsed to drug use after being initially identified as drug users by the public security system. Hence, all participants had experienced at least one relapse when they were enrolled in the compulsory rehabilitation centers at the beginning of the study. The participants were in a state of abstinence.

2.1.2. Participants

We initially enrolled approximately 564 participants from four drug rehabilitation centers in Shanghai. Subsequently, we narrowed down the inclusion criteria to exclusively include female participants (n = 263). Patients needed to meet criteria for heroin dependence according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV): Age over 18 years old, and had a heroin use history in the 30 days before the compulsory rehabilitation. Each participant in the rehabilitation program underwent a face-to-face interview within the initial month. The interviews were scheduled to take place in a comfortable environment with the intention of putting the participants at ease. Initial heroin use data was collected through self-report. Participants in the study belonged to the Han Chinese ethnic group, according to their national identity card. The study specifically focused on females, and their average age of first drug use was 21.79 years. Out of the total sample size, 28 individuals reported having used hallucinogens.

Inclusion criteria included: being 18 years or older, resident of Shanghai, meeting the criteria for heroin dependence according to the DSM-IV, having abstained from heroin for a period of 1 – 30 days prior to enrollment, being put in compulsory detoxification institutions for <1 year, and not receiving any medical treatments at the time of survey. Participants were excluded if they met the DSM-IV criteria for other axis I psychiatric disorders or if they used substances other than heroin. Urine and blood samples were collected and screened for illicit drugs. Additionally, potential subjects were informed that they had the option to decline participation or withdraw from the study at any time. Every patient underwent a mandatory, standardized rehabilitation program. This program consisted of daily exercise and educational sessions focused on preventing relapse.

2.2. SNPs genotyping

An examination was conducted to investigate the SNPs of *COMT* and those related to stress, including rs174696, rs174699, rs4680, rs4818, rs737866, rs933271, rs12953076, and rs44458044.

Genomic DNA was extracted from lymphocytes.

Based on data from the HAPMAP database for Beijing Han Chinese, it was observed that the *CRH* genes demonstrated a relatively conservative pattern without polymorphism distribution in the Chinese population. Therefore, the focus of the research shifted to the CRH receptor 1 (*CRHR1*) and CRH-binding protein (*CRHBP*). Through screening of the *CRHR1* and *CRHBP* genes, as well as the upstream region within a 10 KB range satisfying the criteria of r^2 >0.8 and minor allele frequency (MAF) >10%, specific SNPs (*CRHR1*: rs12953076, rs4458044, rs242924, rs17689966; *CRHBP*: rs1715751, rs3792738, rs32897, rs10062367, rs1875999) were selected. The genotyping of these SNPs was performed using the ABI Prism 7900 sequence detection system. The TaqMan SNP genotyping assay, a well-established and dependable technique in genetic analysis, was employed to conduct the genotyping of genes.

2.3. Statistical analysis

Demographic data including age, gender, education (completed secondary school or not), marriage status (married or not), and employment (employed or unemployed) were gathered. The association between SNPs and personality traits was examined by utilizing Chi-square test (Table 1). Statistical Package for the Social Sciences (SPSS) version 24 was used to conduct statistical analysis.

Missing categorical variables such as genetic variables were replaced with mode of the value while missing non-categorical values were replaced with the mean value. Spearman correlation or Pearson correlation were applied according to normality of the parameters. The selected threshold for the P-value was set at 0.05. In addition, we computed the effect size by utilizing Cramer's V as a measure. The Cramer's V value is presented in Table 1.

3. Results

Overall, no significant relationship was found between personality disorders (paranoid personality disorder, depressive personality disorder, and schizotypal personality disorder) and the SNPs of *COMT* gene and those associated with stress. Only antisocial personality disorder was found to be associated with several SNPs, such as rs1544325, rs4680, rs4818, and rs242924 (all $P < 0.05$). Furthermore, hallucinogen use was associated with rs3792738 ($P < 0.05$), rs10062367 ($P < 0.05$), and rs1875999 ($P < 0.01$) (Table 1).

After conducting correlation tests, we discovered that there is only a weak correlation between certain personality disorders. No significant correlation was found between antisocial personality disorder, schizoid personality disorder, and depressive personality disorder

Table 1. Personality disorders and genetic parameters

	Paranoid personality disorder	Depressive personality disorder	Antisocial personality disorder	Schizotypal personality disorder	Hallucinogen use	Alcohol use
rs1544325	*P*>0.05	*P*>0.05	*P*<0.05; χ^2: 12.082 φ: 0.131	*P*>0.05	*P*>0.05	*P*>0.05
rs174696	*p*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05
rs4680	*P*>0.05	*P*>0.05	*P*<0.05; χ^2: 10.460 φ: 0.124	*P*>0.05	*P*>0.05	*P*>0.05
rs4818	*P*>0.05	*P*>0.05	*P*<0.05; χ^2: 9.601 φ: 0.117	*P*>0.05	*P*>0.05	*P*>0.05
rs933271	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05
rs737866	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05
rs12953076	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05
rs4458044	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05
rs242924	*P*>0.05	*P*>0.05	*P*<0.05; χ^2: 9.202 φ: 0.112	*P*>0.05	*P*>0.05	*P*>0.05
rs17689966	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05
rs3792738	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*<0.05; χ^2: 7.875 φ: 0.104	*P*>0.05
rs1715751	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05
rs32897	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05
rs10062367	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*<0.05, χ^2: 9.342 φ: 0.113	*P*>0.05
rs1875999	*P*>0.05	*P*>0.05	*P*>0.05	*P*>0.05	*P*<0.01; χ^2:13.147 φ: 0.135	*P*>0.05

($P > 0.05$). However, a correlation was observed between antisocial personality disorder and schizotypal personality disorder ($P < 0.05$, $r = 0.150$) as well as between antisocial personality disorder and paranoid personality disorder ($P < 0.01$, $r = 0.187$).

After controlling for the impact of schizoid personality disorder, a weak but significant correlation ($P < 0.05$, $r = 0.124$) was found between depressive and paranoid personality disorder. However, when also considering the influence of antisocial personality disorder in addition to schizoid, the correlation between depressive and paranoid personality disorder was not found to be significant ($P > 0.05$). Figure 2 presents a visual summary or overview of theis work.

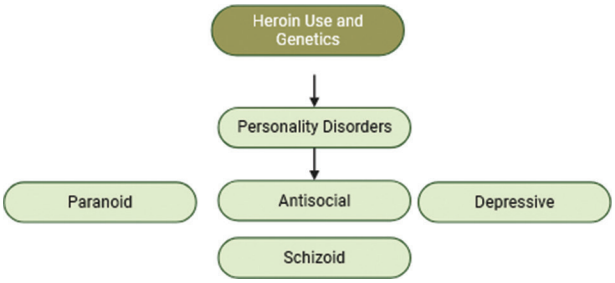

Figure 2. A summary of the main subjects overviewed in the current work

4. Discussion

The main findings of the study indicated that specific personality disorders may be associated with genetic factors related to stress and *COMT*. Our analysis revealed a significant association between antisocial personality disorder and the following SNPs: rs1544325 (χ^2: 12.082), rs4680 (χ^2: 10.460), rs4818 (χ^2: 9.601), and rs242924 (χ^2:9.202).

Furthermore, hallucinogen use was associated with rs3792738 ($P < 0.05$), rs10062367 ($P < 0.05$), and rs1875999

($P < 0.01$). The strongest effect size among the variables investigated was observed in the association between hallucinogen use and a specific SNP (rs1875999).

Genetic factors were not found to be linked with other investigated personality disorders (paranoid personality disorder, depressive personality disorder, and schizotypal personality disorder). Moreover, our analysis did not reveal any significant associations between alcohol use and the SNPs under investigation.

Our findings provide an explanation for the relationship between heroin use and personality changes observed in certain individuals. Genetic factors *(e.g., COMT*) are likely to play a role in explaining this relationship. Our study uncovered a significant association of certain SNPs of *COMT* and those related to stress with the presence of antisocial personality disorder and hallucinogen use. The majority of the pertinent factors were found to be associated with *COMT*. Variations in the *COMT* gene have been associated with differences in cognitive functions,[24] emotional processing,[25] and stress response. Hence, it could be associated with specific personality disorders.

Based on the literature on heroin dependence, numerous factors such as epigenetics, genetics, environmental, treatment-related factors (*e.g.,* duration of drug use), culture, and age are potential confounding variables.

4.1. Confounding factors related to heroin dependence and personality disorders

The diagnosis of psychiatric disorders, such as heroin dependence, can be subject to variations as different clinicians may approach the diagnosis in diverse ways. In heroin dependence studies, a diverse range of variables, such as age, epigenetic factors and psychological factors, that can introduce confusion or distortion were encountered. For instance, heroin dependence could be linked to particular personality disorders, whereas the etiology of schizoid personality disorder is associated with a combination of intrapsychic, cultural, and ethnic factors.[26] The rate of heroin use among women is growing at a faster pace compared to men (Marsh, Park, Lin, and Bersamira, 2018). Moreover, a previous study reports how these two facets of impulsiveness could be associated with different aspects of heroin dependence.[27]

The prevalence of antisocial personality disorder decreases with age.[28] Therefore, age is also one of the major confounding factors in this study. Moreover, the concurrent use of multiple substances, including alcohol and hallucinogens, represents a significant confounding factor in this context.

The inclination for novelty seeking poses a risk factor for developing drug addiction, and the presence of immature character traits and personality disorders heightens the vulnerability to substance abuse.[29] Novelty seeking is influenced by certain genetic factors[30] and is related to certain personality characteristics.[31] Hence, novelty seeking represents a significant influencing factor.

Based on the self-medication hypothesis, the preferences for specific substances are impacted by attachment.[32] Therefore, family environment may be one of the major confounding factors, along with cultural factors related to family environment. Stimulants like heroin may give the addicted individuals, particularly teenagers, a sense of liberating themselves from parental control. Moreover, in our study, it is important to consider that Chinese culture showcases nuances compared to other cultures.

A significant portion of patients dependent on heroin reported experiencing inadequate sleep quality,[33] while a lack of sleep may be related to personality parameters.[34] Furthermore, sufficient sleep plays a critical role in promoting optimal emotional functioning.[34] Therefore, sleep quality is also one of the potential confounding factors in this study. In our study, it is important to note that sleep quality was not recorded, and this omission may represent a potential confounding factor in the study.

Taken together, the diagnosis of psychiatric disorders, including heroin dependence, can vary due to the diverse approaches taken by different clinicians. Various variables analyzed in studies on heroin dependence can introduce confusion or distortion, including age, sleep, duration of drug use, environmental factors, novelty seeking, genetic factors, epigenetic factors, cultural, and psychological factors.

4.2. Heroin and hallucinogen

There is limited literature available that explores the comorbidity between heroin use and hallucinogen use. Hallucinogen use has been associated with the development of psychotic symptoms. The use of hallucinogens has the potential to elicit positive symptoms similar to those observed in schizophrenia. A strong dependence on psychostimulants is linked to an increased risk of psychosis, whereas severe dependence on heroin exhibits a contrasting negative association with psychosis.[35]

Moreover, genetics plays a crucial role in both personality disorders and individual responses to hallucinogen use.

Studies investigating the utilization of hallucinogens have uncovered both potential advantages and potential drawbacks linked to their use. The immediate effects of hallucinogen use can have a significant impact, causing disorientation, cognitive difficulties, and potentially inducing changes in perception.[36]

Moreover, individuals with nonaffective psychosis are at increased risk of heroin.[37] As a result, the use of hallucinogens may influence the probability of heroin use. According to the Swedish system for substance use, all the studied substances are linked to increased risk of psychosis.[38] However, the literature on the heroin use and risk of psychosis is controversial.

Another research paper investigated the usage patterns of heroin and delved into a longitudinal study assessing the outcomes of treatment for heroin dependence. Notably, the study highlights the substantial prevalence of psychiatric comorbidities within this population, including a lifetime occurrence of 37% for post-traumatic stress disorder, 23% for major depression, 75% for anti-social personality disorder, and 51% for borderline personality disorder.[39]

The precise mechanism by which hallucinogens influence genetic factors remains uncertain. One animal study provided the initial evidence showing that the administration of a low dose of d-LSD, which has significant behavioral implicsations, leads to the immediate activation of c-Fos gene in specific regions of the rat forebrain.[40]

In our study, hallucinogen use was associated with rs3792738 ($P < 0.05$), rs10062367 ($P < 0.05$), and rs1875999 ($P < 0.01$). Further research is needed to expand our understanding of the complex relationship between heroin use, hallucinogen use, genetic factors, and psychiatric comorbidity.

4.3. Genetics and personality disorder

Genetic studies indicate that personality disorders classified under DSM-IV axis II exhibit a moderate level of heritability.[41] The heritability of addictions falls within a moderate-to-high range, which presents a paradox since these disorders involve substance use, which is influenced by genetic and environmental factors.[42] Another study proposes that individuals with more impulsive behavior may have an increased risk for substance use disorders due to a reduced expression of the gene responsible for encoding the 5-HTT transporter, which can be attributed to the "S" promoter polymorphism.[43]

Numerous individuals are exposed to addictive substances during pain treatment, yet the majority do not develop addiction, despite experiencing temporary tolerance and dependence. The likelihood of initial substance use and the development of pathological usage patterns are influenced by inherent factors such as genotype, gender, preexisting addictive disorders, or other mental illnesses.[44] To mitigate the influence of gender, we incorporated exclusively female participants in this study.

Another study discovered a positive association between prior hallucinogen use and specific traits related to seeking new sensations, impulsive behavior, and challenges in regulating emotions among adolescents who were hospitalized for treatment.[36] It is important for clinicians to recognize the prevalence of hallucinogen use and the increased likelihood of encountering mental health problems among individuals who engage in such use.[45] The existing body of literature has outlined the current understanding of the molecular genetic responses occurring in the brain in response to psychedelics, and has explored how changes in gene expression can potentially lead to modified cellular physiology and behaviors.[46]

The *COMT* enzyme is responsible for the breakdown of dopamine and other catechols.[47] Comorbid substance use in individuals with schizophrenia was found to be linked to genetic variations in genes associated with dopaminergic neurotransmitter systems.[48] Furthermore, numerous studies have shown that *COMT* gene variants are associated with personality traits.[49] Moreover, a previous study demonstrated that in individuals with substance use disorder, the activity of soluble *COMT* was found to be correlated with the severity of drug dependence. Additionally, it was associated with factors related to impulsivity (self-control and non-planning).[50]

Our study uncovered a significant association between certain genetic factors related to *COMT* and stress and the presence of antisocial personality disorder. The majority of the pertinent factors were found to be associated with *COMT*.

4.3.1. Schizoid personality disorder, genetics and heroin use

Schizoid personality disorder is one of the "cluster A" personality disorders.[51] Individuals with schizoid personality disorder may be at an increased risk for developing addictive behaviors as a means of coping with their emotional detachment and social isolation. The tendency to experience limited emotional range and difficulty forming meaningful connections can lead to a reliance on substances or addictive behaviors, a way to alleviate feelings of emptiness or numbness.

Overall, our study revealed no significant association between schizotypal personality disorder and investigated genetic factors (e.g., *COMT*) in female individuals with heroin dependence.

4.3.2. Paranoid personality disorder

When examining the relationship between paranoid personality disorder and heroin use, it is important to consider the potential implications and interactions. While

research specifically focusing on paranoid personality and heroin comorbidity is limited, there are several factors to consider. Paranoia can be associated with certain substance abuses, such as the use of cocaine[52] and methamphetamine.[53] However, the literature on paranoid personality disorder and heroin use is limited.

Additionally, we observed no association between genetic factors and paranoid personality disorder in females with heroin dependence.

4.3.3. Antisocial personality disorder and heroin

A previous study claimed that heroin dependence is in high degree in comorbidity with antisocial personality disorder.[54] Antisocial personality disorder is a personality disorder characterized by a pervasive pattern of disregard for and violation of the rights of others. Heroin dependence, on the other hand, is a substance use disorder involving a compulsive and harmful dependence on heroin.

Antisocial personality disorder and heroin dependence are two distinct yet interconnected mental health conditions that can significantly impact an individual's quality of life.[55] Another study found that psychopathy may exacerbate decision-making deficits in heroin dependent individuals.[56] The association between 5-HTTVNTR and DATVNTR interactions may be linked to the co-occurrence of antisocial personality disorder in male patients dependent on heroin.[57]

Antisocial personality disorder is associated with increased psychiatric problems[58] and criminal activities.[59] Hence, it is crucial to comprehend the interconnection between heroin use and crime, as well as the causal relationship between the two.

Overall, we found that antisocial personality disorder is associated with following SNPs: rs1544325 (χ^2: 12.082), rs4680 (χ^2: 10.460), rs4818 (χ^2: 9.601), and rs242924 (χ^2: 9.202). Additionally, rs242924 is related to corticotropin-releasing hormone, a neuropeptide that plays a crucial role in response to stress.[60]

In addition, a previous study offers additional evidence supporting the involvement of the *COMT* gene as a modifier that influences the variation between individuals in their inclination towards violent behavior, specifically in subjects without significant mental disorders.[61] Moreover, the role of *COMT* is to facilitate the breakdown of catecholamines-like dopamine.[62] The chronic use of addictive drugs (*e.g.,* heroin) can lead to a reduction in the expression of dopamine receptors in the brain.[63] Moreover, the hyperreactivity of the dopaminergic reward system at the neurochemical and neurophysiological levels can serve as a neural basis for impulsive-antisocial behavior and substance abuse in individuals with psychopathy.[64] The *COMT* gene's impact on dopamine mechanism can have implications for antisocial personality traits, potentially accounting for notable differences observed among individuals with different *COMT* variants.

4.3.4. Depressive personality disorder

The literature is scarce on the relationship depressive personality disorder and genetics in individuals with heroin dependence. Patients with personality disorders had a higher frequency of previous depressive episodes.[65] Depression increases the risk of developing substance use disorders.[66] Furthermore, a previous study claimed that in heroin-dependent individuals, higher levels of depression was correlated with higher levels of psychoticism and neuroticism.[67]

While there is limited research specifically examining the relationship between depressive personality disorder and heroin dependence, there are some connections between the two considering self-medication hypothesis and vulnerability to addiction. In general, our research revealed no significant genetic factors (*e.g., COMT*) associated with depressive personality disorder.

The current literature lacks sufficient evidence on the relationship between depressive personality disorder and genetics in heroin-dependent individuals. However, patients with personality disorders have been found to have a higher frequency of previous depressive episodes, and depression itself has been linked to an increased risk of developing substance use disorders.

5. Conclusion

In individuals with heroin dependence, *COMT* SNPs are associated with the development of personality changes, including antisocial personality disorder. Genetic factors, however, were not found to be linked with other personality disorders, such as paranoid personality disorder, depressive personality disorder, and schizotypal personality disorder, under investigation.

5.1. Limitations

The current study has several significant methodological limitations. Firstly, due to its cross-sectional nature, it is challenging to determine the temporal sequence between the variables. Consequently, we cannot establish whether the variables preceded or followed the symptoms.

Moreover, a substantial portion of the data relied on self-reported measures (personality scale results), which introduce a risk of biased self-presentation. It is important to acknowledge that personality is a complex construct,

whose characterization extends beyond the limitations of scales and categories.

The research findings highlighted a notable prevalence of concurrent multiple drug use among patients. Furthermore, the inclusion of smokers among the participants may have influenced the study outcomes. Moreover, it is crucial to recognize that studies focusing on substance abuse cannot be easily generalized to individuals specifically dependent on heroin. The manner in which personality disorders are conceptualized could also impact our findings.[68]

Experimental validation has consistently confirmed various personality traits among individuals with heroin dependence. Nonetheless, it remains difficult to determine whether these characteristics represent an inherent "addictive personality" that predated drug use, or if they are a result of drug addiction.[69] One of the limitations of the current study is the absence of a control group.

5.2. Suggestions for further studies

Conducting prospective studies will help to further explore the relationship between drug use, genetic factors, personality disorder, and outcomes.

Furthermore, personality studies can be complemented and supported by brain imaging findings. The amalgamation of investigating genetic factors can offer valuable insights into the intricate connection between personality disorders and heroin dependence.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Kadir Uludag
Formal analysis: Kadir Uludag
Investigation: Kadir Uludag
Methodology: Kadir Uludag
Writing – original draft: Kadir Uludag
Writing – review & editing: All authors

Ethics approval and consent to participate

The study protocol was authorized by the review boards at the Shanghai Mental Health Center (SHMC), School of Medicine, Shanghai Jiao Tong University. Informed consent was obtained from study participants.

Consent for publication

Informed consent of the study participants was obtained for publishing this work.

Availability of data

Data are available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Changes in core depressive symptoms over time in peripartum women: A network analysis

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Abstract

Perinatal depression (PND) is a prevalent mental health condition that affects women during pregnancy and after childbirth. Distinct clinical subtypes of PND exist, with the timing of symptom onset being a pivotal element in the classification of these subtypes. However, the specific manifestations of PND across the various stages of pregnancy and the postpartum period remain to be elucidated. This study aimed to explore the changes in depression symptoms with the stage of pregnancy. Women in their second (n = 161) and third trimesters (n = 248) of pregnancy as well as those in their first 6 weeks of the postpartum period (n = 110) were recruited. Each patient was evaluated using the Edinburgh Postnatal Depression Scale. A network analysis approach was used to explore the interconnections among depressive symptoms across the different time periods. Women in the postpartum period exhibited the most pronounced prevalence of PND and severity of depressive symptoms. In the second and third trimesters, "sadness and misery" was the most central symptom. However, its prominence diminished after childbirth. "Fear and panic" was the predominant symptom in the postpartum network. The structural integrity of PND symptom networks was maintained across all three periods, with consistent strength and closeness. This study demonstrates the temporal evolution of PND's central symptoms in women during and after pregnancy, transitioning from depression-centric to anxiety-centric manifestations. These findings advocate for symptom-specific interventions to enhance the mental well-being of mothers and their offspring. Furthermore, this study offers clinical insights into the biological underpinnings of PND subtypes, facilitating precise diagnosis and targeted treatment strategies.

Keywords: Perinatal depression; Different periods; Central symptoms; Network analysis; Subtype

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1. Introduction

Perinatal depression (PND) is characterized by depressive episodes experienced by women during pregnancy (antenatal depression [AND]) as well as in the initial 12 months

postpartum (postpartum depression [PPD]).[1] According to epidemiological studies, the prevalence of PND among women ranges from 13.3% to 19.7%.[2,3] However, according to a meta-analysis, the incidence of AND is higher at 20.7%,[4] and patients in their second and third trimesters are particularly vulnerable to AND.[1] Globally, PPD is projected to impact approximately 17.22% of women,[5] and it usually manifests within 6 weeks of childbirth.[6] Women with PND face an elevated risk of self-harm and suicide as well as challenges in parenting and marital relationships. The risk is particularly pronounced among women who have utilized donor sperm for conception, possess restricted educational and financial means, lack sufficient social support, and have experienced previous episodes of depression disorders.[1,7,8] Furthermore, PND can impact the early brain development of infants, with effects on cognition becoming apparent in primary schooling.[9] PND also increases the risk of depression in the spouse,[10] thus placing a significant burden on families and society.

PND represents a diverse clinical entity, encompassing various subtypes that exhibit distinct symptom profiles and onset patterns at different stages of pregnancy and the postpartum phase.[11,12] Investigating the onset timing is crucial for delineating more accurate phenotypic classifications as well as for biological and genetic studies of PND. For example, although PND typically emerges either in the final trimester of pregnancy or within the first 6 weeks following childbirth,[1] the underlying contributing factors differ. PND onset in the postpartum period is a subtype sensitive to sex hormone fluctuations, as sex hormone levels decline rapidly from high peaks after childbirth. Conversely, PND onset in the third trimester is not hormone-sensitive.[13]

The biological mechanisms underlying the variance in the central symptoms and severity of PND in different periods of pregnancy remain to be elucidated. Previous studies have only addressed the differences in depression severity between AND and PPD.[11,14] In these studies, individuals from different trimesters were grouped together in the AND group, and the core symptoms of PND at each stage were not clarified. Identifying the core symptoms associated with PND subtypes is essential because it can enhance the development of more efficacious intervention strategies.

Employing a novel network analysis approach can provide deeper insights into the pivotal symptoms of PND and their interplay with other symptoms across various time frames. Network theory posits that central symptoms, due to their extensive connections with other symptoms, are instrumental in the etiology, perpetuation, and resolution of mental health disorders.[15] This methodology circumvents the limitations of conventional methods by identifying the most salient symptoms of psychiatric conditions.[16-18] For example, network analysis has revealed that the most central symptoms in individuals diagnosed with obsessive-compulsive disorder are compulsive behaviors and obsessive thoughts.[19] Wang *et al.*[18] applied network analysis to discern shifts in the central symptoms of depression and anxiety from the onset to the post-peak period of the COVID-19 pandemic; their findings highlighted the evolving central characteristics over time. Consistent with network theory, these symptoms exhibit intricate causal interconnections, which are best understood from a causal systems perspective.[20] Thus, the identification of network characteristics through this innovative analytical instrument may yield significant clinical benefits for the diagnosis, treatment, and prevention of mental disorders. However, studies on PND have only analyzed the relationships between specific risk factors and depressive symptoms during pregnancy and the postpartum period.[21,22] or have only exhibited the network structure of depression in the second trimester.[23] The changes in network characteristics in the different trimesters and postpartum period remain to be explored.

The current study aimed to assess the variations in the depressive severity among women in their second trimester, third trimester, and postpartum period to better understand how the core symptoms of PND change over time, especially during high-risk periods for depression. Furthermore, we aimed to estimate the networks of depressive symptoms of PND at different time periods to collect evidence for the precise diagnosis and treatment of PND subtypes. In addition, we aimed to propose recommendations for enhancing the psychological well-being of women throughout pregnancy and the postpartum period. This study is the first to employ network analysis on a cohort of women across various pregnancy stages and the postpartum period, aiming to explore symptom interactions of depression and examine symptom evolution over time. We hypothesized that the network characteristics of depression symptoms would change over the three time periods and that depression severity would significantly differ between the three groups.

2. Methods

2.1. Participants and procedure

The Wenjuanxing platform (Zhongyan Network Technology Co., Shanghai, China) was utilized to facilitate an online survey. The QR code for the online survey was disseminated across platforms such as Intent, WeChat, and Tencent QQ. Women aged 19–49 years who could read and operate a computer or smartphone were recruited from two centers

(Zhongda Hospital, affiliated to the Southeast University, and Nanjing Hospital, affiliated to the Nanjing University of Chinese Medicine) between May 2022 and March 2023. The participants were categorized into three groups based on their pregnancy phase: the second-trimester group (161 women), third-trimester group (248 women), and postpartum group (110 women). This study was approved by the Ethics Committee of Zhongda Hospital (No. 2020ZDSYLL230-P01; October 27, 2020). All participants had to provide and sign a written informed consent available online.

2.2. Instrument

The Edinburgh Postnatal Depression Scale (EPDS)[24] is a well-established instrument for detecting depressive symptoms in both pregnant and postpartum women. This 10-item questionnaire utilizes a self-assessment scale wherein each item is rated from 0 (most of the time) to 3 (not at all). The total score can vary from 0 to 30. A total score of ≥10 suggests the presence of depression, and an elevated total score is indicative of more pronounced depressive symptoms.[25]

2.3. Statistical analyses

Statistical analyses were conducted using SPSS software (version 21.0; 1IBM Corporation, Armonk, NY, USA). One-way analysis of variance (ANOVA) was used to compare the age and EPDS scores among groups. Bonferroni correction was used to perform a post-hoc analysis of the groups. The Chi-square test was employed to assess differences in depression prevalence. A p-value of <0.05 was indicative of statistical significance. All network analyses were performed using R (version 4.2.1).

2.3.1. Network estimation

The symptom networks were depicted through network diagrams, including the overall EPDS network for all participants as well as the EPDS networks specific to each time period. Within these diagrams, "nodes" corresponded to the variables, whereas "edges" signified the correlations existing between them.[26] A least absolute shrinkage and selection operator Gaussian graphical model was applied to infer the structure of the symptom networks, and pairwise correlations delineated the associations among the variables.[27] The selection of the optimal network configuration was guided by the extended bayesian information criterion.[28] For executing this analysis, the "bootnet" R package's "estimateNetwork" function was used, employing "EBICglasso" as the standard approach for network estimation.[29]

2.3.2. Network centrality

The "qgraph" package in R, specifically its "centrality plot" function, was used to ascertain the network's centrality metrics.[30] These metrics included strength, betweenness, closeness, and expected influence (EI), which are integral to characterizing the network's architecture.[18] Strength was calculated as the aggregate weight of edges connected to each node. Betweenness quantified the frequency with which a node lay on the shortest path between pairs of nodes. Closeness was determined as the inverse of the mean distance from a particular node to all other nodes. EI represented the cumulative weight of the edges emanating from a given node.

2.3.3. Network stability

The resilience of the network solution, including the precision of edge weights and the reliability of centrality measures, was assessed using the "bootnet" R package.[26] Network stability was gauged through a bootstrapping procedure that involved 2500 resampling iterations, with 95% confidence intervals (CIs).[16] A wider CI indicated a lower precision in edge weights, whereas a narrower CI indicated a more dependable network structure.[29] The inclusion of "0" within the range of the constructed CIs signified the absence of statistically significant differences in edge weights (or node strength) among distinct symptoms.

To assess the stability of the centrality indices using a case-dropping subset bootstrap method,[16] the correlation stability (CS) coefficient was determined. The network's structure was deemed stable if the CS coefficient remained high even after eliminating a subset of cases. An exemplary CS value should approach 0.7, indicating a 95% likelihood that the correlation would remain 0.7 even after removing the maximum allowable proportion of cases.[29] Furthermore, the CS value should not drop below 0.25, and it should ideally be >0.5.

3. Results

3.1. Demographic characteristics and depressive symptoms

Figure 1 and Table S1 depict the age and EPDS scores during the three time periods. No significant difference in age was found between the three groups ($P > 0.05$). The prevalence of depression in all participants was 32.18%, with the highest prevalence in the postpartum group (45.45%), followed by the second trimester (27.33%) and third trimester (29.44%) groups. Similarly, the postpartum group exhibited the highest total scores, both depression and anxiety scores, and the highest scores for each item of the EPDS (all $P < 0.05$, Bonferroni correction), except for items 5, 7, and 10 ($P > 0.05$).

3.2. Network estimation and centrality

Figure 2 depicts the depression network and the EI of all participant data. Except for EPDS10 ("self-harm")

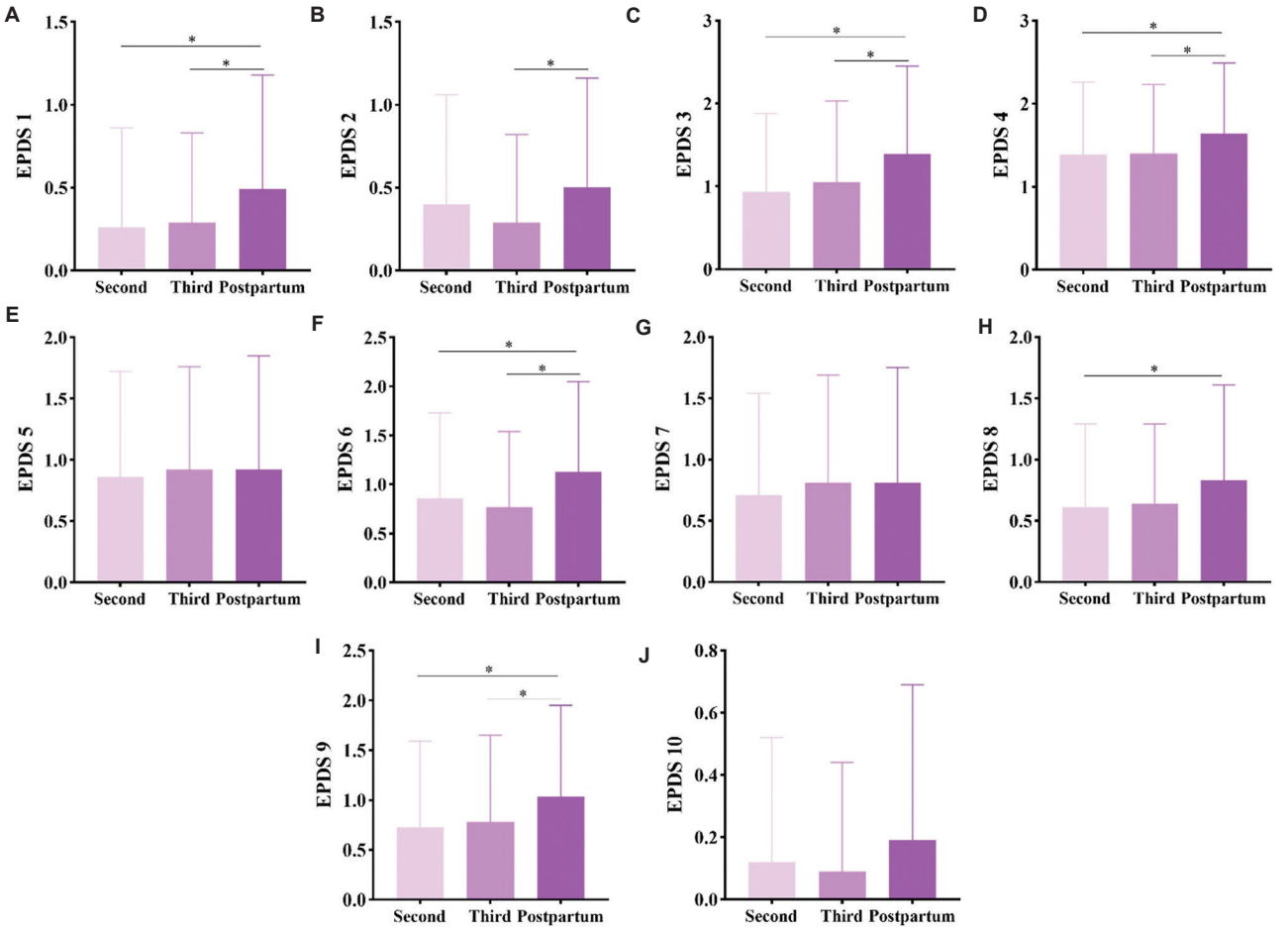

Figure 1. Score of each item on the EPDS in the three study groups. (A-J) Represent comparison of scores at different stages of the EPDS for items 1 to 10, respectively.
Note: *$P < 0.05$ (Bonferroni correction), when compared with the postpartum group.
Abbreviation: EPDS: Edinburgh Postnatal Depression Scale.

and EPDS3 ("self-accusation"), the other depressive symptoms were strongly interconnected within this network, as evidenced by their elevated EI. The networks for the three time periods displayed varied configurations (Figure 3A-C), as reflected by the quantity and intensity of the edges. Figure 3D shows the EI for the networks corresponding to the second trimester, third trimester, and postpartum period. The node EPDS8 ("sadness and misery") emerged with the highest EI in the depression network models for both the second and third trimesters. However, the node EPDS5 ("fear and panic") exhibited the highest EI in the postpartum network model. In addition, almost all nodes, especially the nodes EPDS8 ("sadness and misery"), EPDS5 ("fear and panic"), and EPDS4 ("worrying"), exhibited a relatively high strength in all the time periods (Figure S1), indicating the critical role of these symptoms in the networks.

The detailed edge weights are enumerated in Tables S2-S4. In the second trimester network, the most robust correlation was observed between EPDS4 ("worrying") and EPDS5 ("fear and panic"), followed by correlations between EPDS1 ("laughter and interest") and EPDS2 ("looking forward to the future") and between EPDS7 ("unhappiness and insomnia") and EPDS8 ("sadness and misery"). Similarly, the strongest association in the third-trimester network was observed between EPDS4 ("worrying") and EPDS5 ("fear and panic"), followed by the associations between EPDS8 ("sadness and misery") and EPDS9 ("unhappiness and crying") and between EPDS1 ("laughter and interest") and EPDS2 ("looking forward to the future"). In the postpartum network, the most significant association was identified between EPDS4 ("worrying") and EPDS5 ("fear and panic"), followed by the associations between EPDS1 ("laughter and interest")

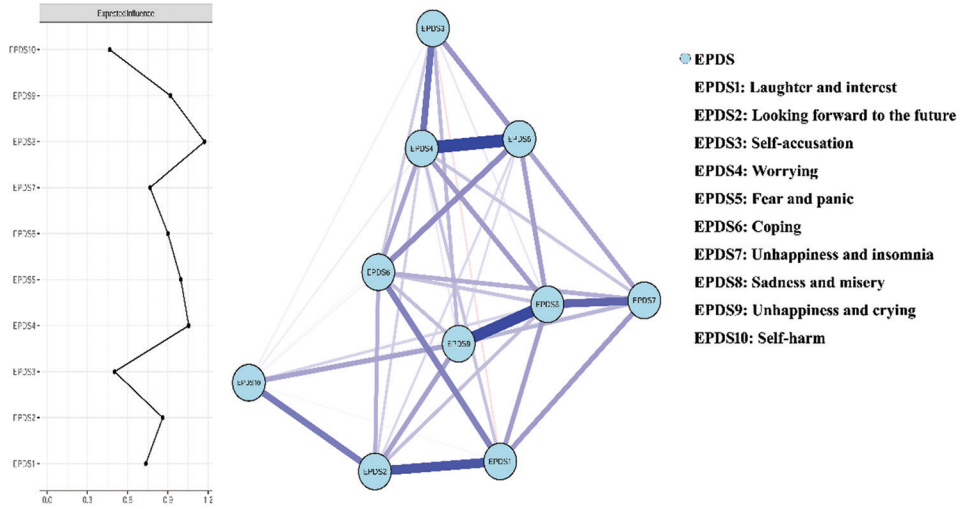

Figure 2. The network of all participants. The expected influence statistics and the network model of depressive symptoms in all participants are shown. Blue nodes represent EPDS items. Blue edges represent positive correlations between nodes, and red edges represent negative associations between nodes. Abbreviations: EPDS: Edinburgh Postnatal Depression Scale.

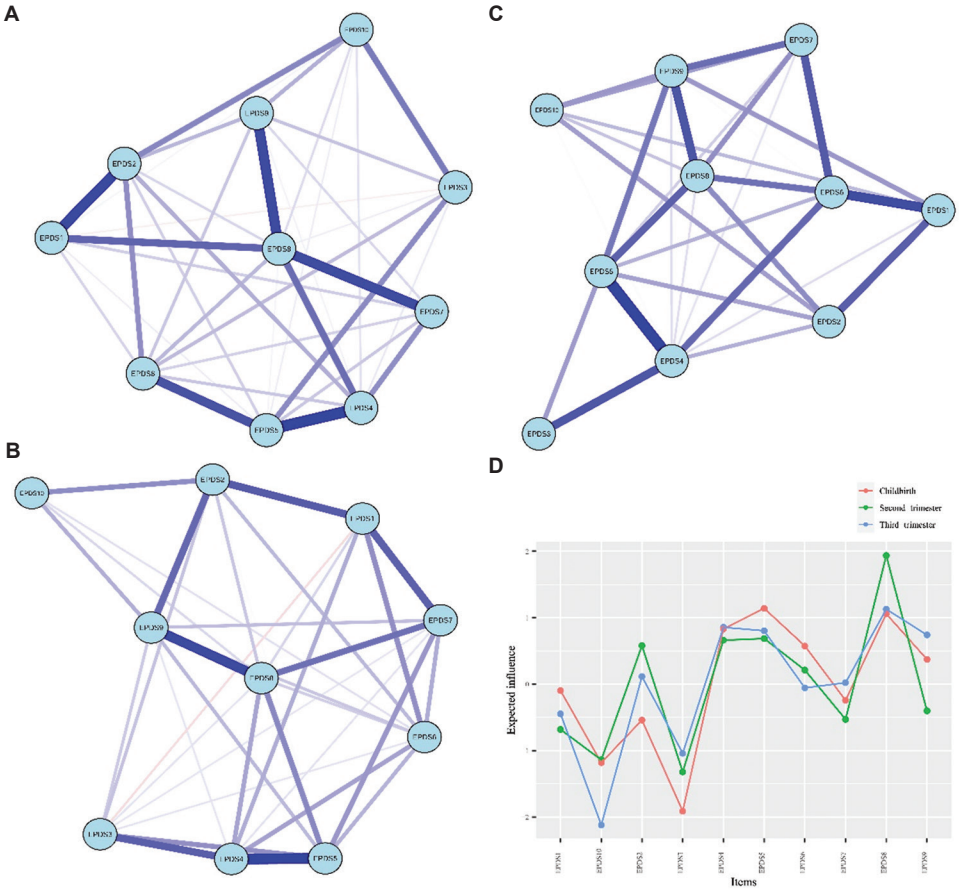

Figure 3. Depressive symptom networks and the expected influences in the 3 time periods. Depressive symptom networks during the (A) second trimester, (B) third trimester, and (C) postpartum period. Blue nodes represent EPDS items. Blue edges represent positive correlations between nodes, and red edges represent negative associations between nodes. (D) The graph depicts the differences in expected influence between the three time periods.
Abbreviations: EPDS: Edinburgh postnatal depression scale.

and EPDS6 ("coping") and between EPDS8 ("sadness and misery") and EPDS9 ("unhappiness and crying").

3.3. Network stability

Figure 4 depicts the stability of the depressive symptom networks in the second trimester, third trimester, and postpartum period, indicating that both the strength and closeness of the networks were relatively consistent. In the second trimester network, the strength ($CS_{cor=0.7}$ = 0.441) exhibited an acceptable level of stability, whereas the closeness ($CS_{cor=0.7}$ = 0.205) exhibited poor stability. In the third trimester network, the strength ($CS_{cor=0.7}$ = 0.516) exhibited good stability, and the closeness exhibited acceptable stability. In the postpartum network, the stability of both strength ($CS_{cor=0.7}$ = 0.364) and closeness ($CS_{cor=0.7}$ = 0.364) were acceptable. However, the betweenness exhibited great instability at all time periods (second trimester: $CS_{cor=0.7}$ = 0.13; third trimester: $CS_{cor=0.7}$ = 0; and postpartum: $CS_{cor=0.7}$ = 0). Furthermore, the stability of the edge-weights precision was validated using the bootstrap method (Figure S2).

4. Discussion

The current study investigated the prevalence and severity of PND across various pregnancy stages and the postpartum phase. It also aimed to identify and elucidate the PND subtypes by evaluating the central depressive symptoms and their associations with other symptoms. We found that women in the postpartum period exhibited the highest rates and most intense manifestations of depression and anxiety compared to those in the second and third trimesters. The network analysis revealed that "sadness and misery" (EPDS8) exhibited the most pronounced centrality in the second and third-trimester networks as well as in the network that included all participants. However, "fear and panic" (EPDS5) emerged as the most central symptom in the postpartum network. The stability of the strength and closeness in all three PND networks was maintained.

Depression was most prevalent in the postpartum period, which is consistent with the finding of a study from Korea.[31] Because a proportion of women with PPD may have experienced depressive symptoms during or before pregnancy,[6] the prevalence of PPD would increase over time. However, other studies have reported a lower prevalence of PPD (11.7 – 23%).[5,32,33] This may be attributed to the different criteria used to define postpartum. In this study, we used 6 weeks postpartum as the criteria of PPD, which is according to the International Statistical Classification of Diseases (10th Revision), and more specifically to refer to the high-risk time period for PPD. However, previous studies have employed the World Health Organization criteria, which extends the postpartum period to 12 months.[14] The diagnostic definition of PPD remains controversial because its complex mechanisms results in diverse clinical features. Furthermore, there may be specific PPD subtypes, which would account for the variation in prevalence. For example, rapid changes in reproductive hormone levels occur only within the first 6 weeks of the postpartum period, which is an important factor that triggers PPD.[34] Therefore, the mechanism underlying the onset of the onset of PPD after 6 weeks, which would result in different depressive features and prevalence, should be evaluated.

Similar to the prevalence of PND, most of the items on the EPDS exhibited the highest scores in the postpartum period in our study, indicating that depression is the most severe within 6 weeks after childbirth. In a previous study, depressive symptoms during pregnancy and 4 weeks postpartum were compared in Chinese women; the results suggested that there are more preterm births and lower birth weights in women with depression onset in the postpartum period than in those during pregnancy.[35] Infant health, breastfeeding demands, diminished

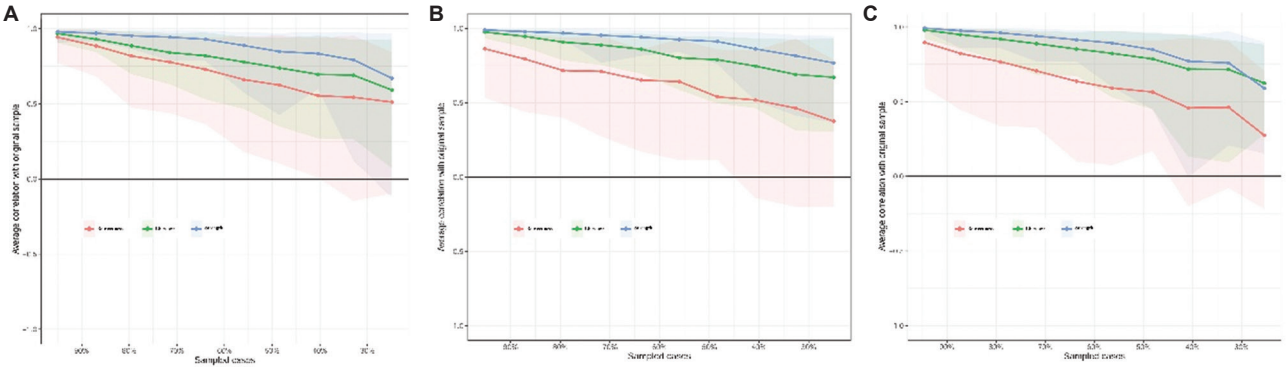

Figure 4. Stability of network structures. The stability of second trimester, third trimester, and postpartum networks is shown in (A-C), respectively. The x-axis represents the included proportion of cases, and the y-axis represents the average correlation between the original and estimated centrality indices after excluding the proportions of cases. Different colored lines indicate different centrality while the shading indicates the 95% confidence interval

personal time, and shifts in the partner relationship, including sexual relationship, may be added stressors in women after childbirth.[36] Moreover, approximately 31% of women with PPD have suicidal ideations.[37] In addition to environmental risk factors, biological factors play an important role in the development of PPD. For example, the estrogen receptor gene is a trigger for PPD, which has been associated with EPDS scores in women in the postpartum period.[38] Furthermore, although more severe depressive symptoms have been observed in women with PPD than in those with AND, the cause remains unclear. However, differences in psychotherapy effectiveness between PPD and AND have been considered as the cause for the difference in depression severity.[39] Therefore, the differences in specific depressive symptoms between the different periods should be identified to better understand the biological mechanisms of PND subtypes.

Consistent with a previous study's finding, we found that most symptoms of depression have high centrality during pregnancy.[22] In the current study, "sadness and misery" and "looking forward to the future" were the most central depressive symptoms in the second trimester. However, the centrality of these symptoms decreased in the third trimester and the postpartum period, indicating that women experienced lower negative moods during postpartum. Conversely, "fear and panic," as one of the most central anxiety symptoms, exhibited the highest centrality in the postpartum period, indicating an increase in women's anxiety after childbirth. The depression symptoms undergo a temporal shift, transitioning from depression-centric to anxiety-centric manifestations. Depression and anxiety can develop concurrently,[40] impacting 75% of women during the postpartum period.[41] This comorbidity status may complicate the identification of PND subtypes because depression and anxiety share some biological mechanisms.[42] Furthermore, depression and anxiety are substantially associated with the genetics of female reproductive system disorders.[43] Therefore, it may be more accurate to focus on the individual items or subscales of the EPDS, rather than the entire scale, to assess PND symptoms throughout a woman's pregnancy. Putnam *et al.*[11] reported that there are three underlying dimensions and five distinct clinical subtypes of PND that are measured using the EPDS, with different levels of anxious depression being subdivided into these five subtypes.

Depression with features of anxiety is characterized by distinct neurobiological signatures when contrasted with depression without anxiety. Furthermore, individuals with anxious depression are more prone to recurrent major depressive episodes and exhibit an elevated risk of suicidal thoughts than those with non-anxious depression.[44] This may account for the central symptoms and higher prevalence and more severe symptoms in the postpartum period than during pregnancy in the present study. Therefore, we propose that more anxiety-centric interventions be administered to women with PPD and more depression-centric interventions be administered to women with AND. A meta-analysis reported that the effect of psychological therapy is highly heterogeneous,[39] which may be attributed to the PND subtypes and their different clinical features. However, psychological therapy is effective and should be considered the first-line treatment for PND.[45] Thus, identifying PND subtypes before the implementation of targeted psychological therapy may improve the consistency of treatment efficacy.

This study had several limitations that warrant recognition. First, the participant pool was not a randomly selected large-scale sample, and symptom data were collected during a particular phase. Moreover, women in their first trimester were not included in this study. Thus, the results may be applicable only to Chinese women in their second or third trimester and those in the postpartum period (within 6 weeks after birth). Future studies should focus on women throughout their pregnancy as well as during the postpartum period to explore the changes in core depressive symptoms. Second, depressive symptoms were not limited to the time of onset in different time periods. The determination of the time of onset may be more indicative of the core symptoms. Third, although this study provides valuable insights into the temporal evolution of the psychological network, the analytical methods employed could not reveal the underlying causal mechanisms. Therefore, the relationships between the networks may be considered bi-directional due to their non-directional nature. However, examining how core symptoms change over time in pregnant and postpartum Chinese women is a novelty of this study. Our study findings have important implications for the identification of PND subtypes and the selection of appropriate interventions for depression during pregnancy and the postpartum period.

5. Conclusion

This is the first study to examine the changes in depressive core symptoms over time in pregnant and postpartum women. The study findings provide valuable information for understanding the interplay between PND symptoms. We identified network configurations between the second and third trimesters and the postpartum period, which revealed a temporal progression in core symptoms from depression-centric to anxiety-centric dominance. Therefore, to improve the mental health of mothers,

fetuses, and infants, more symptom-specific interventions should be used. Collectively, our findings provide clinical evidence for the evaluation of the biological mechanisms of PND subtypes and for the precision in PND diagnosis and treatment.

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Conflict of interest

Yuqun Zhang is an Editorial Board Member of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Conceptualization: Xin Yue
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Methodology: Yuqun Zhang
Formal analysis: Yuqun Zhang, Ju Gao
Writing–original draft: Yuqun Zhang
Writing–review & editing: Xin Yue

Ethics approval and consent to participate

Conducted in adherence to the ethical guidelines of the Declaration of Helsinki, this study received clearance from the Zhongda Hospital Ethics Committee (No. 2020ZDSYLL230-P01). All participants provide written informed consent before their participation.

Consent for publication

All participants gave written consent to publish their data in this study.

Availability of data

The data sets utilized and examined within the scope of this study are accessible upon reasonable request to the corresponding author.

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ORIGINAL RESEARCH ARTICLE

Online complementary interventions for the development of social communication in children during the early stage of the COVID-19 pandemic

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Abstract

For elementary school children, engaging in diverse communication experiences with peers of varying ages during free play is crucial for developing social adaptability. However, the COVID-19 pandemic caused an unprecedented interruption to this learning process, as the new school year in Japan, which typically starts in April, began with widespread school closures. A novel intervention was implemented to address the ongoing societal constraints of the "stay-at-home" mandate and the uncertainty surrounding its duration. This intervention aimed to facilitate and promote peer communication while minimizing the risk of COVID-19 infection. It utilized then-unfamiliar Internet-based conferencing systems on Children's Day, 1 month into the new school year. We explored two main analytical aspects to enhance the efficacy of this communication method: first, the types of play proposed by children that attracted the highest participation from unfamiliar peers; second, the duration of participation and communication, particularly regarding age and gender differences. Remarkably, despite only 2 days' notice, 15 children aged 4 – 14 from five different, previously unknown communities located 1,000 km apart participated enthusiastically. In the first investigation, 12 types of play were introduced by the children. The most engaging activities included collaborative drawing on a shared online whiteboard and a scavenger hunt for specified objects. Notably, older children participated significantly longer in the online presenter's activities, while younger children preferred to play within their own community. This study proposes that online conferencing can facilitate social interaction among children during pandemics. The intervention successfully fostered collaborative play among children of varying ages and from distant locations. In addition, the findings indicate the necessity to adjust the quality and focus of interventions based on age-specific psychological development. Further verification with more implementation examples and a larger participant pool is required.

Keywords: Online video conferencing; Play suggestion and participation; Intercultural communication; Playground; Social learning

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1. Introduction

A developing child learns to be motivated to spontaneously connect with the outside world by interacting with diverse social and physical environments.[1,2] The variety of nature and people within the home, family, school, and society introduces complexities that often create interaction challenges.[3,4] Children become interested in, recognize, understand, and relate to a world filled with diverse challenges. They learn to identify, create, and collaboratively solve problems with others.[5,6] Through repeated experiences and reflection, children are expected to develop the ability to help each other and overcome challenges.[2,7] However, this opportunity to interact with the learning environment is not always sufficiently guaranteed for all children.[6,8] For example, as birthrates decline, children may spend more time in adult-dominated nurturing environments, which limits their spontaneous interactions with other children,[9,10] thus eliminating the chance to encounter difficult social and natural environments essential for their development, potentially leading to learning disabilities.[11] The number of cases of developmental disorders with social maladjustment as a major symptom has recently increased. Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD),[12] for example, are known to include cases of coexistence of some genetic background,[13] and may at the same time raise the possibility of dysfunctional social development,[14,15] which we previously suggested in our model animal studies.[16-23] This may be caused by a lack of experience interacting with such learning environments.[24-26] The importance of encouraging children to learn more in school is greater than in other age groups because the mechanism of learning during the developmental period is well-known in the formation of communication.[18,20,27,28] including the acquisition of a native language. In addition, the "stay-at-home" orders implemented to protect children from COVID-19 began on April 16, 2020, when a state of emergency was declared nationwide in Japan. Most kindergartens and schools remained closed until May 25, as the infection continued to spread.[29] These measures led to children staying at home, which discouraged their willingness to connect with the outside world. Consequently, barriers to communicative experiential learning may have developed.[30-32] Several reports have revealed the psychosocial and mental health impact on children, including mood swings, loss of motivation, depression, and anxiety symptoms to post-traumatic stress disorder due to school closures, confinement, and a lack of peer interaction during COVID-19 lockdown and containment measures.[33,34] Children with ADHD/ASD were particularly vulnerable, exhibiting negative emotional and behavioral effects during the lockdown.[35]

In cases where children lack the social experience to interact and learn from each other, a "playpark" or "playground" has been proposed as a psychological education system to supplement this experience. Playpark encourages children to learn through play, which is based on spontaneity, motivation, creativity, collaboration, and perseverance in overcoming difficulties.[2,8,36]

Information and communication technologies (ICTs), such as smartphones and Internet PC terminals, have the potential to expand and connect children in the home with the outside world, nature, people, and living things.[37] In addition, ICT is known to have a high affinity for children with developmental disabilities.[38,39] On the other hand, it has the potential to be a new educational tool that requires monitoring and reflection on its use, including the risk of captivating children and keeping them away from the outside world and nature.[40-42]

To apply "a digital and analog network playpark," we explored the form of a new system in which children spontaneously connect with the outside world using video and voice ICT. The event was held for the purpose of forming communication online, where participants play together while exchanging play information. At the time, they remained closed from April, the beginning of the school year, and about a month later, Children's Day, a national holiday, was celebrated in a state of closed communication only within their homes. To do something for the psychological development of the children, we proposed and called upon five communities that were unknown to each other, different organizers in Yamaguchi and Chiba/Saitama Prefectures in the southwestern tip of Honshu, a long distance away, where communication is extended and made possible by online ICT, rather than remaining within the same local community. The "1000 km Online Play Park Project" was a challenge in which children proposed their own games, and all participants played together online over long distances. The performance of 15 children proposing their own play to other children and participating in the play of other proposers during the 2-h event was recorded and analyzed. Each individual's behavior species in the video data were observationally identified and defined every 5 s. The purpose summary of this study is to examine the trial of the intervention aimed at communication formation, developed to counteract the panic-stricken pandemic society that had suppressed children's communication learning. To design a communication intervention method with higher efficacy for any child generation and to find any requirements for the future, we explored two main analytical aspects. One was the type of play proposed by the children, which attracted a

greater number of first-time participants, and the other was the duration of participation and communication, with a focus on investigating age and gender differences. To investigate the impact of the ICT-based playpark trial on children's psychology, we evaluated their stay total time in each play, regarded as a quantitative index of willingness to participate, considering gender and age dependence.

2. Materials and methods

2.1. Ethics deliberations, event details, and participants

This study protocol was approved by the Yamaguchi University Review Committee for Non-Medical Research Involving Human Participants (approval ID: 2020-047). Consent for video recording was obtained from all parents, the children themselves, and the organizers. The data were recorded in such a way that individuals could not be identified. The children who were forced to stay at home in abnormal conditions were approached at random, and those who agreed to participate were analyzed. It was not required to ask whether the participants included children diagnosed with developmental disorders, for which quantitative diagnostic methods have not yet been established.

On May 3, 2020, assuming a communication scale of about 15 children, we randomly selected addresses that had participated in previous children's events in each city and sent an email invitation to participate in an event with the theme "Children propose play ideas to each other in an online conference, and the children who received the ideas participate in the play and co-create the play" without prior notice. We invited a total of five children's communities: three in Yamaguchi Prefecture and one each in Saitama and Chiba Prefectures, which are about 1,000 km apart. The number of children and parent participants who presented their own play were eight female and seven male children and two parents. All were included in the analysis. The event began on May 5, 2020, at 1:00 p.m. with an online conference system and at 3:00 p.m. on the Internet using the Zoom online conference application to share information about each other's favorite games and play together. The online conferencing system has three advantages: (i) to maintain a relatively stable connection between terminals for both video and audio; (ii) to separate into multiple groups and maintain communication with each group; and (iii) to securely record video. "Children's Day Project" and "1000 km Online Play Park" were named and announced. Parents were asked to be present on the day of the event. After receiving consent, the event was recorded. The order of the game suggestions was randomized.

2.2. Recording with an online conferencing application

Using the recording functionality standard with the Zoom online conferencing application, the event content was recorded on a local PC. During the event, we switched between a gallery view, in which the camera images of all participants' ICT terminals were displayed on the screen in a small size, and a speaker view, in which the screen of the person who was speaking was displayed in a large size by itself automatically, and selected a screen layout that facilitated observation of play and participants' actions and expressions toward each other.

2.3. Analysis of presented play

All types of play presented by children and parents were analyzed. Four introductory films were presented, which were considered one form of play. The number of children who participated in each type of play was visualized in bar graphs for females (red) and males (blue) and for lower and upper age groups. The age boundary between the lower and upper groups was defined as either 8 years old or younger or 9 years old or older, which is the average age of children in a 6-year elementary school in Japan.

2.4. Classification of each child's behavior

The video recording was viewed, and each child's behavior was classified every 5 s into one of the following eight types of emergent behaviors, which were used as the original data. These eight typical behaviors were preliminary classified and summarized in the same recorded video data by the children's educators, considering the contextual flows and vocal contents.

(i) Engagement: All actions. All time spent at the event.
(ii) Play suggestion: Actions to present and explain the play to the other participants as a time to take charge of the presentation, followed by actions to lead the play with the other children.
(iii) Online participation: Behavior of the play suggested by the presenter together or outside of the time after the presenter's presentation. If the play presented was a self-introduction video, children were considered to be joining the play if they could confirm that other children were watching the video.
(iv) Online conversation: A conversation was considered successful only if a two-way online exchange could be confirmed by reviewing the content of the conversation, e.g., a question followed by its answer or response.
(v) Watch: Watch the screen.
(vi) Satisfaction: Watching with a smile based on subjective judgment (for reference)

(vii) Onsite conversation: Conversation among peers, including conversations with parents and siblings present.
(viii) Onsite participation: Play various games among peers, including parents and siblings present.
(ix) Solitary play: Examples of this behavior include playing unrelated digital games without looking at the terminal's video camera.

2.5. Statistical analysis of age dependency

The time-totals of eight different behaviors were analyzed by linear regression and Pearson product-moment correlation coefficients and intercepts. The probabilities <0.05 were considered significant.

3. Results

3.1. Play ideas presented by children

The event was conducted with five females and two males in the lower grades, three females and five males in the upper grades, and ten adult parents and staff. Regarding the age composition of the children, females were significantly younger than males in the upper grades (Table 1; $P = 0.0240$*), but there was no significant age bias between the sexes in the overall composition of the lower and upper grades (Table 1; [All, $P = 0.1072$]).

For the age composition condition of the participant groups, *P*-values were calculated by a student *t*-test for each mean and standard deviation (Excel, Microsoft) for females and males in the lower and upper age groups.[43]

Figure 1 visualizes a representative image of each play of all the twelve ideas suggested by children with the number of all children who participated and the number of participants who played the same one as the presenter introduced divided into female (red)/male (blue) and lower-/upper-grade groups in the bar graphs.

As an overall summary, the upper-grade group was characterized by frequent viewing of all the play by both females (Figure 1; red) and males (Figure 1; blue), whereas the lower-grade group showed only male participation in the earlier play activities presented. The involvement of multigenerational children in collaborative play was somewhat limited, observed in four types (whiteboard drawing, cat's cradle, bring me something). Below are the play ideas presented in chronological order:

Table 1. The age conditions of the child participants

Age (year)	Lower age		Upper age		All	
	Mean	SD	Mean	SD	Mean	SD
Female	6.2	1.3	9.0	0.0	7.3	1.8
Male	5.5	2.1	11.4	1.5	9.7	3.3
P by *t*-test	0.7241		0.0240*		0.1072	

Abbreviation: SD: Standard deviation. The significant *p* value is less then 0,05 (*: $p<0.05$, **:$p<0.01$, ***:$p<0.001$).

3.1.1. Plate spinner (10-year-old boy)

This play involved rotating a plate on a stick. Originally, a ceramic plate was used, but a child-friendly plastic plate was later utilized, which was shown spinning on the stick.

3.1.2. Rope-jumping (5-year-old girl)

A 5-year-old girl played a single jump with a jump rope in the room.

3.1.3. Lifting (7-year-old boy)

The boy demonstrated a soccer lifting technique indoors using a small soft ball.

3.1.4. My introduction video (three 1-year-old boys and one 9-year-old girl)

Children from various age groups watched the videos together.

3.1.5. Look this way! (9-year-old girl)

The player faces the viewer in front of the screen and points either up, down, left, or right with their arms and fingers while saying, "Look this way." If the viewer faces the same direction as the player, the player wins, and the viewer loses. The activity was canceled earlier because the player was inexperienced in operating the remote meeting camera to display her actions properly.

3.1.6. Whiteboard drawing (7-year-old girl)

Drawing pictures on a white piece of paper with the left hand was asked to guess what it was. The flowchart (Figure 2) summarizes the process of the online sharing feature of the teleconferencing system that was uniquely developed. Child 1 drew a picture on a white piece of paper and showed it over the screen, but it was unclear. So, Child 2 suggested drawing a picture on the whiteboard of the online meeting application. Both the child and parent of the playgivers did not know how to use the whiteboard. Several children and parents explored how to teach them, taking into account their understanding.

3.1.7. Origami: Folding paper to make things (6-year-old girl)

She seemed to be folding origami all the time, not facing the screen. She only showed it when she was finished, while the parent explained instead of her. A girl in the lower age group participated in the game by folding origami.

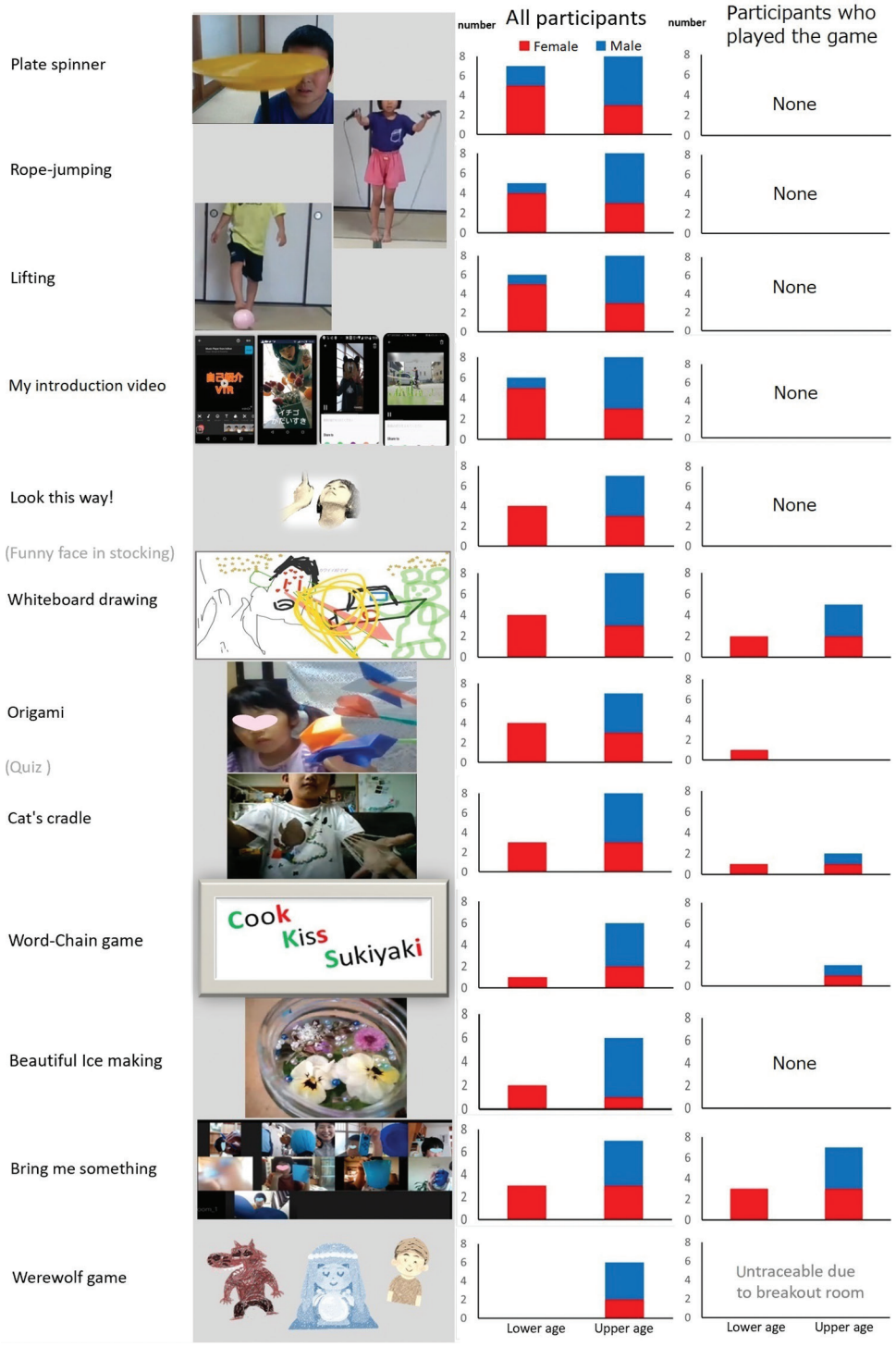

Figure 1. Twelve different play ideas presented by the children, with the number of children participating

3.1.8. Ayatori: Cat's cradle (8-year-old girl)

She demonstrated on camera the process of making a "broom" with Ayatori, from the beginning of creation to its completion. A total of three children played a similar game of Ayatori online.

3.1.9. Word-Chain game (11-year-old boy)

A play where the first person says a word, and the next person thinks of a word whose last letter is at the beginning of the word and says it. The first idea was to use the whiteboard sharing function on the screen and suggested

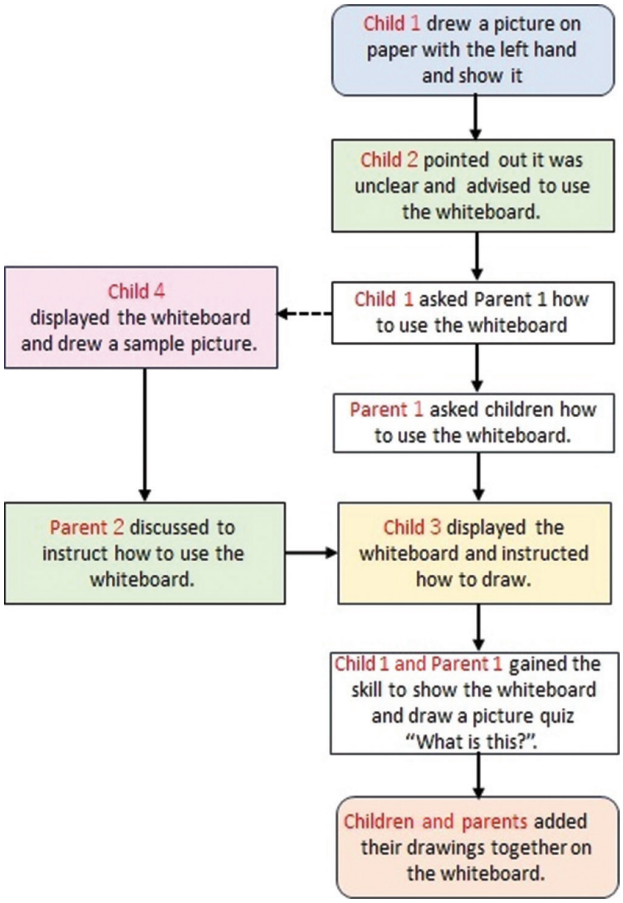

Figure 2. The flowchart of the multi-participant collaborative transformation process from a blank sheet of paper in real space to a shared whiteboard in virtual space

drawing a "Word-Chain game," but screen sharing did not work for some communities, so it was changed to sharing in the chat. Since some people did not know how to play the game through chat, it was confirmed that only two participants understood each other.

3.1.10. Beautiful ice-making (9-year-old girl)

She showed how to collect colorful beads, buttons, flowers from the garden, and other pretty things found around the house, put them in a glass cup, pour water into it, and freeze them in the freezer to make beautiful ice.

3.1.11. Bring me something (14-year-old boy)

The display was set up in a gallery view where all participants could see each other's actions on the screen through a teleconferencing system. A game was introduced: "Bring the blue object into the room," and the first person to bring it back wins. Everyone went for the blue object at the same time, and when they brought it back, it was shown to the other participants on the camera. Other variations of the task, such as "something golden or slippery," were suggested. As a result, all the children who watched the play suggestions joined the game.

3.1.12. Werewolf game (11-year-old boy)

The rules and flow of the game were as follows: in a village, werewolves disguised as villagers are eating villagers one by one at night. There must be at least three villagers and one fortune teller. The victory condition for the village team is to kill all the werewolves. Another team has two werewolves, and the victory condition is that both teams have the same number of werewolves. The person with the most votes at noon is eliminated. At night, the werewolves discuss and decide who will be eaten. The soothsayer can ask the position of a living person. This process is repeated. The chat and breakout room of the teleconferencing system were used. Only the older children in the upper grades participated.

3.2. Play ideas presented by parents

Two games were introduced by two different parents. Figure 3 shows the games proposed and the number of children participating and actually joining.

3.2.1. Funny face in stocking

A parent put a stocking over her head and pulled the stocking with the child, showing "a funny face" and laughing at each other. A boy in the upper grade was amused and tried the same game.

3.2.2. Quiz

The quiz is given a portion of a dictionary semantic sentence and asks what the word is. Example: In the case of the question, "What is a sweet pastry baked with flour, eggs, and sugar?" The answer is "cake." One boy in the upper grades answered the quiz.

3.3. Age dependency analysis of time by eight behavior types

Based on the observation of each 5-s unit of the recorded video during the event, Table 2 summarizes the total recorded time data for each type of behavior in 15 children.

These children's duration data were analyzed for age dependence using a linear approximation equation based on Pearson's product-moment correlation coefficient and its probability in a scatterplot with the horizontal axis, age (y), and the vertical axis, time (s) (Figure 4).

Linear regression and Pearson product-moment correlation coefficients, intercepts, and probabilities <0.05 were visualized as significant with red fonts and asterisks.

The results showed that the total participation time (Figure 4A), the willingness to join the proposed play

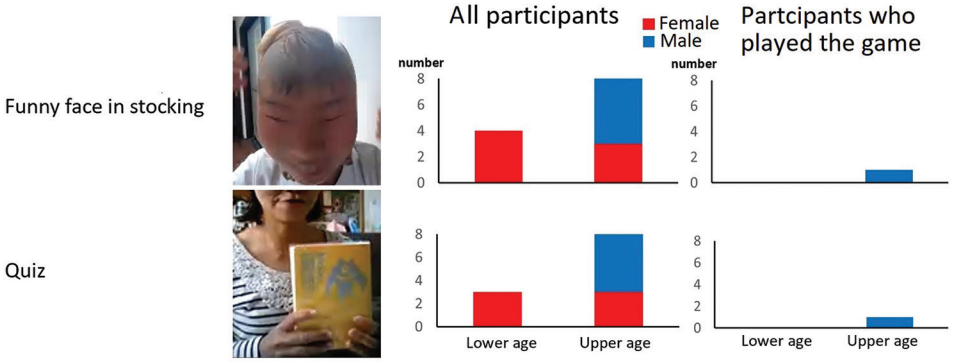

Figure 3. Two play ideas presented by parents and the number of children who watched and joined the play

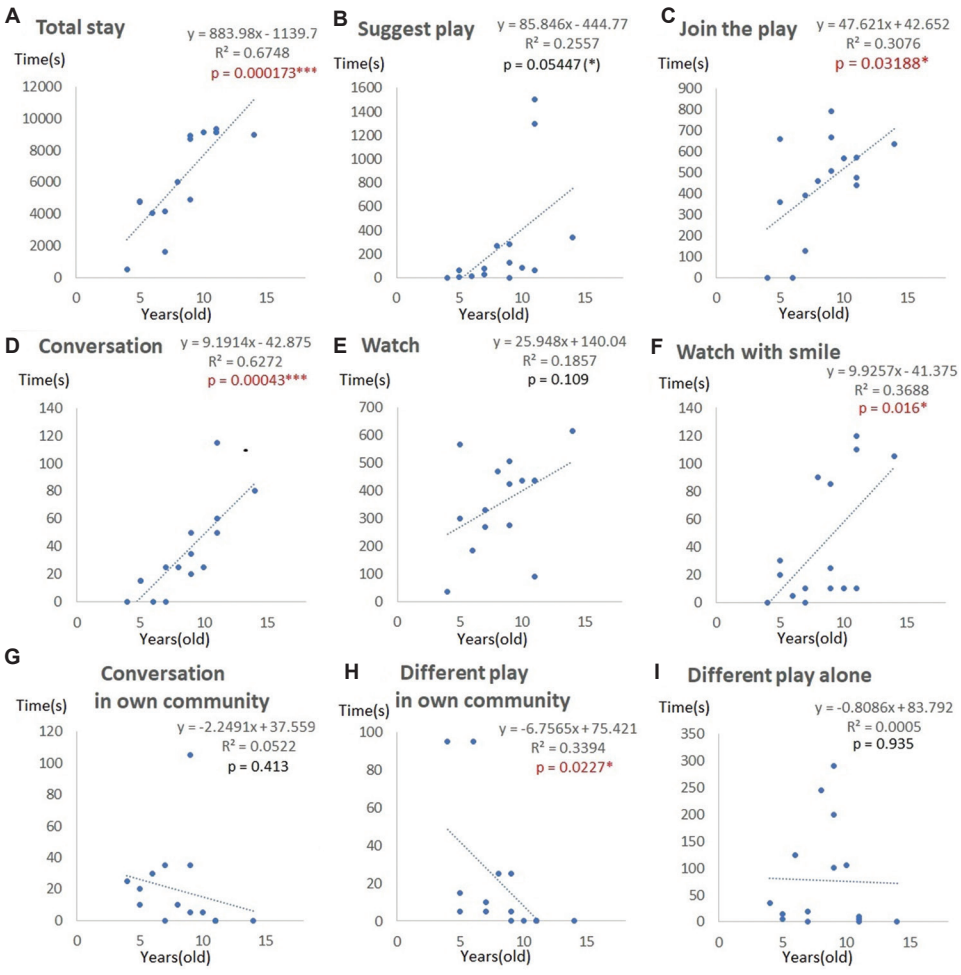

Figure 4. (A-I) Children's action and reaction time and age dependency

(Figure 4C), the online conversation with each other (Figure 4D), and the time spent watching the screen with a smiling expression (Figure 4F) increased significantly with higher age. In addition, although not significant, a similar trend could be seen for the duration of play suggestions (Figure 4B) and viewing (Figure 4E), as older children spent longer. On the other hand, the tendency to engage in other play activities within one's own community, not with each other online, not alone but with several persons, seemed to be significantly higher at younger ages (Figure 4H). A weak tendency for younger children to have longer conversations with other members of their community

Table 2. Time-totals of eight different behaviors in eight females and seven males from five communities: Lower/Upper grades, gender, and mean ± SD

Community -child ID	Age	Grade lower (<9) or upper (≥9)	Gender	Seconds of a child's behavioral types							
				Engagement	Suggest play	Online participation	Online conversation	Watch	Satisfaction: watch with a smile	Onsite conversation	Onsite participation	Solitary play
1 – 1	5	Lower	Female	4730	5	360	15	300	20	10	5	5
1 – 2	7	Lower	Female	4180	75	390	25	330	10	35	5	20
1 – 3	9	Upper	Female	8705	125	790	50	275	25	105	5	100
2 – 4	5	Lower	Female	4820	60	660	15	565	30	20	15	15
2 – 5	7	Lower	Male	1615	30	125	0	270	0	0	10	0
2 – 6	10	Upper	Male	9150	85	565	25	435	10	5	0	105
3 – 7	4	Lower	Male	545	0	0	0	35	0	25	95	35
3 – 8	6	Lower	Female	4090	10	0	0	185	5	30	95	125
4 – 9	8	Lower	Female	6000	265	460	25	470	90	10	25	245
4 –10	9	Upper	Female	4905	0	665	20	505	10	35	25	200
5 – 11	9	Upper	Female	8940	285	505	35	425	85	5	0	290
5 – 12	11	Upper	Male	9135	1295	570	115	435	110	0	0	5
5 – 13	11	Upper	Male	9365	1505	475	60	435	120	0	0	0
5 – 14	11	Upper	Male	9115	65	440	50	90	10	0	0	10
5 – 15	14	Upper	Male	8990	340	635	80	615	105	0	0	0

Abbreviation: SD: Standard deviation.

(Figure 4G). The time spent alone playing games unrelated to those proposed online was the least age-dependent, with the duration being longer for children between the ages of 8 and 10 (Figure 4I).

4. Discussion

School attendance, which was taken for granted under normal circumstances, was prohibited during the COVID-19 pandemic.[44,45] In this situation, communication between children, which should be given the highest priority as a target factor for promoting development, was closed off, and children's social learning was abnormally interrupted.[14,15] To restore communication opportunities for these elementary school children,[46] we attempted a play-interaction event using online conferencing.[47] The different communities met for the first time with each other, against the backdrop of the different local cultures in which they lived; for example, the community in the suburbs of the Tokyo metropolitan area with many older children had already mastered the skills of using the online teleconferencing system and were able to bridge the distance between members in the community divided by the COVID-19 pandemic.[48] Furthermore, the imagery and audio of the play introduction video were skillfully edited using Internet applications, as if the negative social repression of the COVID-19 pandemic might have been a springboard for the complementation of the communication network to promote skill development.[49] In contrast, there were at least some differences in the skills for using the teleconferencing system among the five communities in this study, and parents voiced some confusion in the community that consisted mostly of younger children who were not accustomed to using the system.[50] The fact that younger children are more likely to engage in play rather than online (Figure 4H) may be an expression that resolves the confusion for the children. Since the suppression of communication within one's own community was also considered due to the suppression of communication itself, the activation of communication within one's own community, even if not with a different community online, might be said to have a positive effect.[50] Furthermore, even in communities unfamiliar with the online teleconferencing system, the significant age-dependent[51] increase in viewing time for older children (Figure 4C) and conversation time beyond online (Figure 4D), which statistically confirmed the high attention span of older children and the transfer of information from advanced skill users using the teleconferencing system (Figure 4),[52] was an accomplished finding of this trial. Since the duration for looking at the camera accompanied by a smile was left to subjective identification by the observer, it will require a replication quantification technique using an automatic smile recognition monitor by machine[53] in the future, but at the reference data level, it suggests the possibility that the upper-grade children might be satisfied more.[54]

The play proposed by the younger children basically involves actions that involve physical control of real space, while the older children do not convey actions that involve physical control of real space as they are, but rather, as in the example of "Bring me something blue (3-1-11)," for example, they use online systems and video editing to create new virtual. The higher-order nature of extending functions on the space may be a feature.[55] In this participating child, there are differences between male and female participants at older school ages, and there is a bias toward older boys and younger girls, but the age-dependence analysis in Figure 4 has a certain degree of reliability because it confirms the age-dependence for all ages and genders,[56] where the bias is no longer statistically significant. When others suggested a play, they were observed to play video games alone, regardless of the play, and to repeat, perhaps practice, the behavior before presenting their own play suggestions, indicating that this more self-directed behavior was age-independent (Figure 4I). Its age independence may have suggested, for example, a more self-centered instinctive function that is different from the typically developing social function that is increasingly learned with age.[57-60]

The strengths of this study regarding the online mutual complementary intervention for children's formation of social communication at the early stage of the COVID-19 pandemic included five points: (i) the successful communication between children meeting for the first time over long distances; (ii) the absence of concerns regarding infection or weather, (iii) the mutual learning and thinking observed among the children; (iv) the ability for parents and children to participate together from their own homes; and (v) the fact that many participants genuinely enjoyed the experience and expressed a desire for it to be repeated. The strengths of this online intervention method include the ability to log and analyze participants' behavior and the possibility to statistically infer developmental status by entering participants' age information.

Immediately after the event, a survey was conducted asking participants about the challenges they faced, and the following issues were answered. From the staff, one was the need for initial icebreaker activities to help children get accustomed faster to each other, and another was considerations for providing support and shortening the duration for younger children. Older children have their own issue that they should be more considerate of younger children. The other comment of ours was the

design of a structure where age-specific scenes and mixed-age interactions could be alternated. In addition, a need to devise ways to deepen communication between children who have never met each other before; the need for training to improve skills in ICT operation, calling each other by nicknames, and holding information exchange meetings for all parents and children afterward were suggested. Improvement of these issues should be repeated multiple times, not just for a single event. Furthermore, because of the limitations of only obtaining information online, it is necessary to do about the onsite real space as well.

This study is limited by the small sample size and subjective description of the behavioral classification. A future study is needed to increase the sample size and to develop image deep learning technology to identify different behaviors for reproducible quantification.[2,61]

Another limitation is that although the study intended for children to propose the play ideas on their own, in some cases, the parents proposed the play ideas. Future research should incorporate parents' play ideas as part of the study or ensure the children come to these online play groups without their parents.

5. Conclusion

This study examined the effectiveness of a new intervention method using an online conferencing system to enhance social communication among children who experienced social suppression due to infection avoidance during the early stages of the COVID-19 pandemic. The intervention involved 15 children, who had never met before and were separated by long distances, introducing and playing their games together online. The findings of this study showed that the intervention successfully promoted collaborative play among older children from distant locations, and the total participation time, the amount they proposed play, the online conversation with each other, and the time spent watching the screen with a smiling expression increased significantly with higher age. This study outcome in younger children was to promote different play in their community as an age-dependent social formation style.

Children with ADHD and ASD, who have social disabilities and were reportedly more susceptible to COVID-19 lockdown, may also benefit from this online intervention method, as they tend to have a high affinity for ICTs.

As directions for future research, we suggest improvements in design, primarily with age-dependent consideration with additional care of different ICT utilization skills. It is also necessary to investigate the effects of repeating the event as well as one-time events going forward.

Given the limited number of participants in this study, further exploration is needed, considering these limitations, for future instances of infection-related crises that suppress children's social development. Another limitation of this study is its focus on specific regions, and future research should explore intervention designs suitable for diverse geographical context.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Conceptualization: Fusako Tomoto, Makoto Ota, Mamiko Koshiba
Formal analysis: All authors
Investigation: All authors
Methodology: All authors
Writing – original draft: Fusako Tomoto, Mamiko Koshiba
Writing – review & editing: All authors

Ethics approval and consent to participate

This study protocol was approved by the Yamaguchi University Review Committee for Non-Medical Research Involving Human Participants (2020-047).

Consent for publication

Informed consent for publication was obtained from the relevant participants.

Availability of data

The datasets for this study can be found in the main text.

Further disclosure

Part of the findings was reported in the blog of WEB magazine of the Association of Children's Environment published in May 2020 (https://www.children-env.org/magazine/blogs/blog_entries/index/23?page_id=4) for helping children and family against COVID-19 lockdown society.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Mapping structural and research trends in schizophrenia and metabolic syndrome: A bibliometric analysis

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Abstract

An escalating body of research is directing its focus toward schizophrenia (SZ) patients who grapple with metabolic syndrome (MS). By employing bibliometric approach, this study comprehensively assessed the research landscape and prevailing trends within SZ and MS-related fields. All relevant publications related to SZ and MS were systematically extracted from the Web of Science Core Collection database up to August 15, 2023. Data analysis was conducted using software such as VOSviewer, Citespace, Pajek, and R software, as well as online bibliometric website. A total of 2651 publications on SZ and MS were collected, with the United States emerging as the primary contributor (n = 1970). Pivotal international research collaborations were observed, notably between the United States and the United Kingdom (n = 56). The French Research Universities exhibited prolific contributions. *Schizophrenia Research* emerged as the foremost influential journal in this domain. In addition to "schizophrenia" and "metabolic syndrome," keywords such as "atypical antipsychotics" and "body weight" featured prominently within the literature. Our study underscores the growing significance of SZ with MS research. These findings collectively shed light on the dynamic and evolving nature of research pertaining to SZ and MS, reflecting an unwavering commitment to unravel the complexities and implications inherent in these intertwined domains.

Keywords: Schizophrenia; Metabolic syndrome; Bibliometric analysis; Atypical antipsychotic; Olanzapine

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1. Introduction

Schizophrenia (SZ) is a complex psychiatric disorder characterized by both positive and negative psychotic symptoms, as well as cognitive impairments.[1] At present, the global incidence rate of SZ stands at approximately 7.2/1000 individuals.[1] Given its high prevalence, chronic course, and increased risk of recurrence and deterioration, SZ patients often experience mental disability and labor loss, imposing a substantial burden on both their families and society at large.[2,3] Metabolic syndrome (MS) is a clinical syndrome characterized by central obesity, elevated blood pressure, high glucose

levels, and abnormal blood lipid profiles, frequently referred to as insulin resistance syndrome.[4] In SZ patients, the incidence of MS is 2 – 3 times higher compared to the general population.[5] The exact etiology of MS in SZ patients remains elusive, although numerous studies have implicated it as a consequence of side effects associated with second-generation antipsychotic drugs such as clozapine and olanzapine.[6] SZ patients with MS often experience more pronounced cognitive impairments, with a markedly increased risk of coronary artery disease, cerebrovascular disease, congestive heart failure, and cardiovascular-related mortality; death in people with SZ is significantly higher than that the normal population, second only to suicide as a cause of death among SZ patients.[7]

Bibliometrics, a comprehensive methodology encompassing both quantitative and qualitative approaches, plays a pivotal role in analyzing scientific literature.[8] The bibliometrics currently used can usually be divided into two categories: evaluative and relational.[8] Evaluative bibliometrics is used to describe the characteristics and integration results of published information. The most common forms of evaluative bibliometrics are systematic reviews and meta-analyses.[9] Relational bibliometrics provides an overview of the relationships between different participants. The idea behind relational bibliometrics is that hidden associations can be identified in the metadata collected from various entities, which helps to understand entity sets at a broader level.[9] It can realize frequently cited research, keywords, and collaborative networks involving countries, institutions, and authors in specific research fields, which help to discover hotspots and shortcomings in related fields.[10] In research, one can employ pertinent bibliometric methods as required, including the use of bibliometric coupling.[8] Once the research topic is identified, a thorough search is conducted on relevant academic platforms such as PubMed, utilizing specific search queries and years. The retrieved articles are then imported into dedicated bibliometric software, such as R software, Citespace,[11] online bibliometrics website, and VOSviewer[12] for analysis, followed by targeted refinement and adjustment according to the desired outcomes.[13]

Bibliometrics has been applied in the research on the relationship between SZ and oxidative stress,[14] as well as between SZ and inflammation,[15] and the articles have received widespread attention. However, the burgeoning incidence of MS in SZ patients and the associated body of literature have yet to undergo a systematic analysis. Addressing this knowledge gap, this bibliometric analysis endeavors to construct a comprehensive map of scientific publications pertaining to the intersection of SZ and MS.

2. Methods

2.1. Search strategy

The Web of Science database serves as a prominent academic resource for bibliometric analysis.[15] In this study, we conducted a comprehensive search within the Web of Science Core Collection database, covering literature related to SZ and MS up to August 15, 2023. Our search strategy incorporated the following terms: TS = (SZ OR SZs OR Schizophrenic Disorders OR Disorder, Schizophrenic OR Dementia Praecox) AND TS = (MS OR MSs OR Syndrome, Metabolic OR Syndromes, metabolic OR Insulin Resistance Syndrome). Due to technical and copyright reasons, we only included all related literature within the Web of Science Core Collection database. The relevant articles were subsequently exported and stored in the form of plain.txt, comprising full records and cited references, to facilitate further analyses.

2.2. Data analysis

To conduct this bibliometric analysis, we employed a range of specialized software tools and resources. These included R (version 4.0.4, R Foundation for Statistical Computing, Vienna, Austria), VOSviewer (version 1.6.17, Leiden University, Britain), CiteSpace Software (6.1.R2, The College of Information Science and Technology, Drexel University, America), and Pajek and online bibliometrics website (https://bibliometric.com/). The R package, a versatile tool for quantitative bibliometric research, was utilized for (1) summarizing the total number of publications per year and annual publication volumes for each country; (2) identifying authors, institutions, and journals with the highest publication counts and impact; (3) tracking the annual cumulative occurrences of top keywords/terms and references; (4) calculating production and cooperation frequencies among countries; and (5) creating a visual representation in the form of a three-field plot highlighting keywords, references, and authors.

VOSviewer is a specialized software application designed for the visualization of bibliometric networks. It excels at organizing interconnected nodes into distinct clusters, with the nodes of the same hue representing a stronger correlation. In this study, VOSviewer was used to perform: (1) exploration the collaborative network of authors and their institutions and (2) literature co-citation analysis and keyword co-occurrence network analysis. For the study of intricate nonlinear networks, we utilized Pajek, a robust and large-scale complex network analysis tool. It allowed us to enhance images previously processed using VOSviewer and subjected them to further comprehensive analyses. In addition, the freely available Java program CiteSpace played a central role in our research by

emphasizing dynamic visualization and tracking the evolution of bibliometric networks over time. It served as the primary tool for analyzing references and keywords with citation bursts, providing valuable insights into the evolving landscape of scholarly literature.

3. Results

3.1. Publication summary

Our comprehensive analysis encompassed a total of 2651 papers concerning SZ and MS. Figure 1A illustrates the annual publication count, revealing a noteworthy trend. Over time, the volume of annual publications has shown a substantial increase. The trajectory of annual publications began to stabilize around 2015. To discern the relationship between the overall number of articles and the year of publication, we conducted regression analysis. This analysis allowed us to construct a highly predictive model ($R^2 = 0.9481$) that accurately forecasts the ongoing annual publishing pattern.

Our predictions indicate a continued upward trajectory in the annual publication trend for SZ and MS research over the next decade. According to the prediction curve, the number of articles is expected to reach 269 by 2026 and to 362 by 2032. This projection underscores the enduring significance and research activity in this critical area of study.

3.2. Analysis of the production and cooperation among countries

Figure 1B presents a geographical breakdown of article contributions by different nations. The United States leads with the highest number of publications (n = 1970), followed by China (n = 1435), the United Kingdom (n = 859), France (n = 732), and Australia (n = 704). In contrast, all other nations combined have contributed fewer than 700 articles.

International collaboration patterns are illustrated in Figure S1. Notably, the majority of international research partnerships are observed between nations in the United States, Europe, the United Kingdom, Canada, and China. Prominent collaborations include those between the United States and the United Kingdom (n = 56), the United States and Canada (n = 50), and the United Kingdom and Belgium (n = 47). These collaborative efforts reflect the global nature of research in this field and highlight the fruitful partnerships driving advances in SZ and MS research.

3.3. Analysis of the most productive institutions

A total of 3,551 institutions have actively participated in studies related to SZ and MS. In Table 1, the top 10 most prolific institutions are listed, with the French Research

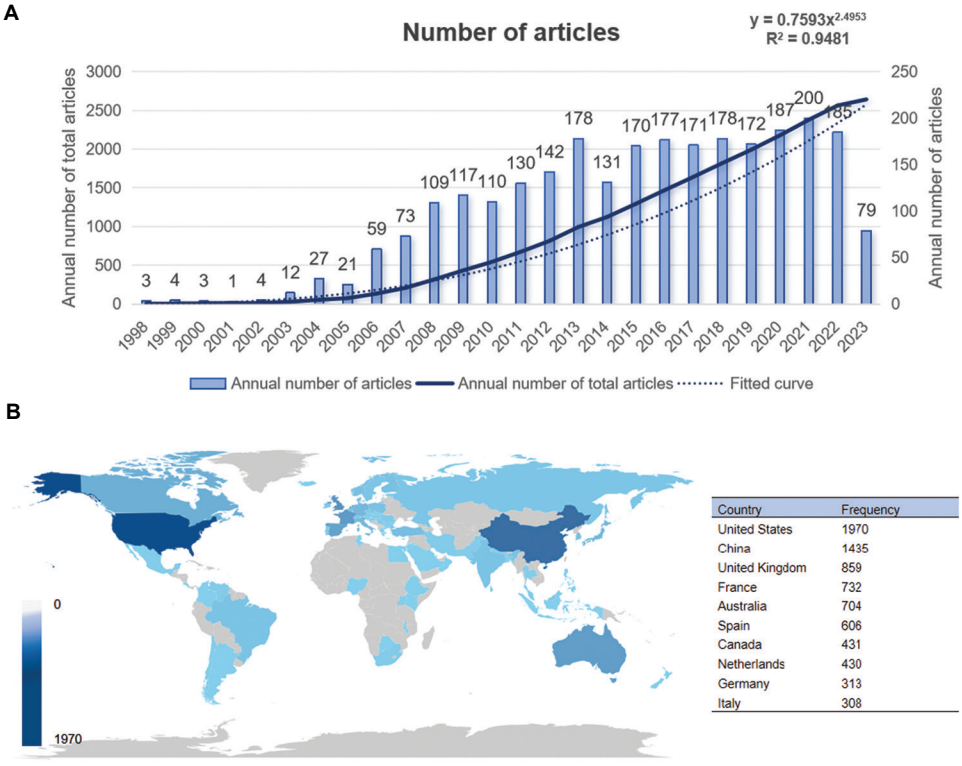

Figure 1. Number of publications by country and year. (A) Annual publications from 1998 to 2023. (B) Publications of top 10 countries

Table 1. Top 10 affiliations with the most publications

Affiliation	Articles
Udice-French Research University	378
University of London	184
King's College London	181
Institut National De La Sante Et De La Revherche Medicale	167
University of Toronto	138
University Paris Cite	130
KU Leuven	112
Cibersam	104
Harvard University	97
Assistance Publique Hopitaux Paris	96

Universities (n = 378), University of London (n = 184), and King's College London (n = 181) occupying the top three positions.

For a comprehensive understanding of institutional collaboration, we visualize the network of collaborative authors. Here, the size of the circles represents the number of publications, the color corresponds to the distinct field of each institution, and the thickness of the connecting lines signifies the intensity of collaboration between institutions. Figure S2A depicts the network of institutional cooperation in this area. It becomes evident that there is ample room for further enhancing global institutional collaboration in this field.

3.4. Analysis of the high-impact journals

A total of 552 journals have actively contributed to the dissemination of research related to SZ and MS. In Table 2, the top 10 journals with the most published papers are included, accompanied by their most recent impact factors (IF) and quartile (Q) ranking in journal citation reports (JCR). Table S1 highlights the most frequently cited journals in this area of study. Of note, 70% of journals in this domain fall within the Q1 category, as per the JCR classification.

Journal *Schizophrenia Research* with an IF of 4.5 leads the way with an annual publication volume of 166, signifying its prominence in the field of SZ and MS. This journal also boasts the highest number of citations, measuring 7,559, and hails from the Netherlands.

3.5. Analysis of influential authors

A total of 11,326 authors have participated in publications related to SZ and MS. In Table 3, the top 10 authors who have made the substantial impact, determined by their productivity, are displayed. The De Hert M. stands out with 70 publications, establishing themselves as the most renowned authors in this field (h-index = 34) and amassing the highest number of citations at 2146. Correll C.U., with 57 articles published and 1515 citations, holds the second-highest spot (h-index = 30). Vancampfort D., who has 48 articles and 1646 citations, ranks third (h-index = 29).

To identify core authors in accordance with Price's thesis, we considered publications with more than 6 articles as the guiding criterion. In total, there are 225 core authors. The collaboration networks between authors are depicted in Figure S2B, with each author having contributed a minimum of 6 papers. Notably, these core contributors represent 16 distinct research fields, indicating the multidisciplinary nature of SZ- and MS-related research. However, the relatively limited interaction among researchers from diverse domains suggests that collaboration across teams and laboratories engaged in SZ- and MS-related research is still in its nascent stages.

3.6. Analysis of research trends and hotspots

3.6.1. Highly cited references

Citation analysis serves as a valuable method for evaluating the impact of articles within specific research fields, with the frequency of citations often reflecting the influence of particular articles.[16] In Table 4, we present the top 10 most cited articles, all of which were published between 1999 and 2015 and have garnered over 200 citations. The cocited references and their interconnections are visualized in Figure 2. In this graphical representation, colors are employed to denote distinct research fields, and circles represent the citation frequencies. Notably, a robust interconnection is observed among three core research fields.

Topping the list in the red zone is the reference titled "*Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) SZ trial and comparison with national estimates from NHANES III.*"[17] This reference holds the distinction of being the most cited in this zone. In the blue zone, "*The positive and negative syndrome scale (PANSS) for schizophrenia*"[18] emerges as the most frequently cited reference. While in the green zone, "*Effectiveness of antipsychotic drugs in patients with chronic schizophrenia*"[19] takes the lead in terms of citations. These highly cited references signify their significant influence and impact in their respective research domains.

3.6.2. Analysis of references with citation bursts

Figure S3 shows an overview of the top 20 references with the most substantial citation bursts. A minimum duration of 4 years was considered for the citation burst, with the blue line depicting the observed time interval from 1998 to 2023 while the red line representing the duration of

Table 2. Top 10 journals with the most publications

Journals	Articles	IF	JCR quartile	Country
Schizophrenia Research	166	4.5	Q1	Netherlands
Psychiatry Research	80	11.3	Q1	Netherlands
Journal of Clinical Psychiatry	76	5.3	Q1	United States
European Psychiatry	73	7.8	Q1	France
Frontiers in Psychiatry	63	4.7	Q2	United States
European Neuropsychopharmacology	53	5.6	Q1	Netherlands
BMC Psychiatry	50	4.4	Q2	England
Journal of Clinical Psychopharmacology	48	2.9	Q2	United States
Progress in Neuro-Psychopharmacology & Biological Psychiatry	45	5.6	Q1	England
Neuropsychiatric Disease and Treatment	44	3.2	Q2	Netherlands

Abbreviations: IF: Impact factor; JCR: Journal citation reports.

Table 3. Top 10 authors with the most publications

Author	Articles	Local citations	h-index
De Hert M.	70	2146	34
Correll C.U.	57	1515	30
Vancampfcort D.	48	1646	29
Stubbs B.	42	734	23
Leboyer M.	31	135	14
Probst M.	30	427	18
Boyer L.	29	115	14
Van Winkel R.	29	1276	21
Lancon C.	28	129	17
Llorca P.M.	27	117	14

the citation burst. Among these references, the article titled "*Antipsychotic-induced weight gain: a comprehensive research synthesis*" published in the *American Journal of Psychiatry* stands out with the most robust citation burst value observed during the period from 2008 to 2013.[20] In addition, the citation burst for articles such as "*Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia*,"[21] "*Metabolic syndrome in psychiatric patients*,"[22] and "*Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology*"[23] is still ongoing, indicating that the subject matter of these articles continues to pique interest and may represent a potential frontier in the field of SZ and MS research in the future.

3.6.3. Analysis of the frequently used keywords

Out of a total of 5906 keywords, we meticulously examined 60 that appeared no <30 times in the literature. The visual representation of these keywords is shown in Figure 3. Node size corresponds to the frequency of keyword usage, while the co-occurrence of two nodes indicates a robust linkage between them. Similar keywords are strategically grouped, thus shedding light on the primary research domains within SZ and MS.

Cluster 1, denoted by red, encompasses keywords such as "metabolic syndrome," "prevalence," "mortality," "obesity," "people," and "bipolar disorder." This cluster delves into critical aspects pertaining to MS and its prevalence. Cluster 2 places a spotlight on antipsychotics and weight gain, featuring keywords such as "atypical antipsychotics," "body weight," "weight gain," "clozapine," "risperidone," and "olanzapine." Cluster 3, represented in blue, explores the intricate connections between SZ and inflammation, with key phrases such as "schizophrenia," "association," "inflammation," "c-reactive protein," and "risk" being at the forefront. Cluster 4 centers its focus on metabolic disorders and medication resistance, with key phrases such as "medication-naive patients," "dyslipidemia," "glucose," and "insulin resistance" occupying the forefront.

To observe the evolving landscape of key terms over time, Figure 4 provides a temporal perspective. Initially, critical keywords included "body weight," "diabetes mellitus," "weight gain," "nutrition examination survey," and "impaired fasting glucose." In recent years, "major depressive disorder," "bipolar disorder," "risk," and "life expectancy" have gained significant prominence as hot topics. In Figure 5, a treemap visually represents the prominence of keywords. "Prevalence" reigns as the most frequently used keyword (n = 489), closely followed by "risk" (n = 465) and "atypical antipsychotics" (n = 323). Notably, "schizophrenia" and "metabolic syndrome" remain central to this body of research.

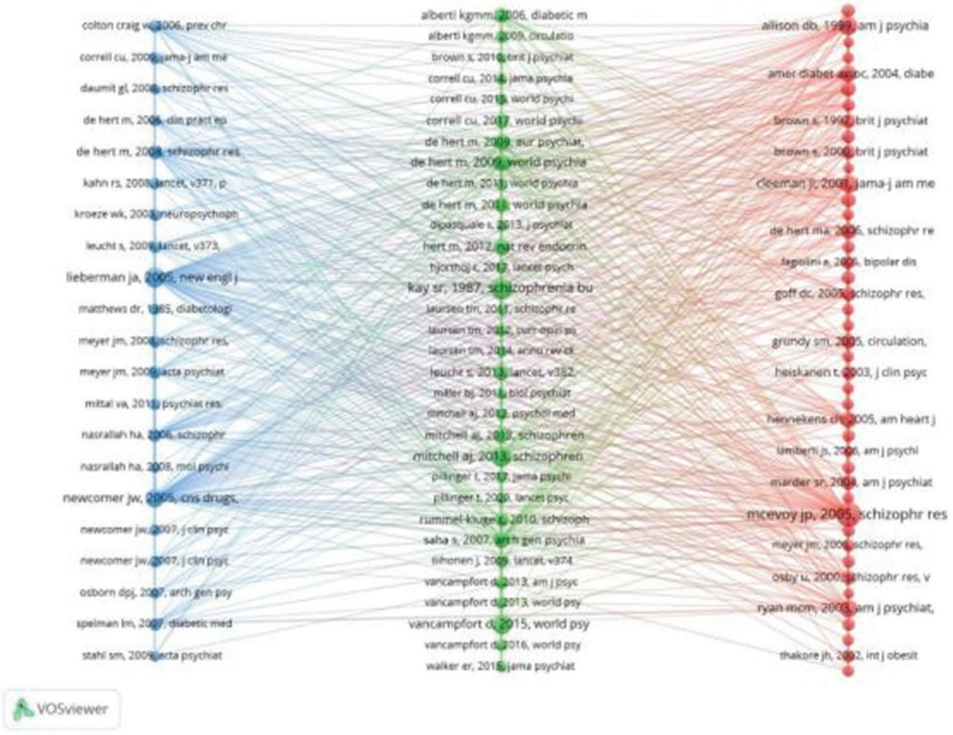

Figure 2. The analysis of co-occurrence citation analysis

Table 4. Top 10 references with the most citations

Cited references	Citations
Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III.	474
The positive and negative syndrome scale (PANSS) for schizophrenia	310
Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders – a systematic review and meta-analysis.	298
Effectiveness of antipsychotic drugs in patients with chronic schizophrenia	295
Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder, and major depressive disorder: a systematic review and meta-analysis	253
Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review	238
Antipsychotic-induced weight gain: a comprehensive research synthesis	222
Metabolic syndrome in people with schizophrenia: a review	216
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III)	211
Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia	203

3.6.4. Analysis of keywords with citation bursts

Figure S4 shows an overview of the top 20 references with the highest keyword bursts. In our analysis, a minimum burst duration of 2 years was considered. The blue line represents the observed time interval from 1998 to 2023, while the red line represents the specific duration of the burst. Of notable significance is the keyword "atypical antipsychotics" which displayed the most robust citation burst between 2004 and 2012, reaching an impressive value of 27.16.

4. Discussion

In this comprehensive bibliometric analysis, we delved into studies pertaining to SZ and MS over the past

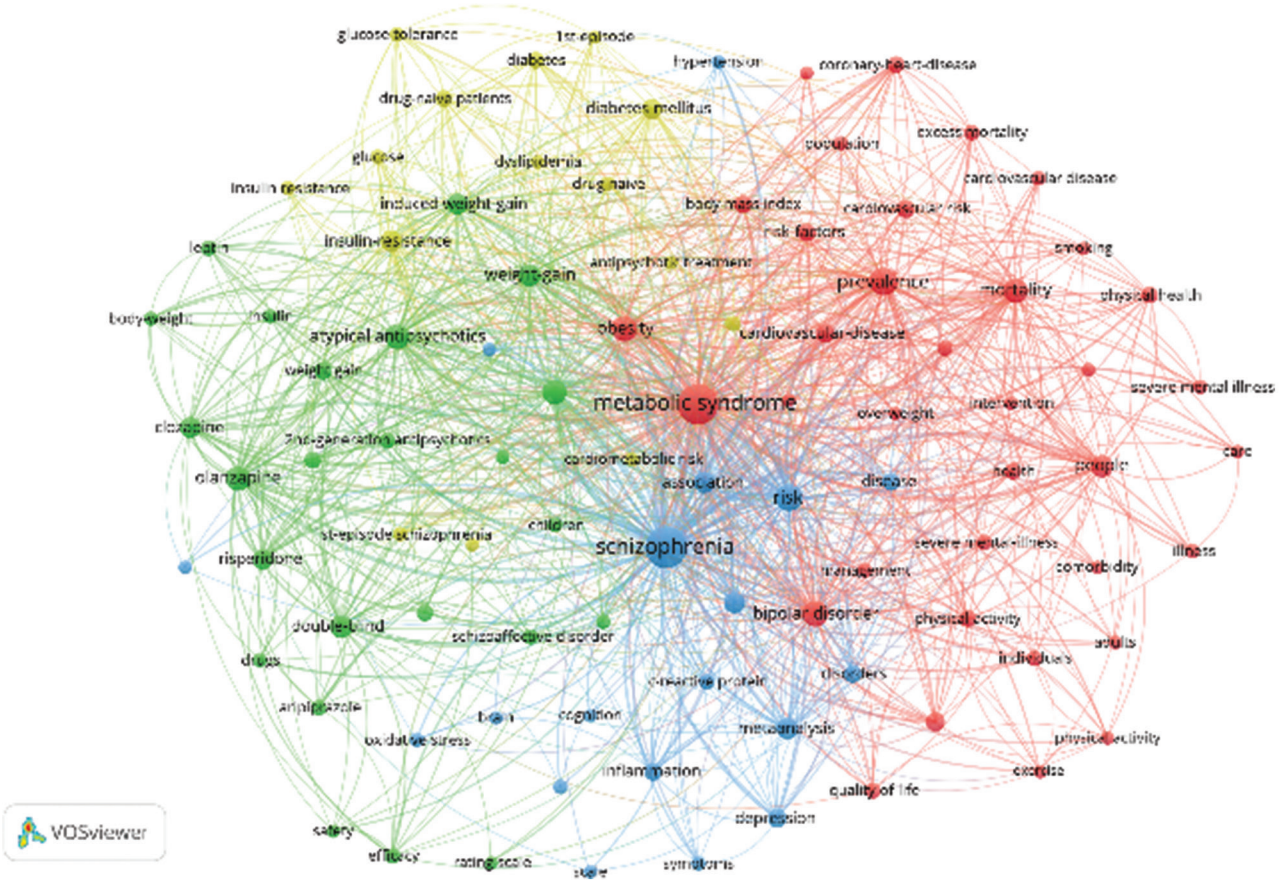

Figure 3. The analysis of co-occurrence keywords analysis

25 years. The scholarly landscape in this domain has undergone a remarkable transformation. Notably, the volume of literature has exhibited significant growth over the past few decades since 2008, eventually stabilizing after reaching its zenith in 2013. The expansion can be attributed, in part, to the mounting awareness of the physiological and psychological ramifications of SZ patients with MS. Indeed, this burgeoning understanding has emerged as a catalyst propelling the field forward, aided by an infusion of research funding. Among the countries and institutions actively contributing to this research sphere, the United States and French Research Universities have taken the lead, emerging as prolific contributors. SZ *Research*, as the most frequented journal and a major influencer in this domain, has been instrumental in shaping the discourse. Furthermore, within the realm of influential authors, De Hert M. holds a prominent position, leaving a lasting mark on this body of research. These key facets collectively underscore the dynamic and evolving nature of SZ and MS research, driven by an ever-increasing commitment to unraveling their complexities and implications.

Citation analysis serves as a valuable metric for gauging the academic influence and significance of publications.[24] Keyword co-occurrence analysis illustrates the semantic proximity and prevalence of pertinent research terms within a specific scientific domain.[25] In our study, the 10 most cited articles shed light on several critical focal points, with an emphasis on the prevalence of MS in SZ patients.[17] Following this, articles examining risk factors[26] and atypical antipsychotic drugs (AAPS)[19] emerged prominently. Our literature co-citation analysis revealed three distinct clusters. In the Cluster 1, titled as "*Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III*" published in 2005 stands out as the most cited reference.[17] This pivotal work, involving over 1460 SZ baseline participants in the CATIE study unearthed a staggering prevalence of MS exceeding 40%. Notably, among female SZ patients, this prevalence of MS exceeded 50%, sparking widespread attention to the compelling association between SZ and MS. As Cluster 1 of keyword co-occurrence analysis also placed a spotlight

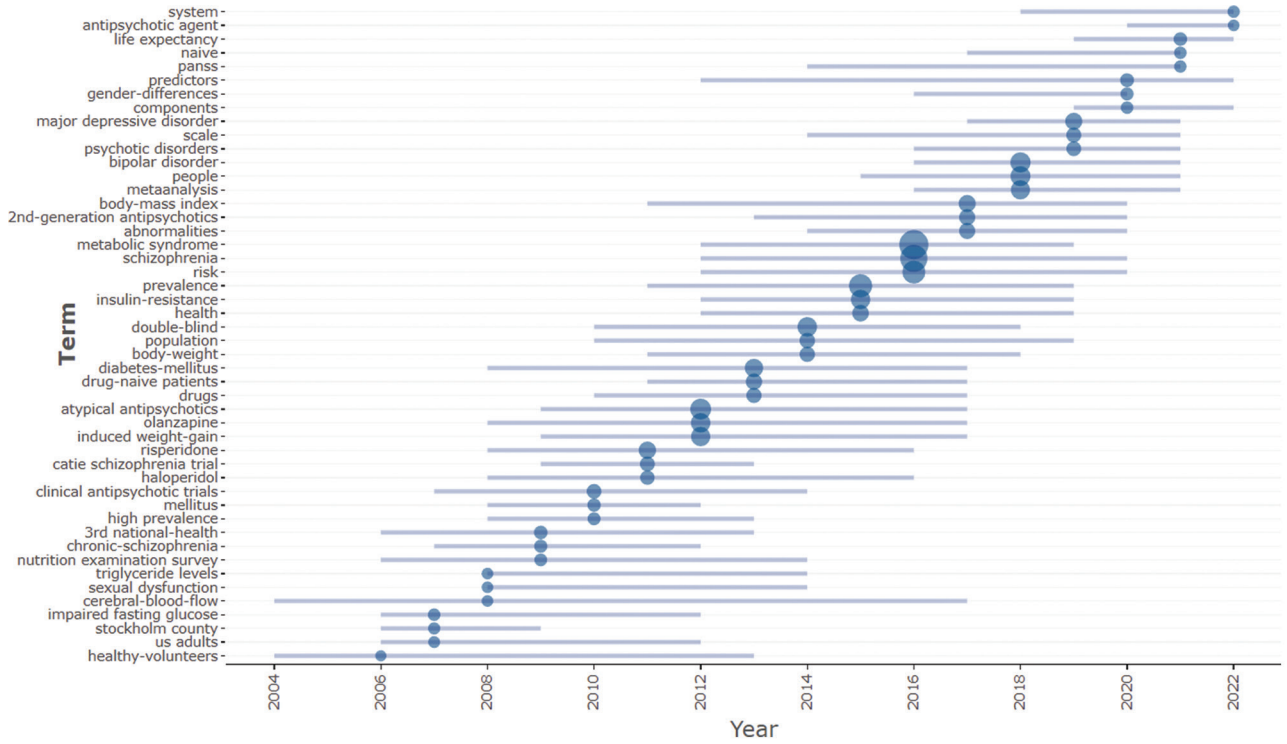

Figure 4. The analysis of keywords evolution

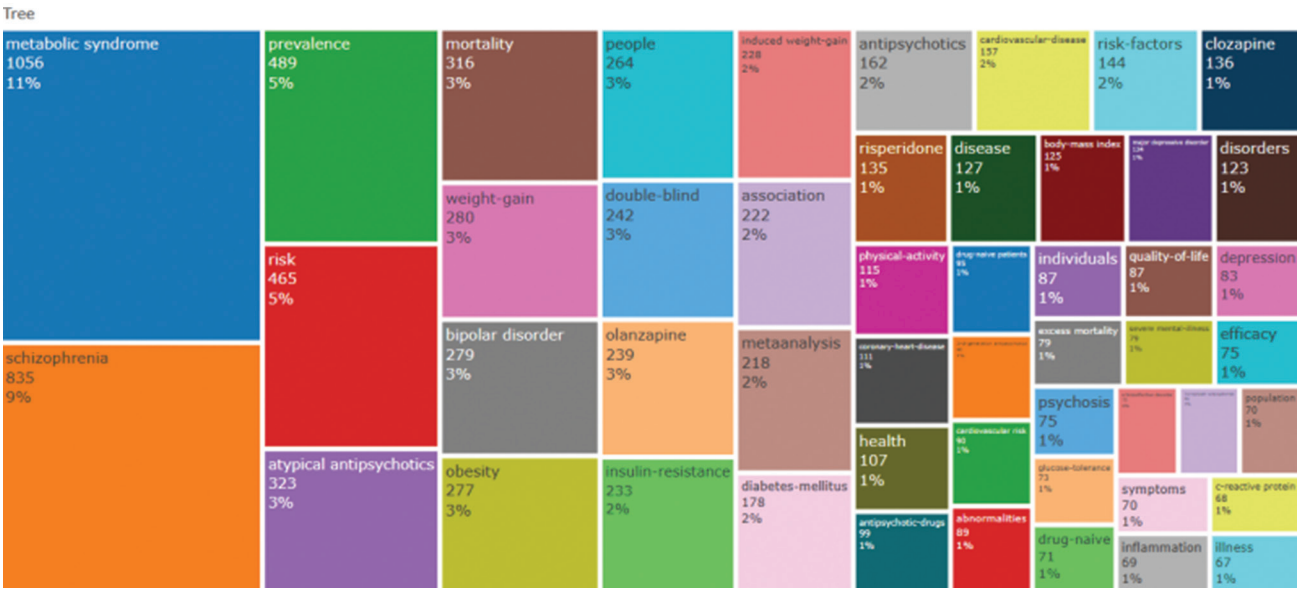

Figure 5. A treemap of keywords

on the incidence and repercussions of MS in SZ patients. MS had a significant impact on the general health status of patients with chronic SZ. MS is defined as the presence of metabolic abnormalities such as large waist circumference, dyslipidemia, fasting hyperglycemia, and high blood pressure.[27] Compared with the general population, the incidence rate and mortality of SZ patients are higher.[27] Cardiovascular problems are the main cause of this death, and the estimated life expectancy has decreased by 10 – 20 years. Therefore, an array of studies was underway to explore avenues for MS prevention.[28] These encompass strategies included promoting aerobic exercise and weight

loss, dietary recommendations such as limiting saturated fatty acid intake,[29] and pharmacological approaches involving antioxidants, melatonin, and probiotics/prebiotics,[30] which was selected targeted treatment based on individual differences.

Cluster 2 spotlighted "*The positive and negative syndrome scale (PANSS) for schizophrenia*"[18] as the most frequently cited article. This reference, a requisite source for numerous SZ-related articles, delved into the positive and negative symptoms experienced by SZ patients, also notable in this cluster was research concerning "*Risk of metabolic syndrome and its components in people with schizophrenia.*"[26] This meta-analysis highlighted that elderly individuals, those taking AAPS such as olanzapine and clozapine, and patients with severe mental illness constituted high-risk factors for SZ patients with MS. Notably, this meta-analysis represented the first large-scale endeavor to explore MS and its risk factors, revealing that antipsychotic drugs significantly contribute to the risk. Similar to the study in Cluster 2, Cluster 3 extended our understanding of the relationship between second-generation antipsychotic drugs and MS. With this cluster, "*Effectiveness of antipsychotic drugs in patients with chronic schizophrenia*"[22] emphasized the duration of treatment cessation for weight gain and MS, notably longer in the olanzapine group compared to quetiapine or risperidone groups. In addition, "*Second generation (atypical) antipsychotics and metabolic effects: a comprehensive quality review*"[29] underscores the treatment-specific risk associated with clozapine and olanzapine, revealing the highest risk of clinically significant weight gain, while the risks associated with other drugs remain relatively low. These insights have significantly contributed to the evolving understanding of the impact of antipsychotic medications on metabolic health in SZ patients. In keyword co-occurrence analysis, Cluster 2 also shined a spotlight on keywords such as "atypical antipsychotic," "weight gain," and "olanzapine." Nowadays, the relationship between MS and SZ is complex and multifactorial, and the current mainstream view was that the use of AAPS played a major role.[31] In addition to the side effects of medication, other factors such as unhealthy lifestyle, reduced physical activity, smoking, improper diet, and genetic predisposition could also contribute to MS.[31] Notably, olanzapine, a second-generation antipsychotic drug, was recognized for its propensity to induce weight gain and further contribute to the development of MS.[6] Research revealed that SZ patients enduring long-term olanzapine use (≥48 weeks) experience an average weight gain of 5.6 kg.[32] The current research underscored the significant impact of AAPS on various organs, including the brain, liver, and pancreas, as well as their influence on the equilibrium of glucose and lipids in tissues. These drugs exert their effects through interactions with receptors such as dopamine, serotonin, acetylcholine, and histamine receptors in the hypothalamus, culminating in heightened sympathetic nerve stimulation, elevated glucagon levels, and increased liver gluconeogenesis levels.[31] Concomitant changes in insulin secretion, dyslipidemia, fat deposition in the liver and adipose tissue, and insulin resistance emerged as compounding factor underlying MS.[31]

In delving into research trends, our citation burst analysis elucidates the evolutionary trajectory of this discipline. The surge in high citation rates from 2004 to early 2012 underscores that "atypical antipsychotic drugs" were a central research focus during this period. At that time, MS was deemed a severe side effect of second-generation antipsychotic drugs such as "olanzapine," "clozapine," and "risperidone" in critically ill patients[33] These studies all reflected that AAPS was a dominant cause and research hotpot of MS recently.

In keyword co-occurrence analysis Cluster 3, "cognition," "inflammation," "depression," and "association" are more frequent keywords. Research elucidates significant positive associations between genetically predicted depression and the risk of MS, waist circumference, hypertension, and triglycerides.[34] This cluster also explores the intricate connections among MS, cognitive function, and inflammation. Additional investigations reveal that MS in middle-aged individuals grappling with depression may potentiate atherosclerosis through inflammatory mechanisms.[35] A meta-analysis involving 27 studies and 10,174 patients with SZ showed that SZ patients with MS or obesity or diabetes have significantly greater overall cognitive deficits.[28] The current research suggests that cognitive impairments associated with MS risk factors are most likely related to metabolic changes, which are associated with microvascular and macrovascular processes believed to cause brain structural abnormalities and subsequently cognitive impairment.[28] In addition, insulin resistance mediates inter-organ communication between adipose tissue and the brain through extracellular vesicles derived from adipose tissue and their cargo microRNAs, leading to cognitive impairment.[36] Hypertension is a major risk factor for both major and minor stroke events, and its most severe form can lead to severe cognitive impairment and vascular dementia.[37] Keyword co-occurrence analysis Cluster 4 delves into "drug-naïve patients," "diabetes," and "insulin resistance." Investigations underscore the coexistence of MS, diabetes, and insulin resistance in drug-naïve patients.[38,39] Notably, research by Chen *et al.* underscores the frequent occurrence of impaired glucose tolerance in first-episode drug-naïve SZ patients,

demonstrating associations with clinical symptoms while exhibiting a less pronounced correlation with early-stage cognitive impairment.[40] At present, research hotspots have shifted toward major depressive disorders, mental disorders, life cycles, and predictive factors, reflecting a transition from mechanistic inquiries to a heightened emphasis on prevention and treatment strategies.[33]

This is the first bibliometric analysis delving into the realm of research connecting SZ and MS. While this study contributes to elucidating prevailing research trends in this interdisciplinary domain, it is crucial to acknowledge its principal limitations. First, while Web of Science stands as a reliable and widely used bibliometric database, its utilization may inadvertently omit certain research, particularly those emanating from non-English language sources and drug discovery efforts by pharmaceutical companies/biotech. Second, the challenge arises when research institutions undergo name changes over time, a nuance that existing bibliometric analysis methods may not fully accommodate.

5. Conclusion

Scholarly attention to the intricate interplay between SZ and MS has burgeoned within academic literature. The trajectory of this trend is poised to persist over the forthcoming three decades. Despite the surge in international cooperation increasing the quantity and significance of research in this area, the United States has, so far, spearheaded productivity in this domain. Furthermore, this keyword analysis within this study uncovers that MS intersects with SZ but also extends its influence into the realm of depression patients. Notably, the thematic focus has evolved, transitioning from risk factors to considerations of life expectancy. Therefore, the forthcoming endeavors in this field may increasingly pivot toward intervention research centering on MS and its relationship with SZ, setting a promising direction for future exploration.

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Conflict of interest

Shen Li is an Editorial Board Member of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Ethics approval and consent to participate

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Consent for publication

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Availability of data

Data are available from the corresponding author upon reasonable request.

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ORIGINAL RESEARCH ARTICLE

Cognitive deficits' profiles of attention and executive functions in epilepsy versus psychogenic non-epileptic seizure patients: A preliminary cross-sectional study

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Abstract

Psychogenic non-epileptic seizures (PNES) resemble epileptic seizures (ES) but lack the associated brain electrical disruptions. Their underlying mechanism remains elusive, even though cognitive deficits are commonly reported in both ES and PNES patients. This preliminary cross-sectional study compared attention and executive functions in 20 patients with ES (ES group) and 18 with PNES or comorbid PNES and ES (PNES group) using the Stroop task and attentional network task (ANT). Both groups exhibited a significant Stroop effect, with no significant differences between them. In the ANT assessment, the ES group had significantly slower reaction times (RTs) in non-tone conditions compared to in-tone conditions ($P < 0.05$). Meanwhile, the PNES group displayed no significant difference in RTs between these conditions, indicating a more pronounced alerting effect in the ES compared to PNES group. No significant disparities emerged in executive control and orientation between the groups. The findings underscore differences in attentional processing between these groups, emphasizing the clinical significance of understanding these cognitive deficits for accurate diagnosis and tailored neuropsychological rehabilitation.

Keywords: Psychogenic non-epileptic seizures; Epileptic seizures; Attention; Executive functions; Alertness; Cognitive deficits

1. Introduction

Psychogenic non-epileptic seizures (PNES) are involuntary episodes of sensation, behavior, or movement that are very similar to epileptic seizures (ES) but lack the electrical activity disruption in the brain that characterizes epilepsy.[1] The accepted method for PNES diagnosis is prolonged video electroencephalography (vEEG) recording showing seizure-like behavior with no epileptic electrical correlates.[1] Estimations suggest that 25 – 30% of patients diagnosed with epilepsy each year may, in fact, have PNES instead of ES. During this delayed diagnostic period, patients often receive antiseizure medications (ASM), many of which are associated with negative side effects in both patients with ES and those with PNES.[2-4] Distinguishing between patients with ES and those with PNES poses a significant diagnostic challenge with important implications for quality of life and treatment.[5] Furthermore, PNES and ES may co-occur in 10 – 73% of PNES patients,[6] making the diagnosis even more challenging.

The etiology of PNES is complex and multidimensional. The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) classifies PNES as a manifestation of functional neurological disorder, whereas the ICD-10 classifies it as a dissociative disorder.[7,8]

Numerous factors have been investigated as potential triggers for PNES.[9] According to the integrative cognitive model, overwhelming and distressing events or memories can destabilize cognitive and emotional systems. When this occurs, the brain may become unable to process the information, causing the sensory and motor systems to become reflexive, eventually leading to a seizure.[10]

Most of the published research has compared PNES and ES, often without contrasting these conditions with healthy controls. These studies have often found that both ES and PNES patients have cognitive deficits.[6,9] While such deficits are a consistent finding in both groups, getting into details presents a complicated picture. In some specific domains, studies noted superior performance in PNES patients,[11] whereas others observed comparable performance between the two groups.[12-14] Binder *et al.* showed that when testing memory and thinking skills using a specific set of tests (the Halstead–Reitan Battery), there were no performance differences between PNES and ES patients; however, both groups performed worse than healthy individuals, except in verbal IQ and certain tasks assessing problem-solving and flexibility.[15] Conversely, Çelik *et al.* reported more dominant attention and executive function problems in PNES patients when compared to ES patients.[16]

The cognitive deficits in patients with ES arise from a variety of organic brain conditions. The same changes in brain functioning that trigger seizures might also have a direct influence on cognition.[17] Structural damage or alterations due to events such as head injuries or infections and imbalanced electrical activity across the brain resulting from seizures.[18,19] Over time, some patients may develop malformations in different brain regions because of diverse causes; these malformations may disrupt the brain's regular communication and function, thereby leading to cognitive impairments.[20,21] Another influencing factor is the side effects of ASM. While crucial for seizure management, ASM may affect cognitive processes by either slowing neural transmission or modifying neurotransmitter levels.[22] In addition, cognitive functions such as memory and attention may also be affected by mood changes or mood disorders in these patients.[18] The cognitive deficits faced by ES patients can emerge from any single factor mentioned or a combination of them, among possible other causes.[6,19]

Studies suggest that the nature of cognitive impairment in epilepsy is intricately linked to the underlying pathophysiology of the seizure disorder.[23] Depending on the specific type of epilepsy, reduced activation is noticeable in different brain regions, such as the right occipital lobe, cerebellum, right frontal lobe, brainstem, and temporal lobe. These identified areas are thought to constitute the neural basis for attention deficits, particularly within the alerting network of temporal lobe epilepsy (TLE) patients.[24]

In cognitive evaluations encompassing areas such as attention, motor coordination, verbal/non-verbal fluency, and response inhibition, both TLE and frontal lobe epilepsy (FLE) patients significantly underperformed compared to healthy controls. Furthermore, results for FLE patients were notably worse than those for TLE patients.[25] Given the central role of the prefrontal cortex in attention and executive functions, this could explain the anticipated deficits in attentional performance in these patients.

An investigation that employed the Stroop task revealed that epilepsy patients are particularly hindered in conditions that evaluate response inhibition and shifting when contrasted with controls.[26] Interestingly, both FLE and TLE patients demonstrated "frontal-like" performances. This similarity may be due to the spread of neural disturbances in TLE patients.[27]

Similarly, major literature indicates that cognitive performance in individuals with PNES is generally poorer compared to healthy individuals.[6,28] However, current literature presents conflicting evidence on the extent to which PNES impacts cognition when compared to ES. Some studies have shown that patients with PNES may perform better than those with ES,[11] whereas others have found no significant differences in cognitive functions

between the two groups. Reported similarities include deficits in working memory, cognitive flexibility, and tasks requiring response inhibition and visuomotor coordination, suggesting that cognitive impairments in PNES patients can be as severe as in those with ES.[12] In addition, neuropsychological research often finds PNES individuals performing below normal levels,[11,29] especially in attention and executive functions, when compared to ES patients.[6,30] These variations in findings may stem from the diverse psychological and neurological profiles of PNES patients.[31]

According to the integrated cognitive-emotional approach,[28] cognitive impairments in PNES are influenced by a complex mix of factors due to the condition's heterogeneous nature. Dissociation, somatization, and post-traumatic stress disorder, which are common in PNES, negatively influence cognitive functioning. Studies comparing the prevalence of somatoform dissociation and compartmentalization in PNES and epilepsy patients show mixed results but generally indicate a higher prevalence of somatoform dissociation in PNES.[32] These psychopathological mechanisms affect cognition differently through their differential impacts on brain regions associated with memory, alertness, perception, and motor functions, illustrating the complex interplay between psychopathology and cognitive impairments in PNES.[28] In addition, patients with PNES exhibit mood disorders and other psychiatric diagnoses which negatively affect their cognitive profiles.[28,33] These patients frequently report significant cognitive concerns and tend to overestimate their cognitive impairments compared to those with epilepsy.[34]

Neurologically, some studies have found that PNES patients demonstrate prefrontal cortex atrophy and neurochemical changes, impacting cognitive function.[4,28] Specifically, there is evidence of substantial atrophy in their prefrontal cortex affecting their executive functions and emotional behavior.[35] In addition, neurochemical changes in the prefrontal cortex, anterior cingulate cortex, and thalamus are linked to attention deficits, inhibitory control problems, and general intelligence issues in these patients. By "general intelligence," we mean evaluating broad cognitive functions through the Wechsler Adult Intelligence Scale, encompassing verbal comprehension, perceptual reasoning, working memory, and processing speed.[36] It has been hypothesized that these structural changes are caused by a history of unnecessary antiepileptic drug treatments as well as high emotional stress.[28,35]

In summary, cognitive difficulties in both ES and PNES patients are multidimensional, stemming from psychological, emotional, neurological, and subjective factors.[18,28] This complexity necessitates a comprehensive approach in both research and clinical evaluation to fully understand and address the cognitive vulnerabilities in this population.

In this current preliminary cross-sectional study, we aimed to evaluate performance in two crucial frontal cognitive functions, attention, and executive control, which are considered essential for effective and adaptive behaviors. We focused on patients with PNES, with or without comorbid ES (categorized as PNES group), in comparison to patients with only ES (categorized as ES group). Smith and Jonides identified five executive functions: inhibition, coding, monitoring, planning, and task management.[37,38] We employed the attentional network test (ANT)[39,40] and the Stroop task[41] to measure these cognitive performances.

As reviewed, findings regarding attention and executive control in PNES patients compared to ES patients are heterogeneous and inconsistent. We hypothesize that adopting an integrated cognitive-emotional approach and the integrative cognitive model,[10] which examines seizures through a comprehensive, multidisciplinary lens – including biological, pathophysiological, neuropsychological, and cognitive-emotional aspects – will more effectively identify discrepancies in attention deficits and executive control between the two groups. Accordingly, we posit:

Patients in the PNES group will exhibit slower reaction times (RTs) on the Stroop index compared to those in the ES group.

(1) Patients in the PNES group will demonstrate slower RTs on the executive index of the ANT compared to those in the ES group.

2. Methods

2.1. Patients

We recruited 38 patients admitted to the neuropsychiatry unit and the epilepsy center at Hadassah Hebrew University Medical Center, Jerusalem, Israel, between January 2021 and June 2023. Inclusion criteria were age 18 – 65, confirmed diagnosis of ES/PNES both diagnoses and the ability to sign informed consent. Patients' diagnoses were verified through a neurological assessment performed by a qualified epileptologist and through ambulatory EEG or gold-standard vEEG monitoring as needed. All patients in the ES and PNES groups had stable or well-controlled ES.

Exclusion criteria included individuals outside the 18 – 65 age range, current psychotic state, active suicidality, current substance abuse, or any cognitive impairment that prevented them from giving informed consent. All medical information was obtained from the electronic medical records, which were then thoroughly reviewed and validated by a physician.

The study was approved by the Helsinki committee of Hadassah Hebrew University Medical Center (application HMO-0651-19), where all data were collected and stored.

2.2. Measures

2.2.1. Demographic clinical questionnaire

A self-report questionnaire, in Hebrew or Arabic, was administered to gather information on various demographic and clinical factors, including age (18 – 65 years), gender (male, female, or other), religion, native language (Arabic and Hebrew), psychiatric diagnosis, seizure severity, and seizure frequency. The severity scale section comprises levels of seizure severity (S-severity), where the severity level is influenced by the type of seizures, their impact on functioning, and the state of consciousness, among other factors. The score ranges from 1 to 6, with 6 indicating higher seizure severity. The frequency scale section includes four levels of seizure frequency, ranging from 0 to 4, with 4 being the highest score. Participants were needed to choose from each scale the option that best matched both the severity and frequency of the seizures experienced.

2.2.2. Psychiatric assessment: Diagnostic interview for anxiety, mood, and OCD and related neuropsychiatric disorders (DIAMOND)

The DIAMOND is a semi-structured psychiatric interview adjusted and aimed at providing psychiatric diagnosis according to the criteria outlined in The DSM-5. In this study, DIAMOND was administered by certified clinicians,[42] using the validated Arabic and Hebrew versions.

2.2.3. ANT

The ANT[40] is a computerized test that combines a flanker task (with arrows)[43] and a cued RT task[39] that measures participants' performance in three separate components of attention: alert, orientation, and executive control.

In this task, participants reacted to target arrows by quickly pressing the keyboard to indicate the target's direction. Participants fixated on a cross until the target appeared. Occasionally, participants received a cue (valid or invalid) hinting at the target, while in some trials, a tone sounded before the target, aiding in preparation. The target, a central arrow among five, pointed in congruent or incongruent directions. Participants quickly pressed "C" for left or "M" for right, indicating the target's direction. Dependent variables were overall RTs and three difference scores: Orientation ("invalid" RTs minus "valid" RTs), alertness ("no tone" RTs minus "tone" RTs), and executive control ("incongruent" RTs minus "congruent" RTs). The task's sequence of events is illustrated in Figure 1.

These three different scores represent three distinct attention networks: alertness, orientation, and executive control. The alertness network primes the brain for sensory input and sustains this heightened state of readiness. As such, it is essential for ongoing information processing. Moreover, alertness is significantly important in diagnosing, managing, and predicting ES.[44]

This task was translated into Arabic and Hebrew using a validated method and version.

2.2.4. The Stroop task

The Stroop task[41] is considered the gold standard of selective attention measurement. In this task, lexical-colored stimuli were presented on the screen one at a time in blue, green, red, and yellow. Participants were asked to respond to the color of the stimulus and to ignore the meaning of the word. The text color and meaning of the word could be either congruent (*e.g.*, the word RED appeared in red), incongruent (*e.g.*, the word RED appeared in yellow), or neutral (*e.g.*, a letter string XXXX appeared in red).

The interference effect, measured by the RT difference between incongruent and neutral stimuli, is large and reliable. In contrast, the facilitation effect, gauged by the RT difference between neutral and congruent stimuli, is small and less stable.[45]

This task was translated into Arabic and Hebrew using a validated method and version.

2.3. Procedure

Patients who met our inclusion criteria were approached when they arrived for their routine appointments at Hadassah Medical Center.

Each subject signed an informed consent form, followed by a computerized demographic questionnaire and a short survey regarding his or her seizures. Then, a computerized cognitive battery task was administered. The order of the cognitive tasks was randomized to rule out confounders. In addition, each patient without a prior psychiatric evaluation underwent a comprehensive assessment conducted by trained psychologists or master's degree psychology students, using a semi-structured interview.[42]

At the end of the session, patients exhibiting psychological distress were given the option to receive psychological treatment at the neuropsychiatric clinic. In addition, those diagnosed with a psychiatric disorder following their evaluation were informed about their diagnosis and were invited to follow up with the clinic's psychiatrist.

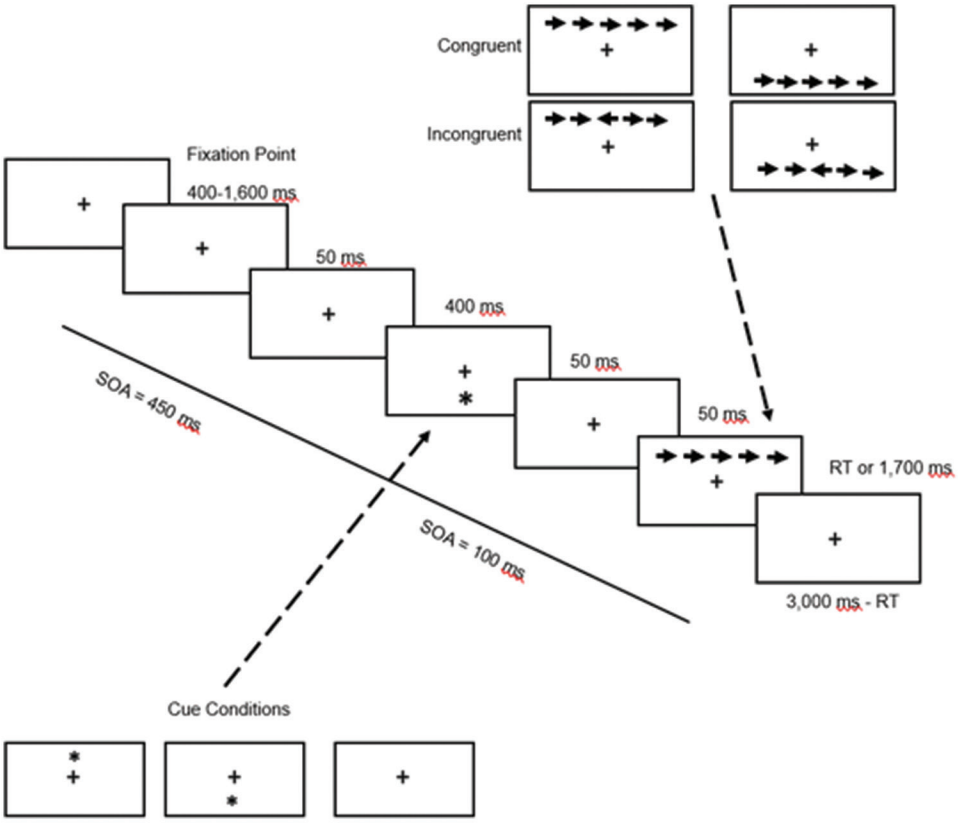

Figure 1. A schematic representation of the attentional network task. Each trial began with a fixation point displayed on-screen for 400 – 1600 ms. In half of the trials, a 50 ms alerting tone was followed. Subsequently, an asterisk cue, signaling the location of the target, appeared above or below the fixation for 50 ms in two-thirds of the trials. After a 50 ms gap, an arrow flanked by four distractor arrows was shown. These distractors were either congruent or incongruent to the central arrow's direction. Participants then indicated the central arrow's direction by pressing a key, followed by a fixation point that lasted up to 3000 ms.
Abbreviations: RT: Reaction time; SOA: Stimulus-onset. asynchrony.

2.4. Statistical analysis

We analyzed the demographic and clinical data using the International Business Machines Statistical Package for the Social Sciences version 26. The statistical analyses for the cognitive data were conducted using the R software. We reviewed the distribution of data to determine normality. Numerical data are expressed as mean±standard deviation (SD), whereas categorical data are presented as counts (percentages). Mann–Whitney *U* and Fisher's exact tests were employed to analyze the demographic and clinical data. Two-way analysis of variance (ANOVA) and four-way ANOVA were conducted for the Stroop and ANT tasks, respectively. The RTs served as the dependent variable for both groups in each task. A $P < 0.05$ was considered statistically significant.

3. Results

3.1. Sample description

The demographic and clinical data of the two clinical groups (the ES group and the PNES group) are summarized in Table 1. Eleven patients were diagnosed with PNES, seven with comorbid ES and PNES, and 20 with ES (ES group). Due to the small sample size, the first two groups were combined into one group, the PNES group (n = 18). No significant differences were found in age, gender, religion, and seizure frequency between the two groups. However, patients in the PNES group exhibited significantly higher instances of psychiatric diagnoses, and significantly greater seizure severity compared to those in the ES group (Table 1).

3.2. Usage of ASM

To present the use of ASM and enable effective comparison and analysis, we followed the approach of Çelik *et al.*,[16] categorizing patients into three subgroups based on the number of ASMs used: none, one ASM, and two or more ASM, as detailed in Table 2.

Considering the variety of ASM classes and instances of polytherapy, we have identified the most commonly

Table 1. Demographic and clinical characteristics (*n*=38)

	ES group (*n*=20)	PNES group (*n*=18)	*P*-value	
	Mean (SD)	Mean (SD)		
Age (years)	36.8 (14.07)	33.41 (13.04)	0.515	
Years of education	12.55 (3.53)	12.67 (3.86)	0.806	
Seizures frequency	1.8 (1.508)	2 (1.455)	0.696	
Seizures severity	3 (1.89)	4.44 (1.58)	0.02**	
	n (%)	*n* (%)	Z	*P*-value
Gender				
Male	11 (55)	6 (33.3)		
Female	9 (45)	12 (66.7)		
			1.79	0.21
Religion				
Muslim	6 (30)	8 (44.4)		
Jewish	12 (60)	10 (55.6)		
Christian	1 (5)	0 (0)		
Other	1 (5)	0 (0)		
			2.36	0.16
Comorbid psychiatric diagnosis				
With	3 (15)	15 (83.3)		
Depression	2	2		
Anxiety	1	4		
Conversion disorder	0	3		
Convulsive disorder	0	3		
Post-traumatic stress disorder	0	1		
BPD	0	2		
Without	17 (85)	3 (16.7)		
			17.74	<0.001**
	n (%)	*n* (%)		
Seizures localization				
Left Temporal	5 (25)	1 (14.2)		
Right Temporal	2 (10)	1 (14.2)		
Right Parietal	2 (10)	1 (14.2)		
Generalized/JME	6 (30)	1 (14.2)		
Frontal Lobe	5 (25)	3 (42.8)		

Notes: Values are presented as counts (percentages) and/or means±SD. The *P*-value indicates the level of significance for comparisons between groups. A $P<0.05$ is considered statistically significant **$P<0.05$.

Table 2. Antiseizure medication usage among ES and PNES groups

Number of ASMs used	ES group (*n*=20) *n* (%)	PNES group (*n*=18) *n* (%)
No ASM	1	7
One ASM	9	8
Two or more ASM	10	3

Abbreviations: ASM: Antiseizure medication; ES: Epileptic seizures; PNES: Psychogenic non-epileptic seizures.

used ASM and their median daily dose. In the ES group, the most frequently used drugs were lamotrigine (400 mg/day), carbamazepine (800 mg/day), and clobazam (10 – 20 mg/day); in the PNES group, the most common drugs were lamotrigine (400 mg/day) and carbamazepine (800 mg/day).

In addition, 13 patients (six with PNES only, three with ES, and four with both PNES and ES) received other medications, including, propranolol, mirabegron,

clonazepam, fluoxetine, quetiapine, hydrocortisone, clozapine, hydroxychloroquine, and sertraline.

3.3. Cognitive functions

From the initial 38 patients, 35 completed the Stroop task, and 34 completed the ANT. In the Stroop task, four patients (two patients with ES and two with PNES only) were excluded from the final analysis as outliers: three patients due to their mean accuracy being more than 2.5 SD from their group mean accuracy and one patient due to their mean RT being more than 2.5 SD compared to their group mean RT. Similarly, in the ANT, five patients (two patients with ES, two with PNES only, and one patient with PNES and ES) were removed from the final analysis for similar reasons: four due to their mean accuracy being more than 2.5 SD from their group mean accuracy and one due to their mean RT is more than 2.5 SD compared to their group mean RT. Consequently, a total of 31 patients remained for the final Stroop analysis, with 17 patients in the ES group and 14 in the PNES group. For the final ANT analysis, 29 patients were included, comprising 15 patients in the ES group and 14 in the PNES group.

3.3.1. Attention control (Stroop task)

Two-way ANOVA for RTs revealed a significant effect for condition (congruent, incongruent, and neutral) ($F[2, 58] = 26.45$, $P < 0.001$, $n_p^2 = 0.477$), and no significant effect for group ($F[1,29] = 0.00$, $P = 0.954$, $n_p^2 < 0.001$). The interaction between condition and group was found to be non-significant ($F[2, 58] = 2.61$, $P = 0.083$, $n_p^2 = 0.082$) (Figure 2). *Post hoc* contrast analysis revealed that patients in the ES group were significantly slower in the incongruent conditions than in the congruent conditions (Stroop effect) (congruent - incongruent; $t(29) = -5.276$, $P < 0.001$). In addition, they were significantly slower in the incongruent conditions compared to the neutral conditions (interference effect) (incongruent - neutral; $t(29) = 5.208$, $P < 0.001$). In contrast, patients in the PNES group were significantly slower in the incongruent conditions than in the congruent conditions (Stroop effect) (congruent - incongruent; $t(29) = -2.886$, $P = 0.019$). Patients in the PNES group showed no differences in RT between the incongruent and neutral conditions (incongruent - neutral; $t(29) = 2.258$, $P = 0.078$). Similarly, no difference was found in the interference effect between the two groups ($t[29] = 1.828$, $P = 0.078$).

3.3.2. Executive functions (ANT)

A four-way ANOVA was conducted with the group as a between-groups factor for each variable network index; (executive control; congruent and incongruent), (alerting; tone and non-tone) and (orienting; valid, no-cue, and invalid). Significant main effects were revealed for each attentional network index (executive control, alerting, and orienting): $F(1, 27) = 36.23$, $P < 0.001$, $n_p^2 < 0.001$; $F(1, 27) = 21.39$, $P < 0.001$, $n_p^2 = 0.442$; and $F(2, 54) = 11.52$, $P < 0.001$, $n_p^2 = 0.299$, respectively. The group × tone interaction was significant, $F(1, 27) = 5.67$, $P = 0.025$, $n_p^2 = 0.174$, reflecting the alerting network (Figure 3). In contrast, no significant interaction was found for group × flanker's congruency interaction in the executive function comparison $F(1, 27) = 1.04$, $P = 0.316$ $n_p^2 = 0.037$. Similarly, the orienting comparison yielded a non-significant effect for group × cue validity interaction $F(2, 54) = 0.19$, $P = 0.825$, $n_p^2 = 0.007$. The three-way and four-way interactions were not significant ($P > 0.05$).

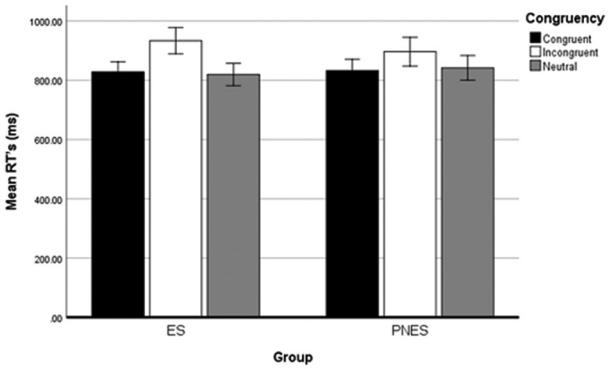

Figure 2. Results of Stroop task: reaction time indexes of the three congruency conditions
Note: Error bars represent standard errors of the mean (error bars ± 1 standard error).
Abbreviations: ES: Epileptic seizures; PNES: Psychogenic nonepileptic seizures; RT: Reaction time.

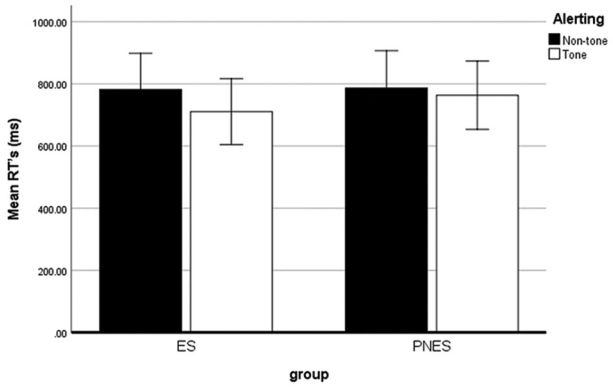

Figure 3. Results of attentional network task, with reaction time indexes of the two alerting conditions as a function of seizure. Error bars represent standard errors of the mean (error bars ± 2 standard error).
Abbreviations: ES: Epileptic seizures; PNES: Psychogenic non-epileptic seizures; RT: Reaction time.

These results suggest that while there were no significant differences between the groups in terms of executive control and orienting; differences were observed in alerting. Specifically, patients in the ES group displayed significantly slower RTs in the non-tone conditions compared to the tone conditions. In contrast, for the PNES group, no significant difference in RTs between the tone and non-tone conditions was found.

3.4. Effect of antiepileptic drug on cognitive assessment

To examine the effect of ASM usage on cognitive processing, data were analyzed using analysis of covariance. The interaction between ASM usage and Stroop task congruency, $F(4, 54) = 1.48$, $P = 0.221$, was not statistically significant, indicating that ASM usage did not significantly affect cognitive interference as measured by the Stroop task. Furthermore, there were no significant interactions between ASM usage and the attentional network indices of executive control, alerting, and orienting: $F(2, 25) = 1.89$, $P = 0.172$, $F(2, 25) = 1.95$, $P = 0.164$, and $F(4, 50) = 0.62$, $P = 0.653$, respectively. This suggests that ASM load – whether participants were on none, one, or multiple ASM – did not significantly influence RT variability across different cognitive task conditions.

4. Discussion

The current preliminary cross-sectional study aims to evaluate the cognitive deficit profiles in ES and PNES patients as assessed by the ANT and the Stroop task.

Our results primarily show a more pronounced alerting effect in the ES group compared to the PNES group, indicating marked differences in attentional processing between the groups. This was a significant observation we did not initially hypothesize. ES patients seem to be more responsive to warning cues, allowing them to achieve and maintain heightened alertness more efficiently than patients with PNES. This may imply that the alerting network in the PNES group is less efficient or sensitive compared to the ES group. However, drawing from prior research in this domain, the difference in the alerting effect might indicate a state of hyper-alertness to the presence of tones in the task among the ES group and not necessarily a deficit in the capacity of the PNES group to initiate and maintain an alert state in response to warning cues.[46,47]

According to the integrative cognitive model mentioned above, the first stage of PNES is marked by a sharp rise in sympathetic arousal. However, following a seizure event, there is a change in the patient's experience as the initial sympathetic response is interrupted, resulting in decreased arousal.[10] This alteration in arousal state may be associated with changes in alertness levels in response to external, non-emotional stimuli. This could explain why the alerting network in the PNES group is less efficient or sensitive compared to the ES group, according to the integrative cognitive model.

Contrary to our hypothesis, the executive score from the ANT revealed no significant difference in executive control between the ES and PNES groups. Similarly, the orienting score showed no notable difference between the two groups. It is possible that these effects were not significant because of the small sample size and the mixture of PNES + ES in the PNES group, which could have increased variability in the sample and interfered with the detection of these effects.

Regarding the Stroop task,[41] a significant Stroop effect was observed in both seizure groups. However, there was no difference in the interference effect among patients in the ES group compared to those in the PNES group, meaning that deficits in selective attention and cognitive control in the ES group may not differ significantly from those in the PNES group.

In addition, the cognitive performance observed in the ANT and the Stroop task is not differentially affected by the quantity of ASM consumed by the patients. This finding is inconsistent with previous studies that found cognitive deterioration in children with epilepsy after using carbamazepine.[48,49] This may be due to the fact that in the current study, participants were adults, part with comorbid PNES, and that we analyzed all kinds of ASMs together and used different cognitive assessment methods. However, this issue should be explored in further studies.

Given the small number of participants and other potential confounding factors that could influence the outcomes, we present these findings with considerable caution. Overall, our findings may indicate more severe cognitive deficits, especially in alertness, among patients with ES, compared to those with PNES and comorbid cases. However, this does not negate the presence of attentional cognitive impairments in PNES patients, which have been documented in previous studies.[28,50]

In our research, we identified a significantly higher rate of comorbid psychiatric diagnoses and greater seizure severity among patients in the PNES group compared to those in the ES group. This is notable, considering that previous studies in this field have consistently established a positive correlation between these factors and attention deficits, which may be significant confounding factors.[44,51] Given the high percentage of comorbid psychiatric diagnoses and the establishment of attentional control

theory,[52] future research can delve deeper into the emotional aspects of patients with ES and PNES.

This preliminary cross-sectional study expands the currently limited body of research, specifically designed to measure attention in patients with PNES and those with comorbid diagnoses (both PNES and ES), comparing them to matched patients with only ES. Our findings enhance our understanding of some cognitive deficits' profiles underlying PNES and ES. Further research is pivotal to validate these findings. Such insights could bolster the validity of diagnosis in ambiguous cases, pave the way for more effective and tailored treatments, and promote intervention programs and strategies to mitigate and manage seizures in these patients.

One of the primary limitations of our research was the small sample size. While smaller groups can offer preliminary insights and highlight potential trends or patterns, they often lack the statistical power necessary to draw broad, generalizable conclusions. For these reasons, while our findings provide a valuable starting point, they should be interpreted with caution until larger more comprehensive studies can validate or refine our conclusions. In addition, it is important to recognize that during the neuropsychological testing, most patients with ES and PNES are on ASM, psychiatric, or other neurological drugs. These medications can lead to several side effects, such as drowsiness or psychomotor slowing, which can adversely impact their performance on the tests.[6] Due to ongoing changes in the administration of antiepileptic or neurological drugs for our participants, we could not account for them in our research, which may be a potential confounder of our results. Psychotherapy use also varied in existence, length, and approach between participants along their medical course, which can also alleviate symptoms and affect results accordingly. Moreover, the cross-sectional nature of our study prevents us from drawing causal conclusions. In addition, the version of the ANT used might not be sensitive enough to detect differences in the attention networks between the ES group and the PNES group. Finally, due to the small sample size, we grouped participants to preserve statistical power. Incorporating patients with dual diagnoses (both PNES and ES) into the PNES group introduced additional variability, complicating the derivation of PNES-specific conclusions. Nonetheless, we recommend that future studies investigate these issues in separate groups to yield more definitive conclusions.

5. Conclusion

In our endeavor to understand the cognitive deficit profiles of patients with ES and PNES, our preliminary cross-sectional study highlighted subtle differences in attentional processing, particularly in alertness and selective attention, between these two groups. A more pronounced alerting effect in the ES group compared to the PNES group indicates differences in attentional processing between the groups. Future investigations should utilize larger participant cohorts and include more comprehensive assessments covering both emotional and cognitive domains. By doing so, they can provide insights into the complex interplay between cognitive deficits and emotional dysregulation. Exploring these underlying mechanisms is crucial for enabling earlier, tailored diagnoses and personalized treatment approaches, ultimately enhancing patients' quality of life.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

The study was approved by the Helsinki committee of Hadassah Hebrew University Medical Center (ethics committee number: HMO-0651-19), where all data were collected and stored. Informed consent from the participants has been obtained before their participation. The consent was acquired through written means, ensuring that participants were fully informed about the study's purpose, procedures, risks, and their right to withdraw at any time.

Consent for publication

Informed consent for the publication of anonymous data was acquired through writing.

Availability of data

Data are available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Involvement of adverse life events in body image distortion in a patient with eating disorders

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Abstract

Adverse life events (ALEs), particularly interpersonal ALEs and those experienced during childhood are associated with adult psychopathology. Altered eating behaviors and body image distortion (BID) have been reported in maltreated children. This study aimed to evaluate the presence of interpersonal ALEs before the age of 13 years in patients with eating disorders (ED) and clarify its relationship with BID. This observational case–control study comprised the ED group, including 79 outpatients with ED, and two control groups, including 20 outpatients with depressive disorder and 41 participants with no history of mental illness. The presence of ALEs was determined using the Traumatic Events Questionnaire. To assess BID, the contouring drawing rate scale was used, and visual BID was distinguished from non-visual BID. Data were collected and processed using Statistical Package for Social Sciences v28. All tests were two-tailed (significance level of 0.05). Patients with ED had a higher proportion of interpersonal ALEs during childhood ($P = 0.065$). In the ED group, patients with interpersonal ALEs during childhood overestimated their shape ($P = 0.021$). The non-visual BID was significantly higher in patients with childhood ALEs. In a logistic regression model, the presence of interpersonal ALEs during childhood as an independent variable predicted visual and non-visual BID in patients with ED. During the estimation of body shape, it appears that the negative emotions experienced during childhood are shifted to the body shape itself. Thus, the BID experienced is attributed more to the unresolved emotions of the maltreated individuals than to the social pressures experienced.

Keywords: Body image; Adverse life events; Childhood abuse; Eating disorders; Perfectionism

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1. Introduction

Eating disorders (EDs) are serious medical conditions that are often comorbid with psychiatric disorders.[1] Poor illness outcomes are associated with body image distortion (BID) and dissatisfaction with one's shape.[2] Patients with ED who have experienced emotional and physical abuse are more likely to have concerns about body shape and weight.[3]

Trauma exposure is considered a non-specific risk factor for ED, and several adverse life events (ALEs), mostly occurring within a trusting relationship, have been implicated in the onset and maintenance of the illness.[4-7] However, it remains unclear whether the onset of psychopathology is due to maltreatment or other factors such as the timing or frequency of traumatic experiences.[8]

Various forms of ALEs, including physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse, have been identified as child maltreatment.[9] Interpersonal trauma has been classified as maltreatment and associated with post-traumatic symptoms.[10] ALEs have also been linked to the development of body image, along with personal, social, and interpersonal factors.[11] In addition, childhood experiences of pain and hunger, exploration of the environment, and relationships with parents have been found to contribute to the development of altered body image.[12] The body image construct includes attitudes, perceptions, emotions, and thoughts.[11,13] A growing body of research indicates that body representation relies on multisensory perceptions toward which therapeutic efforts can be directed.[14]

A recent systematic review of the effects of maltreatment on patients with ED reported alterations in the parietal cortex and thalamic areas involved in the visual perception of shape.[15,16] The early years of development are critical for neurobiological maturation and enhancement of relationship skills.[17] Adverse childhood experiences before the age of 6 years can interfere with the development of secure attachment and good emotion regulation.[14] Exposure to physical or sexual abuse in early childhood has been associated with depression, post-traumatic symptoms, and anxiety in adulthood.[17] Patients with ED who have experienced humiliation from peers or intrafamilial abuse show greater body dissatisfaction, with shame as a mediating factor between ALEs and body image.[15] In addition, ALEs have been associated with alterations in the glucocorticoid or noradrenergic system.[15]

Perfectionism has been identified as a predictor of ED development.[18] Quilliot *et al*. revealed that bullying, sexual abuse, and dissociative symptoms are associated with emotional dysregulation in patients with ED.[19] Armour *et al*. reported that impulsivity was associated with self-injurious behaviors and body rumination in patients with ED and those with affective disorders who had experienced interpersonal ALEs.[20] Emotional dysregulation may be related to body dissatisfaction through perfectionism, according to Donahue *et al*.[18]

To date, no study has evaluated the relationship between ALEs and BID in patients with ED. Some studies have examined different subtypes of ALEs and their association with bulimic symptoms or body mass index (BMI).[3,5] We hypothesized that patients with ED who experienced interpersonal ALEs before the age of 13 years (pre-13 interpersonal ALEs) are more likely to present with BID. This study aimed to examine the relationship between pre-13 interpersonal ALEs and both visual and non-visual BID in patients with ED. In addition, this study examined the relationship between pre-13 interpersonal ALEs and the development of perfectionism and impulsivity.

2. Methods

2.1. Study design and participants

We conducted an observational, cross-sectional, case–control study. Eligible participants (n = 187) underwent an assessment to determine whether they met the inclusion and exclusion criteria. This study involved three comparison groups: A study group (ED group) of patients with ED and two control groups consisting of patients with recurrent major depressive disorder (RMDD) and participants with no history of mental illness. The control groups were selected from non-clinical populations with mood disorders who showed BID.[11,21] In addition, affective disorders are known to be associated with ED.[2] Psychiatrists and psychologists of the relevant treatment units performed the initial selection of outpatients. Based on the inclusion criteria, 107 eligible patients with ED and 35 with RMDD were consecutively recruited by their therapists when they attended their follow-up. For the recruitment of the control group with no history of mental illness, we distributed information leaflets describing the study and containing contact information on the hospital bulletin boards, and 45 eligible candidates were selected.

The inclusion criteria were as follows: Age 18 – 65 years; diagnosis of restricting and purging anorexia nervosa, bulimia nervosa, or binge ED and RMDD according to the diagnostic and statistical manual of mental disorders, 5th Edition[22]; good command of the Spanish language; and provision of written informed consent. The exclusion criteria were as follows: BMI of <15 kg/m^2, high suicide risk, presence of psychotic symptoms, or intellectual disability.

Finally, the study included 140 participants, including 79 (56.4%) patients with ED, 20 (14.3%) patients with RMDD, and 41 (29.3%) controls. The mean age of the participants (total sample) was 38.5 (range: 18 – 60, standard deviation [SD]: 12.3) years; 90% of the participants were females, 68.6% completed college education, and 70% were employed. ALEs were reported by 89.3% of the participants.

2.2. Measurement and procedure

Recruitment was conducted between January 2021 and May 2022. Participants attended a face-to-face interview at

the hospital, where they signed an informed consent form and completed a questionnaire, providing information on age, sex, diagnosis of ED or RMDD, duration of illness, years of treatment, and number of hospitalizations. The interviewer recorded the height and weight of the participants to obtain BMI. The following tests were used to assess the clinical features, ALEs, and body image:

1. Traumatic life events questionnaire.[23] This is a 23-item self-report questionnaire designed to assess ALEs with dichotomous responses (YES/NO). Participants select their most distressing traumatic experiences and report the age at which they occurred and the level of distress associated with them. This allows for the examination of common ALEs, both interpersonal and non-interpersonal, over the course of an individual's lifetime. The questionnaire has been tested on diverse populations and has satisfactory psychometric properties (internal consistency of 0.74 – 0.91).
2. Contour Drawing Rating Scale (CDRS). This scale was developed and validated by Thompson and Gray in 1995.[24] It consists of nine male and nine female drawings that are rated from 1 to 9 based on their size. Participants select the drawing that represents their ideal body and the one that they believed was closest to their actual weight. This scale is useful in assessing body dissatisfaction and BID and has good internal consistency (Cronbach's alpha coefficient: 0.92).
3. Eating disorder inventory (EDI-2): This is also a self-report measure of ED.[25] This questionnaire comprises 91 items and uses a 6-point Likert scale (1 = never; 6 = always). It explores a range of clinical features and is classified into 11 subscales: Drive for Thinness, Bulimia, Body Dissatisfaction, Inefficacy, Perfectionism, Interpersonal Distrust, Interoceptive Awareness, Maturity Anxiety, Ascetism, Impulse Regulation, and Social Insecurity. It can discriminate patients with illness from those who are not clinically ill. Its internal consistency score ranges from 0.83 to 0.93.

The primary outcome of the study was the presence of ALEs. In accordance with a previous study,[10] we classified the recorded ALEs into two categories: (1) interpersonal ALEs and (2) non-interpersonal ALEs. In addition, an analysis that considered the presence of pre-13 ALEs (both interpersonal and non-interpersonal) and the presence of pre-13 interpersonal ALEs was conducted.

The secondary outcomes assessed included levels of perfectionism, impulsivity, and the presence of BID. To examine the presence of BID, the CDRS was used to determine the participants' ideal body image, visual BID, non-visual BID, and actual shape according to their BMI. The body that patients "see" was "separated" from the body that they "feel." First, the participants selected the silhouette they believed represented their body when they looked at themselves in the mirror (visual BID); second, they were instructed to close their eyes and try to feel their body before choosing the body shape (non-visual BID). The difference between the figure they chose and the actual shape according to BMI defined the BID. We defined three categories: (1) overestimation of the body shape, (2) underestimation of the body shape, and (3) absence of BID when the figure they chose was superior, inferior, or equal to the actual BMI, respectively.

2.3. Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 24.0 (IBM Software, Illinois).[26] To examine differences within the ED group, Student's t-test was used to compare the presence of interpersonal ALEs and pre-13 interpersonal ALEs (a dichotomized categorical variable) with the quantitative variables when the sample size was >30. When the sample size was <30, the Mann–Whitney *U* test was used. To examine intergroup differences (ED, RMDD, and control groups) in the quantitative measures of BID, impulsivity, and perfectionism in relation to interpersonal ALEs, pre-13 ALEs, and pre-13 interpersonal ALEs, the one-factor parametric analysis of variance test and Kruskal–Wallis test were used. Similarly, a linear regression model was established to assess the impact of pre-13 interpersonal ALEs on BID, perfectionism, and impulsivity. All statistical tests were performed using a two-tailed approach, with the significance level set at an alpha value of 0.05.

3. Results

3.1. General sample description

As shown in Table 1, 72 patients with ED (91.1%) reported having experienced ALEs in their lifetime, with 69.6% reporting non-visual BID and 65% reporting visual BID. The mean duration of illness was 17.1 (range: 1 – 47; SD: 2.9) years, and 44.3% of patients reported at least one hospitalization (mean: 0.81, range: 0 – 5, SD: 1.1). Furthermore, 100% and 80.5% of participants in the RMDD and control groups reported the presence of ALEs, respectively, and no differences were noted between non-visual and visual BID in 60% of patients in the RMDD group and 61% of patients in the control group. Family and social relationships were considered better in the control group.

3.2. Characteristics of ALEs in the sample

As shown in Figure 1, patients in the ED group (black column) had a higher proportion of interpersonal ALEs

Table 1. Descriptive statistics of the groups

	ED (*n*=79)	RMDD (*n*=20)	CG (*n*=41)	TS (*n*=140)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Sex				
Male	3 (3.8)	6 (30.0)	4 (9.8)	13 (9.3)
Female	76 (96.2)	14 (70.0)	37 (90.2)	127 (90.7)
Marital status				
Single	19 (24.1)	2 (10.0)	16 (39.0)	37 (26.4)
Separated	14 (17.7)	4 (20.0)	4 (9.8)	22 (15.7)
Married and/or cohabiting	45 (56.9)	13 (65.0)	20 (48.8)	78 (55.8)
Widowed	1 (1.3)	1 (5.0)	1 (2.4)	3 (2.1)
Education				
Primary	4 (5.1)	0 (0.0)	2 (4.9)	6 (4.2)
Secondary	5 (6.3)	1 (5.0)	1 (2.4)	7 (5.0)
Professional training	16 (20.3)	9 (45.0)	6 (14.6)	31 (22.1)
University degree	54 (68.4)	10 (50.0)	32 (78.0)	96 (68.5)
Employment status				
Active/student	52 (65.8)	8 (40.0)	38 (92.5)	98 (70.0)
Unemployed with benefit	5 (6.3)	5 (25.0)	1 (2.5)	11 (7.8)
Unemployed without benefit	4 (5.1)	4 (20.0)	0 (0.0)	8 (5.7)
Temporary incapacity for work	7 (8.9)	3 (15.0)	0 (0.0)	10 (7.1)
Permanent incapacity for work	4 (5.1)	0 (0.0)	0 (0.0)	4 (2.8)
Retired	7 (8.9)	0 (0.0)	2 (5.0)	9 (6.4)
Family relationships				
Good	49 (62.0)	13 (65.0)	37 (90.2)	99 (70.7)
Bad	4 (5.1)	1 (5.0)	0 (0.0)	5 (3.5)
Fair	26 (32.9)	3 (15.0)	4 (9.8)	33 (23.5)
Absent	0 (0.0)	3 (15.0)	0 (0.0)	3 (2.1)
Social relationships				
Good	53 (67.1)	13 (65.0)	37 (90.2)	103 (73.5)
Bad	3 (3.8)	3 (15.0)	0 (0.0)	6 (4.2)
Fair	14 (17.7)	4 (20.0)	4 (9.8)	22 (15.7)
Absent	9 (11.4)	0 (10.0)	0 (0.0)	9 (6.4)
BMI at assessment				
Underweight	11 (13.9)	2 (10.0)	3 (7.3)	16 (11.4)
Normal weight	33 (41.7)	13 (65.0)	24 (58.5)	70 (50.0)
Overweight	35 (44.3)	5 (25.0)	14 (34.1)	54 (38.5)
Presence of ALE				
No	7 (8.9)	0 (0.0)	8 (19.5)	15 (10.7)
Yes	72 (91.1)	20 (100.0)	33 (80.5)	125 (89.3)
Visual BID				
No	28 (35.0)	8 (40.0)	16 (39.0)	52 (37.1)
Yes	51 (65.0)	12 (60.0)	25 (61.0)	88 (62.9)
Non-visual BID				
No	24 (30.4)	8 (40.0)	16 (39.0)	48 (34.3)
Yes	55 (69.6)	12 (60.0)	25 (61.0)	92 (65.7)

Abbreviations: ALEs: Adverse life events; BID: Body image distortion; CG: Control group; ED: Eating disorders; NA: Not applicable; RMDD: Recurrent major depressive disorder; TS: Total sample.

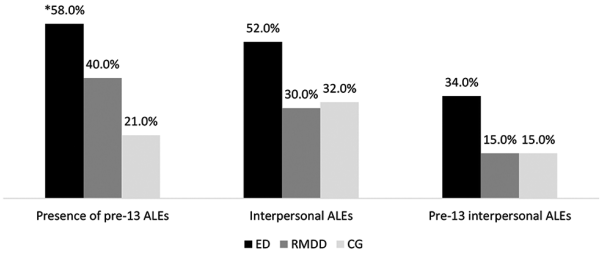

Figure 1. Intergroup differences with regard to ALE categories. *Chi-square test, with $P<0.05$.
Abbreviations: ALEs: Adverse life events; CG: Control group; ED: Eating disorders; RMDD: Recurrent major depressive disorder.

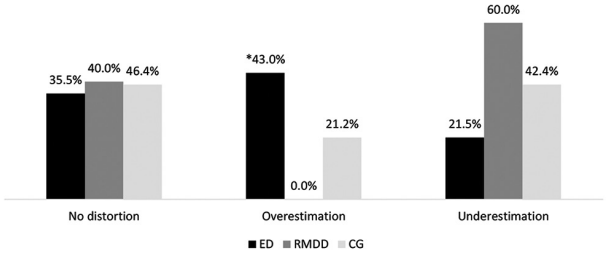

Figure 2. Visual BID. Patients in the ED group (black columns) showed the highest visual overestimation, whereas those in the RMDD group and CG (dark and clear gray columns, respectively) underestimated their shape when looking in the mirror. *Kruskal–Wallis test, with $P<0.05$.
Abbreviations: ED: Eating disorders; RMDD: Recurrent major depressive disorder; CG: Control group.

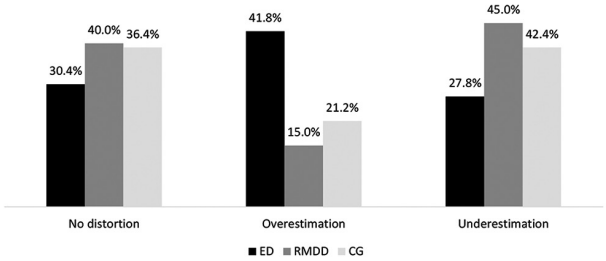

Figure 3. Non-visual BID. In this histogram, patients in the ED group overestimated their shape whereas the other groups mostly underestimated their shape
Abbreviations: ED: Eating disorders; RMDD: Recurrent major depressive disorder; CG: Control group.

($P = 0.062$) and pre-13 interpersonal ALEs ($P = 0.065$) than those in the other two groups. When considering pre-13 ALEs, whether interpersonal or non-interpersonal, the ED group reported a significantly higher number of childhood ALEs than the other two groups ($P = 0.042$).

The control group exhibited significantly lower levels of extreme distress than the other two groups ($P = 0.036$). Furthermore, the age of reporting the most distressing ALE was lower in the ED group than in the other two groups ($P = 0.051$).

3.3. Characteristics of BID in the sample

Figures 2 and 3 depict the BID of patients with ALEs. Patients in the ED group overestimated their shape. However, they evaluated their figures more accurately when looking in the mirror. Although not significant, a larger proportion of patients displayed non-visual BID (69.6%) compared with visual BID (64.5%). Patients in the RMDD group reported a non-visual overestimation of their figure that was not present when they looked in the mirror. The ED group showed significantly higher visual BID ($P = 0.034$) than the other two groups.

The analysis of intragroup differences regarding the type of BID revealed that non-visual overestimation of the shape was prevalent in the ED group with more body dissatisfaction ($P = 0.034$). Conversely, in the control group, body dissatisfaction was associated with visual BID ($P = 0.020$). The RMDD group did not report any differences.

3.3.1. Relationship between ALEs, impulsivity, perfectionism, and BID among the groups

Table 2 illustrates the discrepancies in the levels of perfectionism, impulsivity, and BID with regard to ALE categories.

Regarding interpersonal ALEs, the ED group displayed more pronounced levels of perfectionism, whereas the RMDD group exhibited reduced levels of impulsivity compared with the other two groups. Regarding pre-13 ALEs (interpersonal or non-interpersonal), the ED group displayed higher levels of impulsivity and perfectionism, although the difference was not significant. Similarly, patients in the ED group who experienced both interpersonal and pre-13-year ALEs exhibited higher levels of impulsivity and perfectionism than those in the other two groups, although this effect was not statistically significant.

Regarding BID, patients in the ED group who experienced interpersonal ALEs overestimated their body shape both visually and non-visually. However, only the visual BID differed significantly between the ED group and the other two groups. Patients in the other two groups underestimated their body shape. Furthermore, the ED group demonstrated a markedly higher prevalence of body dissatisfaction. When considering pre-13 ALEs (interpersonal or non-interpersonal), the ED group demonstrated higher levels of visual and non-visual BID and body dissatisfaction than the other two groups. When considering pre-13 interpersonal ALEs, the ED group displayed heightened levels of body dissatisfaction and visual BID. Nevertheless, the non-visual overestimation

Table 2. Differences in perfectionism, impulsivity, and BID with respect to ALE categories

	ED Mean (SD)	RMDD Mean (SD)	CG Mean (SD)	*P**
Interpersonal ALEs				
EDI-P	**7.90 (4.02)**	5.33 (4.92)	4.30 (4.31)	0.028
EDI-I	5.61 (6.00)	1.33 (1.21)	2.53 (5.57)	0.034
Visual BID	**0.80 (1.80)**	−0.83 (1.21)	−0.70 (0.95)	0.038
Non-visual BID	0.70 (2.11)	−0.75 (1.22)	0.00 (1.35)	0.158
CDRS BD	**3.29 (2.12)**	1.41 (1.02)	0.69 (0.75)	0.002
EDI-BD	**18.90 (10.81)**	6 (6.35)	4.69 (4.92)	0.002
BMI	21.58 (6.79)	22.6 (4.19)	23.82 (4.52)	0.385
ALEs (both interpersonal and non-interpersonal) before the age of 13 years				
EDI-P	7.4 (4.11)	7 (4.32)	3.16 (3.33)	0.489
EDI-I	5.05 (5.94)	2.62 (3.02)	2.33 (5.71)	0.082
Visual BID	**0.82 (1.60)**	−0.75 (1.06)	−0.5 (0.83)	0.004
Non-visual BID	**0.85 (1.85)**	−0.68 (1.48)	−0.66 (0.51)	0.015
CDRS BD	**3.20 (2.19)**	1.62 (2.08)	0.66 (0.81)	0.013
EDI-BD	**17.85 (10.95)**	10.87 (10.42)	6.66 (5.24)	0.033
BMI	25.24 (8.91)	29.08 (9.03)	22.7 (1.33)	0.546
Interpersonal ALEs before the age of 13 years				
EDI-P	8.34 (3.94)	6 (4.66)	3.00 (4.24)	0.082
EDI-I	6.15 (6.37)	1.20 (1.30)	3.50 (7.00)	0.218
Visual BID	**1.01 (1.83)**	−1.00 (1.27)	−0.5 (1.00)	0.021
Non-visual BID	0.98 (2.09)	−0.90 (1.88)	−0.75 (0.50)	0.070
CDS BD	**3.55 (2.20)**	1.55 (1.11)	1.00 (0.81)	0.022
EDI-BD	**19.65 (10.48)**	7.20 (6.30)	7.00 (5.88)	0.016
BMI	25.59 (10.36)	28.34 (7.23)	22.85 (1.70)	0.513

Note: We represent the significant differences in bold. *Kruskal–Wallis test, with $P<0.05$.
Abbreviations: ALEs: Adverse life events; BD: Body dissatisfaction; BID: Body image distortion; BMI: body mass index; CDRS: Contour Drawing Rating Scale; CG: Control group; ED: Eating disorders; EDI-BD: Eating disorder inventory, subscale body dissatisfaction; EDI-I: Eating disorder inventory, subscale impulse regulation; EDI-P: Eating disorder inventory, subscale perfectionism; RMDD: Recurrent major depressive disorder; SD: Standard deviation.

in the ED group was not significantly different compared with that in the RMDD and control groups.

3.3.2. Relationship between ALEs, impulsivity, perfectionism, and BID in the ED group

At the intragroup level, patients in the ED group who reported interpersonal ALEs exhibited heightened levels of perfectionism (P = 0.041) and impulsivity (P = 0.056). Conversely, patients in the RMDD group who had interpersonal ALEs showed reduced impulsivity (P = 0.002).

Patients in the ED group who showed pre-13 ALEs (P = 0.038) demonstrated a heightened propensity for non-visual BID. No significant differences were observed in the RMDD or control group with regard to this ALE category.

With regard to the category of pre-13 interpersonal ALEs, the analysis yielded significant differences in the levels of perfectionism, which were higher (P = 0.017) among patients in the ED group who had experienced such an event than among those who had not. Obsessive thoughts about weight loss and impulsivity exhibited tendencies that approached statistical significance (EDI-Drive for thinness, P = 0.052; EDI-Impulsivity, P = 0.055).

A linear regression analysis was conducted to investigate the relationship between pre-13 interpersonal ALEs and BID. To gain further insight into the potential predictors of pre-13 ALEs, several alternative models were examined. The initial model was constructed using BMI. The second model incorporated pre-13 interpersonal ALEs. The third model included pre-13 interpersonal ALEs, along with BMI and the number of hospitalizations. The results indicated that experiencing interpersonal ALEs before the age of 13 years is predictive of a visual BID in adulthood. Moreover, this model was effective in predicting non-visual BID. The influence of pre-13 interpersonal ALEs on other variables was examined, and this traumatic factor was found to be a predictor of impulsivity (P = 0.001) and perfectionism (P = 0.021).

4. Discussion

This study assessed the presence of interpersonal ALEs in patients with ED and elucidated the relationships of pre-13 interpersonal ALEs with BID, impulsivity, and perfectionism. As hypothesized, the results indicated that patients in the ED group who reported pre-13 interpersonal ALEs had significantly higher levels of BID than those in the other two groups. Patients in the ED group overestimated their body shape, both visually and non-visually. However, the difference in overestimation between the groups was significant only for visual BID.

Studies have reported a relationship between BID in patients with ED and changes in brain function in the parietal cortex while undergoing visual self-assessment.[15,27] Chemisquy and Helguera suggested that individuals with high perfectionism are particularly vulnerable to stressful relationships.[28] Children who experience interpersonal ALEs may develop strategies to cope with negative emotions, including exerting control over their bodies. This may affect the accuracy of self-evaluation when looking in the mirror because of the influence of their perfectionist tendencies. This could explain why patients with ED and interpersonal ALEs tend to report negative self-evaluations

in the form of overestimation when looking at themselves in the mirror. In addition, if they have a family dynamic based on physical appearance, they may judge themselves with the notion of the body image that their parents helped to create.[11,14] Moreover, patients in the ED group who had interpersonal ALEs showed a higher level of perfectionism than those in the other two groups. Conversely, the RMDD and control groups underestimated their body shape in and out of the mirror, indicating a tendency to adapt their body shape to social requirements.[11] Patients in both groups had higher BMIs than those in the ED group.

Patients in the ED group, who reported pre-13 ALEs, regardless of type, had significantly higher visual and non-visual BID than those in the other two groups. Body identity is formed through sensory experiences in the early months of life and develops during the 1st few years of life when the mother/parent–child relationship is paramount.[12,14,29] ALEs have been implicated in the development of body image.[12,16,30] Individuals with secure attachments and trusting relationships are generally more satisfied with their bodies.[12,14,30] Therefore, it is hypothesized that the presence of interpersonal ALEs during early adolescence affects body image. Negative emotions related to previous interpersonal ALEs may influence body perception when patients close their eyes.

To test this hypothesis, the body that patients visually perceived was distinguished from the body that they accurately perceived after closing their eyes and physically feeling their body shape before selecting the figure that corresponded to their true appearance. Patients with ED overestimated their body shape, both visually and non-visually, whereas participants in other groups tended to underestimate their body shape.

The RMDD group overestimated their body shape when they felt their body, but not when they looked at themselves in the mirror. This non-visual overestimation occurs in patients who are overweight, and they underestimate their body shape in the mirror. In general, underestimation is associated with a high BMI.[11] When patients with depression look at themselves in the mirror, they judge themselves with the social requirement of a thin body. In line with this finding, a recent study reported body distortion associated with weight bias in patients with depression with the negative effects influencing perception.[31] Thus, the visual BID of patients with depression might be based on this weight bias, whereas the non-visual BID might respond to negative emotions derived from ALEs.[15]

Interestingly, the non-visual bias is intensified when non-visual senses are engaged, such as interoceptive, proprioceptive, and emotional experiences, which become apparent after closing the eyes. This indicates that interpersonal ALEs affect the activation of regions involved in body awareness.[16] These regions have been linked to emotional regulation and show changes in adults who suffered childhood abuse.[16] Thus, promoting a connection to the inner emotional world by encouraging patients to feel their bodies may lead to altered body evaluation in individuals with interpersonal ALEs.[14] This supports the notion that body evaluation is not only socially influenced, as individuals with ALEs may also experience an alteration in their ability to mentalize, which is associated with emotional dysregulation.[14] This concept is supported by the finding that in the ED group, body dissatisfaction was significantly related to non-visual BID, whereas in the control group, body dissatisfaction was related to visual BID. Furthermore, social bias may influence visual perception, and emotional bias may create a negative embodiment that generates non-visual BID.[14,31-33]

Consistent with this idea, several studies have indicated the prevalence of somatoform symptoms, emotion dysregulation, insecure attachment, and anxiety in adults who experienced interpersonal ALEs in childhood.[34,35] The ED population with interpersonal ALEs has been described as having insecure attachment in addition to body dissatisfaction and emotion dysregulation.[14,30] This may lead to challenges in identifying bodily sensations and distinguishing them from emotional states, as reported previously in patients with ED.[32,33] Our findings are consistent with this idea, as we found higher non-visual BID in patients with pre-13 ALEs. ALEs may lead to insecure attachment, which in turn is related to an unacknowledged emotional state affecting the body.[14,32] The lack of positive family experiences or emotions such as shame after bullying has been associated with a negative body image.[33] Family functioning based on control may influence how people experience their bodies.[32] The ED group reported less support from their parents or peers. Thus, we cannot exclude the possibility that BID is influenced by an insecure attachment derived from patients' family experiences.

At the intragroup level, pre-13 interpersonal ALEs identified patients with ED who show higher levels of perfectionism and significantly different levels of impulsivity. At the intergroup level, the ED group with interpersonal ALEs (regardless of age) had higher levels of perfectionism than the other two groups. Patients with depression and those without mental illness did not show significant differences with regard to body image and ALE category. Only patients with RMDD and interpersonal ALEs had lower levels of impulsivity ($P = 0.002$). This difference could be explained by the sample size, with the RMDD group reporting a lower proportion of interpersonal ALEs.

Finally, linear regression analysis revealed that pre-13 interpersonal ALEs predicted both visual and non-visual BID. The model was also suitable for predicting the levels of perfectionism and impulsivity in the ED group. BID is considered an independent factor for predicting low body weight in patients with anorexia nervosa or fasting in patients with bulimia nervosa.[36] This study suggests that BID is dependent on interpersonal ALEs during middle childhood. In general, interpersonal ALEs have been associated with the cognitive aspects of body image in patients with ED.[3,7,33] Possible mediators include post-traumatic stress disorder and binge eating.[5,15] Impulsivity and perfectionism are fundamental psychopathological dimensions of individuals with ED that can be used as prognostic factors for assessing disease progression.[36,37] The experience of interpersonal trauma during childhood may lead to starvation and body control as a means to manage negative emotions, likely due to unrecognized feelings such as shame.[33] If this mechanism fails or if the patient exhibits high impulsivity, binge eating may assist in the management of negative emotions.

The results of this study revealed that there may be a transfer of negative self-perceptions and emotions onto the body when evaluating body shape. Therefore, the evaluation of BID should be replaced with a cognitive–affective one. This change is considered necessary because individuals with ED do not experience a change in body perception; instead, they engage in a negative evaluation of their bodies.[32,33,38]

4.1. Strengths and clinical implications

The methodology used in this study could be easily replicated. It categorizes the perceptual component of body image into visual and non-visual images, making it easier to understand body image. The visual image could respond to a social bias influence, whereas the non-visual image could respond to an emotional bias. This may help promote specific interventions for patients with ED who have recognized ALEs to achieve a better outcome, such as the narrative approach or multiple access psychotherapy, where the therapist adapts the strategy according to the patient's report.[32] ED-trained clinicians performed the diagnostic evaluation using the DSM5 diagnostic guidelines.[22] The assessment included a control group of healthy participants and a study group of patients with affective pathology. This approach differs from conventional studies that typically focus only on the ED population. In addition, a dimensional perspective was used to comprehensively examine the common aspects across all treatable EDs.[39]

Our findings suggest that BID is not primarily based on social influence. Preventive interventions to reduce ED symptoms usually attempt to change/criticize the ideal image of a thin body. Therapeutic interventions should focus on identifying patients who have experienced interpersonal ALEs during childhood. This will facilitate the application of appropriate interventions based on reestablishing a secure attachment through a therapeutic relationship, thereby enabling patients to reconstruct a positive body image.[13,32]

4.2. Limitations

Regarding the study limitations, the small number of participants in each subgroup should be noted, particularly in the RMDD group. This is because the sample was collected during the COVID-19 pandemic. In addition, the ED sample was heterogeneous because it included patients with active disease and patients who had recovered, the trauma assessment was retrospective without the possibility of establishing cause–effect relationships, and the assessment was observational and non-experimental. Although retrospective trauma assessment may have recall bias, only a few false positives have been reported in other studies, and the questionnaires were administered anonymously, which may encourage honest responses.[40] Finally, due to the small sample size, a more robust statistical analysis could not be performed.

5. Conclusion

On closing our eyes, we experience internal or external sensory experiences that may be pleasant or unpleasant. Consequently, the negative perception of BID experienced by patients with ED is arguably attributed to unresolved emotions rather than social pressure.[30,32,33]

The results of this study suggest that impulsivity and perfectionism act as non-specific risk factors for ED development and that experiencing a pre-13 interpersonal ALE could be a risk factor for the development of BID, impulsivity, and perfectionism in adulthood. On the contrary, BID in patients with ED appears to have a non-visual component that is likely related to negative internal emotions resulting from childhood ALEs. In addition, individuals with childhood ALEs may seek to control their bodies due to the presence of unacknowledged emotions. Thus, to identify interpersonal risk situations, body image should not be considered as an independent factor but as a dimension that can be modified through early intervention strategies during childhood.

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Conflict of interest

The authors declare that they have no competing interests. The authors alone are responsible for the content and writing of the paper.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Miguel University Hospital (date of approval: September 2020). All participants provided written form consent.

Consent for publication

All participants gave written consent to publish the results of the study after concealing any identifying information

Availability of data

Data are available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

Journal of Clinical and Basic Psychosomatics

BRIEF REPORT

Examining the psychopathology of COVID-19 patients

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Abstract

Examining the psychopathology of patients who have contracted coronavirus disease 2019 remains important. The current study aims to investigate the relationship between depression, cognitive and executive functions, and their impact on quality of life. First, a comprehensive bibliographic review of relevant scientific articles and studies was carried out. Data were then collected using weighted and appropriate questionnaires. Analysis of variance and multiple regression analyses were conducted to examine the relationship between the independent variables (depression, cognitive and executive functions, and demographic factors) and the dependent variable (quality of life), to interpret and analyze the resulting associations. In contrast to depression, cognitive and executive functions did not appear to significantly influence patients' quality of life and well-being. Further scientific research is necessary to explore these factors and their potential effects more thoroughly.

Keywords: Depression; Cognitive-executive functions; Psychopathology; Life-quality

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1. Introduction

The coronavirus disease 2019 (COVID-19) is a highly infectious disease caused by the novel strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 pandemic has triggered one of the most severe public health crises in recent years globally. Both patients who remained at home and those hospitalized or admitted to intensive care units (ICUs) have experienced significant psychological effects, which continue to be a critical area of concern. Cognitive and psychopathological problems in patients with COVID-19 not only affect their physical, emotional, and spiritual health but also diminish their overall quality of life. Research suggests that complex psychopathological effects appear to persist in former COVID-19 patients even after discharge from the hospital. The coronavirus can induce psychopathological sequelae either indirectly through an immune response or directly by infecting the central nervous system (CNS). This can result in persistent neuropsychiatric symptoms, including

behavioral, emotional, and cognitive symptoms, which can occur at regular intervals after the initial infection.[1]

COVID-19 is transmitted through droplets from pre-symptomatic, asymptomatic, or symptomatic individuals carrying the virus. COVID-19, primarily a respiratory and vascular disease, is caused by SARS-CoV-2, which mainly targets the respiratory and vascular systems. Post-COVID-19 syndrome can manifest a wide range of complications, including respiratory, renal, cardiovascular, rheumatologic, dermatologic, neuropsychiatric, endocrinologic, urologic, and gastrointestinal issues. Depression, insecurity, stress, brain fog, declines in cognitive and executive functions, difficulty communicating with family and healthcare professionals, eating disorders, confinement, fear of death, uncertainty about recovery, stigmatization by others, and social isolation are significant factors contributing to the worsening psychopathology in these patients.[2,3]

Depression and anxiety are major contributors to the mental health burden, with long-term economic and social consequences being inevitable. Comorbid psychiatric illnesses have been shown to increase the vulnerability of individuals with depressive symptoms during the pandemic. Current literature suggests that the interaction between neurocircuitry and neuroinflammation plays a key role in the development of depression. Therefore, the neuroimmune response likely played a critical role in the development of depression during the pandemic. In addition to direct viral infection, an indirect immune response to the virus, such as cytokine production, may have contributed to the development of psychiatric symptoms. The association between gut microbiota and mood disorders remains under scrutiny. Numerous studies have linked depression and anxiety to an imbalance in gut flora, which leads to dysfunction in the gut-brain axis.[4,5]

Patients with severe COVID-19 have exhibited persistent deficits in executive function. Several initial symptoms were found to be predictors of long-term outcomes, indicating that systemic inflammation and neuroinflammation contribute to acute-phase COVID-19 symptoms. ICU stays have also been associated with reduced executive function, which highlights the importance of oxygen therapy. Hospitalized individuals are more likely to experience impairments in attention, executive function, category fluency, verbal memory, and information processing speed compared to non-hospitalized individuals. COVID-19 patients reporting cognitive symptoms showed deficits in attention, executive function, episodic memory, and visuospatial processing. Furthermore, COVID-19 survivors who required intubation displayed significantly slower mental processing speeds and less accurate verbal reasoning, with cognitive losses estimated to be equivalent to a reduction of approximately 10 IQ points.[6,7]

The impacts of COVID-19 on quality of life have not been evenly distributed among populations of Organization for Economic Cooperation and Development countries. Although older individuals and men were more likely to die from COVID-19, women, and younger individuals were more likely to experience severe declines in mental health and overall quality of life. Those with lower incomes, the unemployed, and racial and ethnic minorities experienced worse mental and physical health outcomes compared to the general population. Moreover, children from disadvantaged households were at greater risk.[8]

Wong *et al.*[9] highlighted a dramatic decrease of at least 33% in the quality of life of hospitalized COVID-19 patients, compared to the healthy population, 3 months after hospital discharge. Survivors of COVID-19 have an increased prevalence of comorbid conditions, which often lead to severe, progressively worsening clinical outcomes.[9,10]

Biopsychosocial factors may contribute to the high rate of psychiatric symptoms in COVID-19 survivors. Direct viral infection of the CNS, or indirect effects through the immune response, may lead to the development of psychopathology in these patients. Social factors such as quarantine, isolation, social distancing, and economic hardship further exacerbate the psychopathology of COVID-19 survivors. Additionally, the widespread use of the internet and smartphones has led to an overload of information, contributing to confusion, excessive worry, and unnecessary fear. ICU admission, in particular, has been noted to contribute to patients' psychopathology. During the outbreak, many individuals were also stigmatized due to their illness, further impacting their psychological well-being.[11,12]

Hall *et al.*[6] demonstrated that symptomatic SARS-CoV-2 infections were associated with psychiatric symptoms and cognitive dysfunction. The coronavirus can cause psychopathological sequelae either indirectly through immune responses or directly through CNS infection. Mechanisms contributing to COVID-19-related neuropathology include a combination of direct viral infection, neuroinflammation, severe systemic inflammation, neurodegeneration, and microvascular thrombosis.[13]

The purpose of the present research is to investigate the psychopathology of patients who have contracted COVID-19. The main objectives are to examine, measure, study, and analyze the impact of depression, cognitive and executive functions, and demographic factors on patients' quality of life. The research hypotheses are formulated as follows:

- H1: Depression has a significant impact on the quality of life of patients who contracted COVID-19.
- H2: Executive and cognitive functions of patients who contracted COVID-19 affect their quality of life
- H3: Demographic characteristics of research participants influence the quality of life of patients whose physical health has been affected by the COVID-19 pandemic.

2. Methods

2.1. Participants

Data for the current research were collected from a post-COVID-19 clinic at the Regular Outpatient Clinics of Sotiria Thoracic Diseases Hospital in Athens, Greece, where follow-up was provided to patients who had either been mildly ill or hospitalized with COVID-19. All participants (n = 49) in the present study were fully informed about the voluntary nature of the research. They were provided with a consent form, which emphasized their right to withdraw from the study at any time without consequence. The survey took place from July 1 to July 30, 2023. Participants were adult males and females, fluent in Greek (except for one Georgian woman), and all were at least 20 years old. The sample consisted of 20 male participants (40.82%) and 29 female participants (59.18%). Participants were divided into three age categories: 20 – 40 years (men: n = 4; women: n = 7), 41 – 60 years (men: n = 13; women: n = 19), and 61 years and older (men: n = 3; women: n = 3). Regarding employment status, 22 participants (37.9%) worked in the private sector, 8 (13.8%) in the public sector, 7 (12.1%) were self-employed, 7 (12.1%) were unemployed, 2 (3.4%) were retired, and 3 (5.2%) were students (Table 1).

Table 1. Employment distribution of participants

Employment type	Measurement	%
Private sector	22	37.9
Public Sector	8	13.8
Self-employed	7	12.1
Unemployed	7	12.1
Pensioner	2	3.4
Student	3	5.2

2.2. Study design and settings

This quantitative research examined categorical, nominal, and numerical variables in the study of participants. We used one-way analysis of variance (ANOVA) to critically examine the relationship between independent variables and the dependent variable, to interpret and analyze correlations in detail. The independent variables included demographics, depression, and cognitive and executive functions, while the dependent variable was quality of life. Thus, cognitive and executive functions, demographics, and depression were the predictor variables, while quality of life served as the criterion variable.

2.3. Questionnaires

Psychometric tests and closed-ended questions were used to test the hypotheses, allowing us to obtain both quantitative and qualitative information, leading to more comprehensive results. Demographic characteristics collected included gender, age, marital status, educational level, employment status, and region of residence. The questionnaires used in this study were: (i) Patient Health Questionnaire (PHQ-9), (ii) Health Survey Questionnaire Short Form (HSQ SF-36), (iii) Montreal Cognitive Assessment (MoCA), and one demographic questionnaire.

2.4. Statistical analysis

The research objectives were examined through one-way ANOVA and two multiple regression analyses to determine and interpret correlations accurately. Statistical reliability was established with a robust internal consistency, demonstrated by a Cronbach's alpha coefficient of 0.803. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS Statistical Package for Windows (version 28.0).[14]

3. Results

3.1. First multiple regression analysis

The first multiple regression analysis examined the relationship between quality of life (HSQ SF-36) as the dependent variable and depression (PHQ-9) and cognitive and executive functions (MoCA) as the independent variables. Before interpreting the results, the assumptions underlying the regression model were assessed.

In the Pearson correlation coefficient analysis, multicollinearity was assessed to ensure that the correlation coefficients between the independent variables were not >0.8. The correlation between MoCA and PHQ-9 was −0.077, which falls within acceptable limits. In addition, the correlation between MoCA and SF-36 was marginally significant, with a P = 0.057, close to the 0.05 threshold. In contrast, the correlation between PHQ-9 and HSQ SF-36 was stronger, with a significant P = 0.001 (Table 2).

3.2. Second multiple regression analysis

The second multiple regression analysis explored the relationship between quality of life (HSQ SF-36) (dependent variable) and demographics (independent variable). As

with the first analysis, the underlying assumptions were examined before proceeding with interpretation.

None of the independent variables showed multicollinearity (correlation >0.8). The results suggest that both gender and employment status had a statistically significant impact on quality of life, with gender showing a $P = 0.046$ and employment status marginally significant at 0.052 (Table 3).

3.3. One-way ANOVA

A one-way ANOVA was applied between the HSQ SF-36 and demographic variables, as the data could be grouped into at least three categories, with each group containing at least three measurements. One-way ANOVA was used to investigate differences in quality of life (HSQ SF-36) across age groups, assuming equal variances. The results showed no statistically significant difference in quality of life between age groups, with a $P > 0.05$, meaning we cannot reject the null hypothesis. However, it is worth noting that individuals aged 20 – 40 reported better quality of life compared to those aged 41 – 60 (Table 4).

Similarly, when analyzing the relationship between SF-36 and employment status, the ANOVA indicated no statistically significant difference in quality of life between employment categories. However, retirees reported higher quality of life, while individuals employed in the private sector reported lower quality of life (Table 5).

Table 2. Pearson correlation coefficients of the first multiple regression analysis

	SF_36	Moca	PHQ
Pearson correlation coefficient			
HSQ SF-36	1.000	0.228	−0.435
MoCA	0.228	1.000	−0.077
PHQ	−0.435	−0.077	1.000
Statistical significance			
HSQ SF-36	0.000	0.057	0.001
MoCA	0.057	0.000	0.299
PHQ	0.001	0.299	0.000

Abbreviations: MoCA: Montreal Cognitive Assessment; PHQ-9: Patient Health Questionnaire; HSQ SF-36: Health Survey Questionnaire Short Form.

4. Discussion

The primary objective of the present study was to evaluate the psychopathology of patients who had contracted COVID-19 and were monitored by a post-COVID-19 clinic in the Regular Outpatient Clinics of Sotiria Thoracic Diseases Hospital in Athens, Greece. Specifically, this study aimed to determine whether depression, cognitive and executive functions, and demographic characteristics influenced the quality of life of these patients, as assessed through the PHQ-9, HSQ SF-36, and MoCA questionnaires. The participants included Greek adults, both men and women, with the exception of one Georgian woman, all aged >20 years. Notably, there were fewer male participants ($n = 20$) compared to females ($n = 29$) in the samples.[15]

The first multiple regression analysis sought to predict the quality of life (HSQ SF-36) in patients who had recovered from COVID-19, based on their cognitive and executive functions (MoCA) and depression levels (PHQ-9). The findings demonstrated that depression significantly negatively affected the quality of life in COVID-19 patients. This finding aligns with existing research showing that quality of life is significantly influenced by

Table 3. Pearson correlation coefficients of the second multiple regression analysis

	SF_36	Gender	Age	Education	Employment
Pearson correlation coefficient					
HSQ SF-36	1.000	−0.244	−0.105	−0.118	0.235
Gender	−0.244	1.000	−0.074	0.024	−0.324
Age	−0.105	−0.074	1.000	0.115	−0.120
Education	−0.118	0.024	0.115	1.000	−0.167
Employment	0.235	−0.324	−0.120	−0.167	1.000
Statistical significance					
HSQ SF-36	0.000	0.046	0.237	0.210	0.052
Gender	0.046	0.000	0.305	0.436	0.012
Age	0.237	0.305	0.000	0.216	0.206
Education	0.210	0.436	0.216	0.000	0.126
Employment	0.052	0.012	0.206	0.126	0.000

Abbreviation: HSQ SF-36: Health Survey Questionnaire Short Form.

Table 4. One-way ANOVA: HSQ SF-36 and age

	Sum squares	*df*	Means of squares	*F*	Statistical significance
Among groups	510.522	2	255.261	0.789	0.460
Inside groups	14,884.365	46	323.573		
Total	15,394.888	48			

Abbreviation: HSQ SF-36: Health Survey Questionnaire Short Form.

Table 5. One-way ANOVA: HSQ SF-36 and employment

	Sum squares	*df*	Means of squares	*F*	Statistical significance
Among groups	1,335.592	5	267.118	0.817	0.544
Inside groups	14,059.296	43	326.960		
Total	15,394.888	48			

Abbreviation: HSQ SF-36: Health Survey Questionnaire Short Form.

physical and mental health, personal beliefs, and social relationships in individuals affected by the COVID-19 pandemic.[16] The deterioration of mental health, specifically the exacerbation of depression in people suffering from COVID-19, was closely associated with a decline in quality of life, as demonstrated by the statistical analysis. In contrast, the use of the MoCA questionnaire did not reveal that cognitive and executive functions exerted a significant negative influence on the quality of life of individuals recovering from COVID-19. Although previous studies have confirmed that cognitive impairments can affect the quality of life in patients affected by COVID-19, this specific study found no such association. The cognitive and executive function evaluations in this sample did not have a measurable negative impact on quality of life.[7,17]

The second multiple regression analysis explored whether demographic characteristics – such as age, gender, employment status, and education – were related to the quality of life in patients who had been infected with SARS-CoV-2. The results indicated that none of these demographic factors had a significant impact on quality of life, as the *P*-values for gender (0.191), education (0.594), employment status (0.352), and age (0.526) were all >0.05. Consequently, demographics did not negatively influence the quality of life in this study, despite similar research showing a significant effect.[18] However, the data did suggest that quality of life was better for individuals aged 20 – 40 years and worse for those aged 41 – 60 years. The decline in quality of life in the 41 – 60 age group was likely due to the impact of work-related issues, unemployment, limitations in daily activities, compliance with preventive and social distancing measures, isolation, and loneliness.[19]

Furthermore, retirees reported a better quality of life compared to individuals employed in the private sector.[20] This may be attributed to the unique living conditions created during the COVID-19 pandemic. The private sector, in particular, faced significant challenges in many countries, despite government interventions aimed at mitigating economic challenges.[21,22] In the ANOVA results related to the multiple regression analysis, the significance (*P*-value) was <0.05, indicating that some correlations were statistically significant. Depression had a significant impact on the daily lives of the participants in this study. However, cognitive and executive functions did not affect the quality of life in this specific cohort. One possible explanation for this finding could be the relatively small sample size (n = 49. It is likely that with a larger sample, the results might have been different. Similarly, the lack of significant impact from demographic factors on quality of life could also be due to the limited sample size.[23]

5. Conclusion

The current study aims to examine the psychopathology of patients who contracted COVID-19, with a particular focus on the role and effects of depression and cognitive and executive functions, as assessed by the PHQ-9 and MoCA questionnaires, in relation to their quality of life. The findings support the need for further exploration into the impact of depression on patients' quality of life and well-being, and the development of cost-effective approaches for managing these effects. Future research should prioritize the early diagnosis of depression, as it is often difficult to detect without close observation by family members or healthcare providers. Ongoing clinical research is necessary to identify the underlying mechanisms of depression and to develop strategies to mitigate its effects, thereby preserving and enhancing quality of life.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

The study was approval by Sotiria Chest Diseases General Hospital of Athens, Athens, Greece (approval no.: 15324/08-06-2023). All participants gave consent to participate in this study.

Consent for publication

The participants gave consent to publish their data in this study.

Availability of data

Data used in this work are available from the corresponding author on reasonable request.

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ACCSCIENCE PUBLISHING

Journal of Clinical and Basic Psychosomatics

CASE REPORT

Recurrent catatonia in a patient with bipolar disorder and polycythemia: A case report

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Abstract

We report the diagnostic and management challenges encountered in a case of a 57-year-old male patient with bipolar I disorder and comorbid polycythemia secondary to obstructive sleep apnea, who was treated in our inpatient psychiatric unit for suicidal ideation and recurrent catatonia. He was found to have catatonia with a Bush–Francis Catatonia Rating Scale score of 18. He subsequently exhibited a positive response to the lorazepam challenge test. Before discharge, his daily lorazepam dose was titrated to 6 mg, which led to resolution of catatonic symptoms, and was tapered to discontinuation. During the second hospitalization, the patient's catatonia returned, but due to lorazepam-induced bradycardia, he refrained from taking more than 1 mg of the medication. Divalproex sodium and memantine were initiated as off-label catatonic treatment plus lurasidone for bipolar depression. The patient was also found to have a positive antinuclear antibody titer (1:160). The hemato-immunological abnormalities present in our patient complicated his catatonic condition, underscoring the need to explore medical and neuropsychiatric catatonic factors for accurate diagnosis of this neuropsychiatric syndrome.

Keywords: Catatonia; Bipolar disorder; Polycythemia; Neuropsychiatry; Antinuclear antibody

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1. Introduction

Catatonia is a neuropsychiatric condition characterized by various motor and behavioral abnormalities, such as immobility, reduced verbal communication, unusual actions, and impaired volition.[1,2] It is crucial to differentiate catatonia from other psychiatric disorders, including different types of mood disorders, psychotic conditions with significant negative symptoms, and selective mutism.[3,4] Catatonia presents in different forms, including stuporous, excited, malignant, and neuroleptic-induced types.[3,5] Originally classified under schizophrenia, catatonia is now recognized in association with various medical and psychiatric conditions. Initially, in the 1800s, Kahlbaum described catatonia as a psychomotor syndrome associated with different underlying disorders.[6] Shortly thereafter, Kraepelin instead defined catatonia as a manifestation of dementia praecox (an obsolete term for schizophrenia) rather than a separate illness.[7] Approximately one century later, this erroneous classification was rectified.[7] Today,

approximately 2.7 – 17% of acute psychiatric patients demonstrate catatonia, a setting-dependent statistic.[8]

2. Case presentation

A 57-year-old Caucasian male with a history of bipolar I disorder (BD1) and polycythemia was evaluated by our psychiatric team for depressive symptoms and suicidal thoughts after being admitted to hospital due to loss of consciousness. Initial neurological assessments, including magnetic resonance imaging of the brain and electrocardiogram for syncope and stroke, were normal. Laboratory results showed elevated hemoglobin (18.9 g/dL) and hematocrit (57%), with decreased erythropoietin levels (2.5 mIU/mL). He tested negative for a *JAK2* V617F mutation. Arterial blood gas analysis showed a partial pressure of carbon dioxide (pCO_2) of 35.0, a partial pressure of oxygen (pO_2) of 79.7, and pH of 7.432. Following therapeutic phlebotomy, he was transferred to the psychiatric unit and started on lurasidone 40 mg daily for bipolar depression. The patient had stopped receiving psychiatric treatment for 30 years and had recently experienced social and economic stressors, including a career change and moving in with family. Notably, the patient had never undergone any preventative psychotherapy or counseling.

During his psychiatric stay, he was diagnosed with catatonia, with a Bush–Francis Catatonia Rating Scale score of 18. His symptoms included immobility, mutism, echolalia, as well as abnormal willpower and behavior. He exhibited a positive response to the lorazepam challenge test. A daily 6 mg lorazepam led to the significant resolution of the catatonic symptoms, and lorazepam was tapered before discharge after 2.5 weeks of hospitalization.

Two days later, the patient returned with worsening bipolar depression. We increased lurasidone to 60 mg, but catatonia reappeared 1 week thereafter. Lorazepam was reintroduced into the treatment regimen, but due to bradycardia, he could not tolerate doses of lorazepam above 1 mg. No rigidity, fever, or leukocytosis was observed in the patient, and normal levels of ferritin and creatinine phosphokinase were recorded. Due to logistic and administrative obstacles, electroconvulsive therapy (ECT) was not performed due to inability; otherwise, he may have been a candidate. Divalproex sodium and memantine were initiated as alternative treatments.

The second hospital admission lasted 3 weeks, during which the patient's condition stabilized following the administration of tolerable doses of lorazepam. During the second hospital stay, other potential medical causes were explored given the recurrence of catatonic signs after a prolonged hospital stay and stabilization. In addition, the patient initially presented with a syncopal-type event and had been psychiatrically stable and functioning in the community without medication for years before this presentation. Further investigation revealed a positive antinuclear antibody (ANA) titer of 1:160, which warranted a rheumatology consultation. No additional systemic issues were identified, and the patient's hemoglobin level and hematocrit remained stable. The patient showed signs of gradual improvement and was discharged with plans for follow-up care. A timeline of the patient's overall clinical course is shown in Figure 1.

3. Discussion

Catatonia can arise from various medical conditions, and benzodiazepines are used as the primary treatment approach for this syndrome.[9] The polycythemia described in this case may be related to obstructive sleep apnea and a positive ANA titer, but its implications for the development of catatonia in this patient remain unclear. This patient did not display delirium, which often coexists with catatonia,[9] and his laboratory results were otherwise negative for metabolic derangements.

Alternative treatments for catatonia include memantine, anti-epileptic drugs, and amantadine.[9] Memantine and amantadine are used primarily in schizophrenia spectrum disorders, while anti-epileptics such as carbamazepine and valproic acid may be beneficial in mood disorder cases.[10] It has been reported that patients with catatonia and underlying mood disorders positively responded to carbamazepine in a daily dose of 100 – 1,000 mg, without taking benzodiazepines concurrently.[10] Valproic acid, in a daily dose of 600 – 4,000 mg, has also been used as an effective monotherapy in patients with excited catatonia complicated by schizophrenia spectrum illnesses.[10] Daily topiramate at a dose of 200 mg, together with benzodiazepine as an adjunct, has also been used to treat catatonia in four patients, as described in one case series.[10,11] The application of levetiracetam[12] and zonisamide[13] for the treatment of catatonia has also been conducted and described in the literature.[10]

ECT is a viable option for refractory or severe cases involving malignant features, malnourishment, and severe depression, but it was not accessible in this instance.[9] We believe that our patient would have been a potentially suitable candidate for ECT if it was available in our facility.

Regarding further pharmacological treatments, antipsychotics are generally avoided in patients with catatonia due to the heightened risk of neuroleptic malignant syndrome or worsening catatonia. Despite this, if needed, a second-generation antipsychotic should be used. Clozapine is the recommended antipsychotic to be

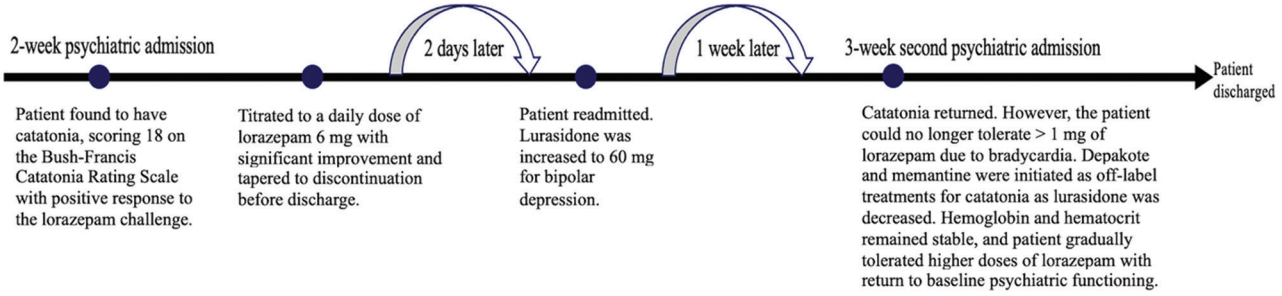

Figure 1. Timeline of inpatient clinical course

used in catatonia owing to the highest levels of efficiency and efficacy demonstrated in previous research.[14-17] Coupling of the increased dopamine release in the striatum through 5-HT_{1A} receptor stimulation and low D2 receptor occupancy may produce a net effect on overall dopamine neurotransmission, which is potentially responsible for the anticatatonic effects of clozapine.[14] Despite advantages in treating catatonia, the use of clozapine requires a baseline evaluation, slow titration, and close monitoring.[14] Lurasidone and cariprazine may be useful for mood disorder-related catatonia,[18] which justifies its use in our patient.

Hypoxia, induced by obstructive sleep apnea, may exacerbate catatonia. One case in the literature involved a 20-year-old male patient with central hypoventilation presenting with resistant catatonia.[19] He had a history of hypoventilation at birth and was supported by 24-h mechanical ventilation for the first 5 years of his life.[19] During hospitalization, laboratory result indexes, including complete blood count, of this patient were normal, as opposed to polycythemia accompanied by an increased hemoglobin and hematocrit identified in our patient. A fluorodeoxyglucose positron emission tomography scan during hospitalization showed a hypometabolic distribution, which is characteristically consistent with hypoperfusion.[19] Increased mechanical ventilation successfully resolved his psychiatric symptoms.[19] Despite the rarity, hypoxia from (central or obstructive) apnea is possibly linked to catatonic symptoms in our patient. This association may imply that increased PCO_2 and decreased PO_2 (the latter of which was seen in our patient) may have pathophysiological implications for catatonic symptoms. Phlebotomy can increase oxygenation and thus serve as a treatment for polycythemia, which holds the potential, in addition to lorazepam, to resolve catatonia symptoms.

In patients with positive ANA value of 1:160, autoimmune causes and/or comorbidities should be explored. Immune dysregulation is the mechanistic driver for a variety of neuropsychiatric disorders, such as narcolepsy, dementia, depression, and psychosis.[3] Autoimmune disorders such as anti-N-methyl-D-aspartate (NMDA) receptor encephalitis and hyponatremia with subsequent extrapontine myelinosis secondary to Addison's disease have been cited as triggers of catatonia.[3] In some cases, autoimmune disorders appeared to be the proximate cause of catatonia (NMDA receptor encephalitis); in other cases, the autoimmune disorder was a more distal cause (Addison's disease).[3]

The major limitations of the current case were patient's loss to follow-up and non-attendance at scheduled mental health, rheumatology, and hematology outpatient visits. In addition, there is limited literature on catatonia with comorbid polycythemia and hematological-immunological disorders. More case reports and studies are needed to enhance our understanding of these associations.

4. Conclusion

Managing recurrent catatonia in a patient with BD1, polycythemia, and a positive ANA titer presents complex challenges. The presence of hemato-immunological abnormalities adds a layer of complexity to the detection and management of catatonic symptoms, underscoring the need for comprehensive exploration of the neuropsychiatric and systemic factors of catatonia to help strengthen our understanding of the neuropsychiatric condition.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Investigation: All authors

Writing–original draft: Tiffany Eatz
Writing–review & editing: All authors

Ethics approval and consent to participate

Verbal consent of the patient was obtained for participating in this case study.

Consent for publication

Verbal consent of the patient was obtained for releasing his data in this paper. No photographs or images of the subject were included for publication. All data of the subject were deidentified to safeguard his privacy and anonymity.

Availability of data

Data are available from the corresponding author upon reasonable request.

Further disclosure

The current case has been presented at The Academy of Consultation-Liaison Psychiatry annual meeting on November 10, 2022.

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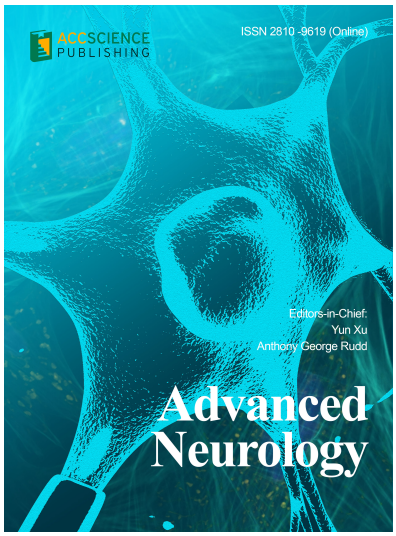

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