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Special Issue Reprint

Future Challenges for the Diagnosis and Management of Affective Disorders

From Preclinical Evidence to Clinical Trials

Edited by
Antonio Ventriglio, Mario Luciano and Andrea Fiorillo

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Guest Editors

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About the Editors

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Preface

This Reprint arises from the pressing need to deepen and broaden our understanding of affective disorders, which remain among the most prevalent, disabling, and costly conditions in psychiatry. Despite decades of research, they continue to cause profound suffering, premature mortality, and a large economic burden, while treatment outcomes remain suboptimal. The aim of this Reprint is to explore clinical, biological, and social correlates of major depressive disorder and bipolar disorder through multiple complementary lenses, spanning pharmacological innovations, neurobiological biomarkers, environmental determinants, psychosocial processes, comorbid medical conditions, and therapeutic strategies. It also seeks to provide a coherent synthesis of contemporary research and to make it accessible as a unified resource for clinicians, researchers, and policymakers, reflecting the multifactorial and interdisciplinary nature of these disorders. By collecting contributions from different methodological and conceptual domains, the Editors and contributors aim to accelerate translational dialog and highlight directions for future progress. This Reprint is thus aimed at psychiatrists, psychologists, neuroscientists, social scientists, and health professionals in related fields, as well as graduate students and policymakers engaged in the complexities of mental health systems.

A major theme emerging here is the field's shift beyond monoaminergic hypotheses toward multidimensional frameworks. Among the most innovative contributions is the meta-analysis by Salvetti et al., which provides strong evidence for psilocybin's efficacy in major depressive disorder and treatment-resistant depression. Both single- and two-dose regimens were associated with significant symptom reductions, with the two-dose protocol showing greater durability. These findings align with a growing body of literature indicating that psilocybin produces rapid and, in some cases, sustained antidepressant effects. Recent meta-analyses show moderate effect sizes compared with placebo, while randomized clinical trials in end-of-life populations and postpartum depression highlight the transdiagnostic potential of psychedelics when combined with structured psychotherapeutic frameworks. Reports of durable remission extending up to five years in subsets of patients further underscore their promise, though ethical, regulatory, and methodological challenges remain. Including such findings in this Reprint exemplifies its purpose of presenting emerging evidence in a way that fosters both scientific rigor and clinical innovation.

Another central focus is the role of neurotrophic biomarkers, particularly brain-derived neurotrophic factor (BDNF), in mood disorders. De Felice et al. critically review evidence suggesting that BDNF levels fluctuate across illness phases in bipolar disorder and may serve as a state marker, while the Val66Met polymorphism has been inconsistently linked to risk and course. Complementary systematic reviews suggest that BDNF levels, alongside other growth factors such as PDGF-AA and PDGF-BB, may help to distinguish unipolar from bipolar depression with high sensitivity and specificity. Epigenetic studies indicate that hypermethylation of BDNF promoters correlates with reduced expression and greater symptom severity, possibly modulated by early life adversity and pharmacological treatment. The neurotrophic hypothesis of depression, which posits that deficient neurogenesis and synaptic plasticity contribute to mood disorders, continues to generate translational opportunities. By including such diverse contributions, this Reprint emphasizes that biomarkers are not yet ready for routine clinical use but remain a key frontier for precision psychiatry.

Environmental exposure and the broader concept of the exposome are also addressed. Menculini et al. examine light pollution as a pervasive urban stressor that disrupts circadian rhythms, suppresses melatonin, and contributes to affective dysregulation, highlighting chronobiological disruption in

the etiology of mood disorders. Rejek et al. assess cumulative exposomic risk factors—including childhood trauma, urbanicity, cannabis use, and obstetric complications—demonstrating associations with multiple domains of psychopathology across diagnostic boundaries. Together, these works align with dimensional models of psychopathology and underscore the need to investigate environmental load as a determinant of both the incidence and trajectory of affective disorders.

Relational and psychosocial processes emerge as additional key dimensions. Altamura et al. show that insecure attachment increases the risk of perinatal depression through maladaptive coping, pointing to mechanisms amenable to preventive interventions. This aligns with evidence that maternal mental health during pregnancy and postpartum is shaped by relational patterns and coping resources, with implications for both the mother and child. Cipolla et al. investigate psoriasis patients, demonstrating that comorbid pain, insomnia, arthritis, and female sex are strong predictors of anxiety, depression, and impaired quality of life. These findings highlight the bidirectional interplay between chronic somatic illness and affective states and the importance of integrated multidisciplinary care.

Longitudinal and phenotypic factors are also considered. Janiri et al. report that polarity at onset in bipolar disorder—whether first presenting with mania or depression—predicts the long-term course, temperament, and treatment response. This adds to the growing body of literature on clinical staging and stratification, which seeks to move beyond static diagnoses toward dynamic trajectories. Finally, a randomized controlled trial protocol for psychoeducational family interventions in major depression illustrates how psychosocial interventions can be systematically tested for their impact on symptoms, relapse prevention, functioning, and quality of life. Although family-based interventions have long been recognized as beneficial, rigorous trials remain limited, and this contribution outlines a methodology to address this gap.

The motivations for assembling this Reprint are multifaceted. First, the global burden of affective disorders remains staggering: the World Health Organization ranks depression as a leading cause of disability worldwide and bipolar disorder among the top causes of years lived with disability. Second, current treatments are often inadequate, with many patients experiencing incomplete remission, frequent relapses, or intolerable side effects. Third, the literature is fragmented, with pharmacological, biological, environmental, and psychosocial findings often published in separate silos. By bringing them together, the Editors aim to foster integrative perspectives and stimulate dialog between basic science, clinical research, and health services. Fourth, there is a pressing need for translational pathways that bridge cutting-edge findings with real-world implementation—from psychedelic-assisted therapies to biomarker-informed stratification and family-based interventions. Finally, this Reprint reflects a commitment to interdisciplinarity, recognizing that progress in affective disorders requires contributions from neuroscience, psychiatry, psychology, epidemiology, and social science.

The intended audience is broad yet defined. It includes clinicians needing up-to-date evidence to guide practice, researchers seeking to identify emerging questions and gaps, policymakers tasked with resource allocation and system design, and graduate students or trainees who require a comprehensive introduction to this evolving field. By presenting curated contributions spanning pharmacological, biological, environmental, and psychosocial domains, this Reprint serves both as a reference and as a stimulus for future research agendas.

At the same time, this Preface must acknowledge the limitations and challenges in this field. Psychedelic research remains in its early stages, with methodological heterogeneity, expectancy effects, and regulatory barriers. Biomarker studies are inconsistent, often confounded by medication, comorbidity, or sample heterogeneity. Environmental and exposomic studies face challenges of

measurement and causal inference. Psychosocial interventions, though promising, require robust trials and clear implementation frameworks. Yet, by juxtaposing these domains within one Reprint, we can recognize both the progress made in this field and its frontiers.

In conclusion, this Reprint reflects the state of the art in affective disorder research, integrating biological, environmental, and psychosocial perspectives, and addressing both established knowledge and frontier challenges. Its scope is deliberately broad, with its aim being to provide synthesis and orientation, its purpose being to stimulate translational progress, its motivation being rooted in the enduring burden and treatment gaps of depression and bipolar disorder, and its audience being the community of professionals, researchers, and students dedicated to improving the lives of individuals affected by these conditions.

Antonio Ventriglio, Mario Luciano, and Andrea Fiorillo

Guest Editors

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Editorial

Future Challenges for the Diagnosis and Management of Affective Disorders: From Preclinical Evidence to Clinical Trials

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Affective Disorders (ADs) include a broad spectrum of clinical conditions, ranging from dysthymia and Major Depressive Disorder (MDD) to various forms of bipolar disorders (BD) and affective psychoses. The burden of these disorders is substantial at both the individual and familial levels, with significant implications for healthcare systems worldwide. ADs are not only associated with marked emotional distress and functional impairments but also with a substantial disruption in patients' familial and social relationships [1,2]. Their high global burden reflects their prevalence, recurrent course, and the elevated mortality risk, with nearly 15% of individuals with MDD or BD dying by suicide [3].

According to the World Health Organization (WHO), MDD affects over 280 million people and is recognized as a leading cause of disability worldwide. BD, on the other hand, affects around 40 million individuals globally, with a severe impact on personal and professional functioning [4]. Beyond the individual burden, the economic impact of ADs is noteworthy, with considerable direct costs associated with treatment, hospitalizations, and long-term care. However, the indirect costs—including lost productivity, absenteeism, and disability claims—further exacerbate the financial strain on global economies. Research indicates that MDD alone costs the global economy over $1 trillion per year in lost productivity. Similarly, in the United States, the total economic burden of BD is estimated to exceed $45 billion annually, underscoring the far-reaching financial impact of these conditions beyond healthcare expenditures [5]. The economic burden is further compounded by the fact that many individuals remain undiagnosed or untreated, perpetuating a cycle of worsening symptoms and increased healthcare utilization [5].

The internalized stigma experienced by individuals with ADs is a major barrier to care, often leading to delays in seeking treatment due to fear of discrimination, exacerbation of symptoms, and reduced chances of full recovery [6]. In many low- and middle-income countries, mental health services remain underfunded and inaccessible to large segments of the population, further impeding effective management. Addressing stigma and enhancing mental health literacy through public health campaigns and educational initiatives are essential steps toward reducing the burden of ADs and minimizing the duration of untreated illness [7]. In this regard, delayed diagnoses and treatments are among the most critical factors contributing to poor outcomes in ADs. For many patients, it might take years before receiving an accurate diagnosis, leading to increased recurrence rates, greater severity of episodes, higher functional impairment, and higher risk of developing psychiatric and medical comorbidities [8]. For instance, individuals with bipolar disorder who were initially misdiagnosed as affected by MDD often receive antidepressant treatment, which

may trigger manic or hypomanic episodes. Similarly, untreated depression can evolve into a chronic and treatment-resistant condition, significantly reducing the likelihood for clinical and personal recovery [7,8]. Prolonged delays in diagnosis are also associated with an elevated risk of suicide, as untreated individuals may experience worsening despair and hopelessness over time [6]. Improving screening, enhancing access to mental healthcare, and providing intervention as early as possible are crucial in order to mitigate the long-term impact of these disorders.

Another key factor shaping the clinical course of ADs is the high prevalence of psychiatric and medical comorbidities. In fact, individuals with mood disorders have an increased risk of developing cardiovascular disease, metabolic syndrome, immune-inflammatory dysregulation, and neurodegenerative disorders, among other conditions. Moreover, psychiatric comorbidities such as anxiety disorders, substance use disorders, and psychotic symptoms are frequent, leading to misdiagnoses and suboptimal treatment strategies. The bidirectional relationship between psychiatric and medical conditions suggests a shared pathophysiological basis, reinforcing the necessity for a holistic and integrative approach to diagnosis and treatment [9]. Current diagnostic criteria primarily rely on clinical observations and self-reported signs or symptoms, which are inherently subjective and susceptible to variability. In particular, the substantial symptomatic overlap between depression and bipolar disorder—especially during depressive episodes—frequently results in misdiagnosis and inappropriate treatment selection. A notable challenge is the frequent misclassification of bipolar depression as unipolar depression, leading to inappropriate antidepressant prescriptions that may exacerbate mood instability and increase the risk of manic episodes [10].

The Research Domain Criteria (RDoC) initiative, launched by the National Institute of Mental Health, represents a promising effort to move beyond traditional diagnostic categories by integrating behavioral, cognitive, and neurobiological markers [11]. Advances in neuroscience and biomarker research have provided compelling evidence for improving the diagnostic accuracy of ADs [12]. Emerging findings indicate that mood disorders are characterized by significant alterations in inflammatory markers, oxidative stress levels, and metabolic dysregulation [13]. Additionally, neuroimaging and genetic studies have identified distinct neurobiological and genetic features, reinforcing the potential of biomarker-based approaches in clinical practice. The increasing use of machine-learning algorithms and computational psychiatry models allows for the integration of large-scale datasets encompassing clinical, neurobiological, and genetic information, facilitating improved diagnostic precision and personalized treatment strategies [14]. Furthermore, precision medicine approaches incorporating biosignatures hold promise for optimizing therapeutic outcomes, reducing trial-and-error prescribing, and enhancing long-term prognosis.

Beyond biomarkers, novel therapeutic approaches are emerging in the treatment of ADs. Neuromodulation techniques, including Transcranial Magnetic Stimulation (TMS) and Deep Brain Stimulation (DBS), have demonstrated efficacy in treatment-resistant affective disorders. Additionally, psychedelic-assisted therapy—particularly with compounds such as psilocybin and ketamine—is gaining increasing empirical support for its rapid-acting antidepressant effects. Meanwhile, evidence-based psychosocial interventions, including cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and psychoeducational programs, have demonstrated significant efficacy in reducing relapse rates and improving overall functioning [15].

This Special Issue, "Future Challenges for the Diagnosis and Management of Affective Disorders: From Preclinical Evidence to Clinical Trials", seeks to bridge the gap between preclinical research and clinical applications. By exploring novel diagnostic tools,

biomarker-based approaches, and innovative therapeutic strategies, this collection provides up-to-date insights into the complexities of ADs and potential pathways for improving their management. Contributions in this issue address the multifaceted nature of these disorders from interdisciplinary perspectives. In this context, authors illustrate how the integration of biological, psychological, and social factors remains fundamental to understanding the heterogeneity of ADs and optimizing their management.

Conflicts of Interest: The authors declare no conflicts of interest in the preparation of this editorial.

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Article

Factors Associated with Anxiety, Depression, and Quality of Life in Patients with Psoriasis: A Cross-Sectional Study

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Abstract: Background: Psoriasis is a chronic skin disorder affecting 2–3% of the global population, and is associated with several comorbidities, including psychiatric disorders. This study aimed to identify factors influencing anxiety, depression, and quality of life (QoL) in patients with psoriasis. Methods: This observational study included 112 patients diagnosed with psoriasis. Dermatological and psychiatric assessments were conducted using Psodisk, the Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Symptom Checklist-90-Revised (SCL-90-R), and 36-Item Short Form Health Survey (SF-36). Descriptive statistics, correlation analyses, and multivariate regression models were employed. Results: The sample was predominantly middle-aged males (mean age 48.91 years). Females ($p < 0.001$), patients with arthritis ($p < 0.05$), and those with a sedentary lifestyle ($p < 0.05$) showed higher anxiety and depression scores. Psodisk subscales significantly correlated with psychiatric symptoms and QoL measures ($p < 0.001$). Pain (B: 0.63, $p < 0.05$; B: −2.03, $p < 0.01$) and sleep disturbances (B: 0.68, $p < 0.01$; B: 0.60, $p < 0.01$; B: −1.46, $p < 0.01$; B: −1.57, $p < 0.05$; B: 3.91, $p < 0.05$) emerged as major predictors of poor mental health and reduced QoL. Conclusions. The study underscores the complex relationship between psoriasis, psychiatric comorbidities, and QoL. Key factors exacerbating anxiety and depression include female gender, arthritis, and sedentary lifestyle. Comprehensive management of psoriasis should address both dermatological and psychological aspects, with a focus on pain relief and improving sleep quality to enhance overall patient well-being.

Keywords: psoriasis; quality of life; anxiety; depression; affective disorders; mental health; psychiatric comorbidities

1. Introduction

Psoriasis is a chronic, immune-mediated skin disorder characterized by the presence of erythematous and scaly plaques, affecting about 2–3% of the global population [1]. The etiopathogenesis of psoriasis is complex and still partially unknown: it seems to involve a complex interplay between genetic predisposition and environmental factors, and those risk factors may act together as triggers, leading to an aberrant immune response [2–5]. This results in the hyperproliferation of keratinocytes and chronic inflammation [6].

Psoriasis can be associated with systemic comorbidities, including cardiovascular diseases, hypertension, metabolic syndrome, obstructive sleep apnea, other inflammatory diseases [7,8], and psychiatric disorders [9–12]. A systematic review and meta-analysis

reported that the prevalence of depression in patients with psoriasis ranges from 20% to 30%, while the prevalence of anxiety ranges from 15% to 20% [13]. Furthermore, higher rates of self-harm and suicidality have been found in patients with psoriasis when compared with the general population or individuals with different dermatological conditions [14–16], as well as sleep disorders and sexual dysfunctions [17–20].

The psychological burden of psoriasis is substantial and multifaceted. Patients frequently experience stigma, social isolation, and reduced self-esteem due to the visible and often disfiguring nature of the disease [21,22]. These psychosocial stressors can precipitate or exacerbate psychiatric conditions such as anxiety and depression [23–25]. The psychological and psychiatric morbidity is often a significant proxy of distress, even greater than that associated with the dermatological manifestations of the disorder [26].

However, the relationship between dermatological and psychiatric symptoms is still unclear [27], being complex to ascertain to which extent psychiatric symptoms are due to the underlying psoriasis rather than to the psychosocial implications derived from living with a chronic disease [28]. In fact, psychiatric comorbidities may be intertwined with the pathophysiology of psoriasis itself, as the chronic inflammatory state inherent to psoriasis has been implicated in the pathogenesis of many psychiatric disorders such as anxiety and depression [29]. This overlap underscores the importance of addressing both physical and mental health aspects in the management of patients with psoriasis. Furthermore, the presence of psychiatric comorbidities can adversely affect treatment adherence [30–32], disease severity [13,33], and overall prognosis, thereby compounding the disease burden [15,23].

It is not surprising that perceived stress in patients with psoriasis, as well as in several other chronic inflammatory diseases, may predict a poor quality of life (QoL) [34]. Studies have consistently shown that patients with psoriasis score lower on QoL measures compared to healthy controls, with the severity of skin lesions and the presence of arthritis being significant contributors [35–38]. Quality of life is a critical consideration in the holistic management of psoriasis, and the impact on QoL is not limited to physical discomfort, but extends to mental and emotional well-being and the resulting social and work disability [39].

Given the intricate relationship between psoriasis, psychiatric disorders, and QoL, it is essential to identify factors that influence these outcomes [40,41]. This knowledge can inform targeted interventions aimed at improving overall patient well-being [42]. However, comprehensive analyses incorporating multiple variables and their interactions are limited. While individual studies have examined the impact of specific factors like disease severity [43], treatment adherence [44,45], and psychiatric comorbidities [40] on QoL, few of them have integrated these elements into a coherent model that can guide comprehensive patient care strategies. Recent research has started to unravel these complex interactions. Despite this, gaps remain in understanding the multifactorial influences on QoL in patients with psoriasis, particularly regarding the interplay between physical symptoms, mental health, and lifestyle factors such as physical activity and sleep quality.

In this study, we aimed to identify factors influencing anxiety, depression, and the deterioration in mental and physical QoL in patients with psoriasis. Using a comprehensive analytical approach, we aimed to clarify the interactions among multiple variables, including demographic characteristics, lifestyle factors, disease severity, and psychiatric comorbidities. Understanding these relationships is crucial for developing comprehensive, patient-centered management strategies that address both the dermatological and psychological aspects of the disease. Specifically, we focused on the roles of pain and sleep disturbances in predicting mental health outcomes and overall QoL, thereby highlighting potential targets for therapeutic interventions.

2. Materials and Methods

2.1. Study Design and Settings

This was a cross-sectional observation study carried out in a real-world setting. The recruitment of patients took place in the outpatient unit of the Department of Dermatology of the University of Campania Luigi Vanvitelli. Patients were included if they met the following criteria: (1) age between 18 and 70 years; (2) diagnosis of psoriasis by an experienced dermatologist, according to NICE guidelines [46]; (3) ongoing topical and/or systemic treatment for psoriasis; and (4) willingness to undertake a psychiatric assessment. Exclusion criteria were: (1) inability to give written consent to participate in the study; (2) lack of proficiency in the Italian language; (3) presence of other physical diseases not stabilized or untreated at the time of enrollment; and (4) personal history of alcohol or substance abuse.

All patients gave their written informed consent to participate in the study after receiving a full description of the study aims and design. The study was carried out in accordance with the latest version of the Declaration of Helsinki for experiments involving humans and was approved by the Ethics Committee of the University of Campania Luigi Vanvitelli (130/2014).

2.2. Assessment Tools

Patients' sociodemographic and clinical characteristics, including gender, age, marital and employment status, educational level, lifestyle habits, age of psoriasis onset, previous and ongoing treatments, and family and personal history of psychiatric disorders were recorded with an ad hoc schedule at the time of recruitment.

Dermatological assessment was performed by an experienced dermatologist. Psychopathological status of each enrolled patient was assessed by an experienced psychiatrist. Only validated Italian versions of assessment instruments were adopted.

2.2.1. Psodisk

Each dermatological assessment included the administration of Psodisk, a user-friendly 10-item questionnaire designed to capture the multifaceted nature of psoriasis providing insights into how psoriasis affects various aspects of daily living [47,48]. Psodisk is meant to be completed by both patients and physician together, and the answers are given on a 10-point visual analogue scale, ranging from "absolutely not" to "definitely yes," graphically represented on a disk. The tool consists of ten subscales, each targeting a different domain of life affected by psoriasis: health, physical pain, itch, sleep, social life, work and other daily activities, peace of mind, sexual life, shame, and skin involvement. Responses are typically rated on a Likert scale, with higher scores indicating a greater negative impact of psoriasis. Psodisk was used as covariate, and Cronbach's alpha for the Italian version of Psodisk is 0.927 [48].

2.2.2. Hamilton Anxiety Rating Scale (HAM-A)

The Hamilton Anxiety Rating Scale (HAM-A) is a 14-item clinician-related questionnaire. Each item is scored on a 5-point scale, and a higher total score indicates more anxiety symptoms [49]. HAM-A total score was used as outcome variable to assess the level of anxiety in participants, and for the Italian version of the scale, Cronbach's alpha was found to be 0.86 [50].

2.2.3. Hamilton Rating Scale for Depression (HAM-D)

The Hamilton Rating Scale for Depression (HAM-D) is a 21-item questionnaire assessing depressive symptoms, with higher scores indicating severe depression symptoms [51]. The HAM-D served as outcome variable to measure depressive symptoms, and the Italian version of this tool has a Cronbach alpha of 0.833 [52].

2.2.4. Symptom Checklist-90-Revised (SCL-90-R)

The Symptom Checklist-90-Revised (SCL-90-R) is a self-report inventory designed to evaluate a broad range of psychological problems and psychopathological symptoms that consists of 90 items, each rated on a 5-point scale of distress (from "not at all" to "extremely"). These items are organized into nine primary symptom dimensions: (1) somatization (SOM), (2) obsessive–compulsive (O–C), (3) interpersonal sensitivity (I-S), (4) depression (DEP), (5) anxiety (ANX), (6) hostility (HOS), (7) phobic anxiety (PHOB), (8) paranoid ideation (PAR), and (9) psychoticism (PSY). The Global Severity Index (GSI) reflects the overall level of psychological distress, and higher scores indicate greater psychological distress and symptom severity [53,54]. The GSI was used as outcome variable in statistical analyses, and the Italian version of SCL-90-R has a Cronbach alpha of 0.96 [55].

2.2.5. 36-Item Short Form Health Survey (SF-36)

The health-related quality of life was assessed by the 36-Item Short Form Health Survey (SF-36), a widely used questionnaire designed to capture a broad range of health dimensions and applicable to diverse patient populations, making it a valuable tool in both clinical practice and research. The SF-36 consists of 36 items that cover eight health domains, divided into two main categories: physical and mental health. The physical component summary (PCS) aggregates scores from the following four physical health domains: (1) physical functioning (PF), (2) role limitations due to physical health (RP), (3) bodily pain (BP), and (4) general health (GH). The mental component summary (MCS) aggregates scores from the following four mental health domains: (1) vitality (VT) or energy/fatigue, (2) social functioning (SF), (3) role limitations due to emotional problems (RE), and (4) mental health (MH) or emotional well-being [56]. Higher scores refer to a better health-related quality of life. PCS and MCS scores were used as outcome variables, and the Italian version of the SF-36 has a Cronbach alpha > 0.77 [57].

2.3. Statistical Analysis

The statistical data related to the sociodemographic and clinical characteristics of the sample, as well as those from other relevant assessment instruments, were calculated and are presented as means and standard deviations (SDs) or frequencies and percentages (%), as appropriate. The Kolmogorov–Smirnov test was adopted to check the normality of distribution of our sample. Student's *t*-test for independent samples was performed to assess differences in HAM-A, HAM-D, PCS, MCS and GSI mean scores with discrete variables. Correlation analyses were performed to explore the association between those same scores and continuous variables, including Psodisk subscales. A generalized linear regression model was finally applied to detect possible predictors of anxiety, depression, psychopathological distress, and physical and mental quality of life in our cohort of patients. The level of statistical significance was set at $p < 0.05$. The data were analyzed using IBM Statistical Package for Social Sciences (SPSS), version 26.

3. Results

3.1. Sociodemographic Characteristics of the Sample

The total sample consisted of 112 patients, mainly male (67, 59.8%) and with a mean age of 48.91 ± 12.73 years. Almost half of them were middle school graduates (41.1%) and only 7.1% of the sample had obtained a university degree. Mean body mass index (BMI) was 29.33 ± 6.45 and 89 subjects (79.5%) declared having a sedentary lifestyle, with low-to-absent physical activities performed during the day. Slightly more than half of the subjects (54.5%) were smokers and 97.3% drank alcohol regularly. Nevertheless, these data fall within regular alcohol consumption in the context of the Mediterranean diet [58] and are not indicative of an alcohol use disorder, as this was an exclusion criterion. Most of the sample (64.3%) reported another dermatological disease. Our cohort included patients diagnosed with psoriasis with a median illness duration of 17.4 ± 12.49 years. In addition, in 31 cases (27.7%), arthropathic psoriasis was diagnosed. Mean Psodisk total score was 52.24 ±

26.22. Overall, 14% of the sample had a positive family history for psychiatric disorders, nine subjects (8%) had a personal history of psychiatric disorders, twelve patients (10.7%) were in treatment with anxiolytics, and nine (8%) were on antidepressant drugs. No other psychiatric medications (such as antipsychotics and mood stabilizers) were mentioned by the enrolled subjects. Mean HAM-A total score was 12.59 ± 9.56, and mean HAM-D total score was 11.93 ± 7.67. Mean GSI scored 60.79 ± 53.63. The main sociodemographic and clinical characteristics of the sample are reported in Tables 1 and 2, respectively.

Table 1. Sociodemographic characteristics of the sample (N = 112).

	n	**%**
Gender		
Male	67	59.8
Female	45	40.2
Age (years)	48.91	±12.73
Education		
Elementary school	26	23.2
Middle school	46	41.1
High school	32	28.6
University	8	7.1
Marital status		
With partner	87	77.7
Without partner	25	22.3
Employed, yes	56	50

Note: Data for continuous variables are expressed as the mean ± standard deviation.

Table 2. Clinical characteristics of the sample (N = 112).

	n	**%**
BMI	29.33	±6.45
Sedentary lifestyle, yes	89	79.5
Smoker, yes	61	54.5
Alcohol consumption	109	97.3
Family history of psychiatric disorders, yes		
Positive	16	14.3
Personal history of psychiatric disorders		
Positive	9	8
Ongoing psychiatric drugs administration		
Anxiolytic	12	10.7
Antidepressant	9	8
HAM-A total score	12.59	±9.56
HAM-D total score	11.93	±7.67
GSI	60.79	±53.63
DoPI (years)	17.4	±12.49
Arthritis	31	27.7
Psodisk total score	52.24	±26.22

BMI: body mass index; DoPI: duration of psoriatic illness; GSI: Global Severity Index; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Rating Scale for Depression. Note: Data for continuous variables are expressed as the mean ± standard deviation.

3.2. Univariate Analyses

To assess differences in psychopathological scores within discrete variables, independent samples *t*-tests were performed (Figure 1). The mean HAM-A total score was statistically significantly higher in female subjects (d = 7.15; $t = 4.16$; $p < 0.001$), in patients who reported a positive personal history of psychiatric disorders (d = 7.57; $t = 2.32$; $p = 0.02$), and in patients with arthritis (d = 5.39; $t = 2.48$; $p = 0.02$). Furthermore, the mean HAM-D total score was higher in female patients (d = 5.39; t = 3.87; $p < 0.001$) and in patients with a sedentary lifestyle (d = 4.01; $t = 2.68$; $p = 0.005$). The mean PCS score was significantly lower in females (d = 11.02; $t = 2.45$; $p = 0.016$) and in patients with arthritis (d = 11.87;

t = 2.40; p = 0.018), indicating a greater impairment of the physical component of quality of life recorded with the SF-36. On the other hand, the mean MCS score was significantly lower in female patients (d = 13.22; t = 3.17; p = 0.002. Finally, female patients showed a significantly higher score than male patients on the GCI scale (d = 33.11; t = 3.35; p = 0.001). No statistically significant differences were found in the scores of the psychopathological scales considered in the patient groups defined on the basis of smoking habits, alcohol consumption, or family history of psychiatric disorders.

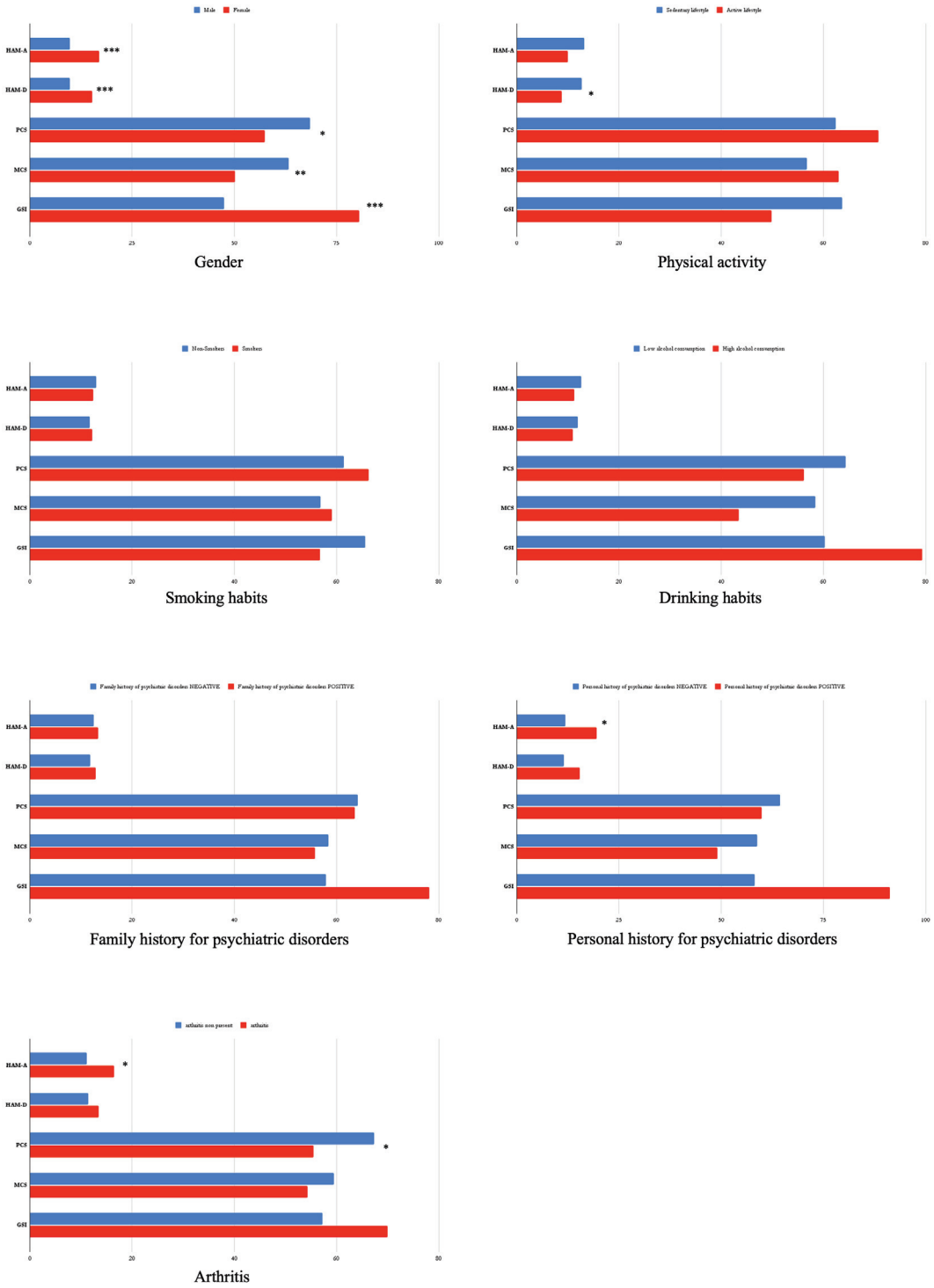

Figure 1. Student's t-tests. Comparison of assessment scale scores by sociodemographic and clinical characteristics in the study population (statistically significant results are highlighted as follows: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).

In Table 3, results of the correlation analyses between age, BMI, duration of psoriatic illness, Psodisk subscales, and psychopathological variables such as HAM-A, HAM-D, PCS, MCS ,and GSI scores are reported. The analysis evidenced that age and BMI were inversely correlated with PCS (r = −0.242, p = 0.010; r = −0.222, p = 0.018 respectively) and MCS (r = −0.204, p = 0.031; r = −0.225, p = 0.017 respectively) subscales of the SF-36. No significant correlation was found between duration of psoriatic illness and the psychopathological scales. Significant correlations were also found between most Psodisk subscales and the psychopathological variables considered, with the only exception of the work and other physical activities dimension and the HAM-D total score. In particular, health subscales of Psodisk correlated with HAM-A and HAM-D total scores (r = 0.500, p < 0.001 and r = 0.462, p < 0.001, respectively) and with GSI, PCS and MCS scores (r = 0.493, p < 0.001; r = −0.523, p < 0.001; r = −0.464, p < 0.001, respectively); the pain subscale of Psodisk also correlated with HAM-A and HAM-D total scores (r = 0.525, p < 0.001; r = 0.415, p < 0.001) and with GSI, PCS and MCS scores (r = 0.442, p < 0.001; r = −0.563, p < 0.001; r = −0.443, p < 0.001). The itching item of Psodisk correlated with HAMA-A (r = 0.321, p = 0.001), HAM-D (r = 0.313, p = 0.001), GSI (r = 0.359, p < 0.001), PCS (r = −0.278, p = 0.003) and MCS (r = −0.389, p < 0.001). Psodisk sleep subscale correlated with HAM-A (r = 0.456, p < 0.001), HAM-D (r = 0.409, p < 0.001), GSI (r = 0.467, p < 0.001), PCS (r = −0.435, p < 0.001), and MCS (r = −0.488, p < 0.001). Social life subscale correlated with HAM-A and HAM-D (r = 0.331, p < 0.001; r = 0.220, p = 0.020), and with GSI, PCS and MCS (r = 0.383, p < 0.001; r = −0.228, p = 0.016; r = −0.324, p = 0.001). Work and other daily activities Psodisk item correlated with HAM-A (r = 0.265, p = 0.005), GSI (r = 0.246, p = 0.009), PCS (r = −0.345, p < 0.001), and MCS (r = −0.349, p < 0.001). The Psodisk subscale of peace of mind correlated with HAM-A (r = 0.399, p < 0.001), HAM-D (r = 0.333, p < 0.001), CGI (r = 0.405, p < 0.001), PCS (r = −0.390, p < 0.001), and MCS (r = −0.520, p < 0.001). The sexual life item of Psodisk showed correlations with HAM-A (r = 0.241, p = 0.011), HAM-D (r = 0.197, p = 0.038), GSI (r = 0.356, p < 0.001), PCS (r = −0.245, p = 0.010), and MCS (r = −0.320, p = 0.001). The shame item correlated with HAM-A (r = 0.331, p < 0.001), HAM-D (r = 0.289, p = 0.002), GSI (r = 0.407, p < 0.001), PCS (r = −0.237, p = 0.012), and MCS (r = −0.346, p < 0.001). Finally, the skin involvement measured by Psodisk showed correlations with HAM-A and HAM-D (r = 0.288, p = 0.002; r = 0.315, p = 0.001), and GSI, MCS, and PCS (r = 0.341, p < 0.001; r = −0.224, p = 0.018; r = −0.294, p = 0.002).

Table 3. Pearson's rho correlation between age, BMI, duration of psoriatic illness, Psodisk subscales and psychiatric assessment tool scores (N = 112).

			SF-36		**SCL-90**
	HAM-A	**HAM-D**	**PCS**	**MCS**	**GSI**
Age	0.108	0.005	−0.242 *	−0.204 *	0.032
BMI	0.182	0.081	−0.222 *	−0.225 *	0.099
DoPI	−0.089	−0.086	−0.022	0.094	−0.048
Psodisk					
Health	0.500 ***	0.462 ***	−0.523 ***	−0.464 ***	0.493 ***
Pain	0.525 ***	0.415 ***	−0.563 ***	−0.443 ***	0.442 ***
Itch	0.321 ***	0.313 ***	−0.278 **	−0.389 ***	0.359 ***
Sleep	0.456 ***	0.409 ***	−0.435 ***	−0.488 ***	0.467 ***
Social life	0.331 ***	0.220 *	−0.228 *	−0.324 ***	0.383 ***
Work and other daily activities	0.265 ***	0.132	−0.345 ***	−0.349 ***	0.246 **
Peace of mind	0.399 ***	0.333 ***	−0.390 ***	−0.520 ***	0.405 ***
Sexual life	0.241 *	0.197 *	−0.245 **	−0.320 ***	0.356 ***
Shame	0.331 ***	0.289 ***	−0.237 *	−0.346 ***	0.407 ***
Skin involvement	0.288 ***	0.315 ***	−0.224 *	−0.290 **	0.341 ***

* p < 0.05; ** p < 0.01; *** p < 0.001. BMI: body mass index; DoPI: duration of psoriatic illness; GSI: Global Severity Index; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Rating Scale for Depression; MCS: SF-36 mental component summary; PCS: SF-36 physical component summary; SF-36: Short Form Health Survey 36; SCL-90: Symptom Checklist.

3.3. Multivariate Analysis

The results of the regression linear analysis are reported in Table 4. The model was run to assess the independent predictors associated with the psychopathological scales.

Table 4. Regression analysis (N = 112). Sociodemographic and clinical characteristics of the sample and Psodisk subscale scores are used as independent variables; psychopathological scales are the dependent variables.

					SF-36				SCL-90	
	HAM-A B (95% IC)		HAM-D B (95% IC)		PCS B (95% IC)		MCS B (95% IC)		GSI B (95% IC)	
Adjusted R^2	0.440		0.300		0.382		0.390		0.310	
Age	0.05	(−0.07/0.17)	−0.06	(−0.17/0.05)	−0.20	(−0.52/0.12)	−0.26	(−0.56/0.03)	−0.27	(−1.03/0.49)
Gender (male)	−3.92 *	(−7.35/−0.49)	−3.42 *	(−6.52/−0.32)	2.31	(−6.65/11.27)	7.69	(−0.65/16.02)	−14.44	(−35.87/6.98)
BMI	0.13	(−0.10/0.36)	−0.02	(−0.23/0.18)	−0.60	(−1.19/0.00)	−0.46	(−1.02/0.09)	0.10	(−1.33/1.53)
Physical activity (sedentary lifestyle)	2.71	(−1.07/6.49)	4.02 *	(0.60/7.43)	−6.34	(−16.21/3.53)	−2.48	(−11.66/6.70)	8.99	(−14.61/32.58)
Personal history of psychiatric disorders (negative)	−4.84	(−10.33/0.65)	−1.47	(−6.43/3.49)	−0.91	(−15.25/13.43)	4.50	(−8.83/17.83)	−20.07	(−54.35/14.21)
DoPI	−0.14 *	(−0.27/−0.02)	−0.09	(−0.20/0.03)	0.11	(−0.22/0.43)	0.27	(−0.03/0.57)	−0.37	(−1.14/0.41)
Arthritis (absent)	−2.22	(−6.07/1.62)	−0.12	(−3.60/3.35)	2.60	(−7.45/12.65)	−0.22	(−9.57/9.13)	−4.18	(−28.21/19.85)
Psodisk										
Health	0.24	(−0.47/0.96)	0.51	(−0.13/1.16)	−1.10	(−2.96/0.76)	−0.47	(−2.19/1.26)	3.10	(−1.34/7.53)
Pain	0.62 *	(0.05 7/1.19)	0.28	(−0.24/0.79)	−2.03 **	(−3.52/−0.54)	−0.46	(−1.85/0.93)	1.52	(−2.05/5.09)
Itch	−0.39	(−0.98/0.19)	−0.18	(−0.71/0.34)	0.49	(−1.04/2.02)	0.21	(−1.21/1.63)	−0.78	(−4.43/2.88)
Sleep	0.68 **	(0.20/1.17)	0.60 **	(0.16/1.04)	−1.46 **	(−2.73/−0.19)	−1.57 *	(−2.75/−0.39)	3.91 *	(0.87/6.95)
Social life	0.21	(−0.40/0.82)	0.13	(−0.42/0.68)	0.14	(−1.45/1.73)	0.15	(−1.33/1.63)	0.91	(−2.89/4.72)
Work and other daily activities	−0.29	(−0.82/0.23)	−0.31	(−0.78/0.16)	−0.10	(−1.46/1.26)	−0.31	(−1.58/0.95)	−1.63	(−4.89/1.63)
Peace of mind	0.54	(−0.12/1.20)	0.15	(−0.45/0.75)	−1.07	(−2.80/0.66)	−2.30 **	(−3.91/−0.69)	0.91	(−3.22/5.05)
Sexual life	−0.15	(−0.77/0.48)	−0.30	(−0.86/0.27)	−0.22	(−1.85/1.41)	−0.05	(−1.57/1.46)	1.23	(−2.67/5.14)
Shame	0.13	(−0.47/0.72)	0.12	(−0.42/0.66)	0.12	(−1.43/1.67)	0.10	(−1.34/1.54)	1.56	(−2.15/5.26)
Skin involvement	−0.02	(−0.75/0.72)	0.04	(−0.63/0.71)	1.33	(−0.59/3.26)	0.89	(−0.90/2.68)	−0.22	(−4.83/4.38)

* $p < 0.05$; ** $p < 0.01$. BMI: body mass index; DoPI: duration of psoriatic illness; GSI: Global Severity Index; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Rating Scale for Depression; MCS: SF-36 mental component summary; PCS: SF-36 physical component summary; SF-36: Short Form Health Survey 36; SCL-90: Symptom Checklist.

Patients with higher HAM-A scores were more likely to be female (B = 3.92, $p = 0.026$), have a shorter duration of illness (B = −0.14, $p = 0.026$), and experience more physical pain (B = 0.62, $p = 0.034$) and sleeping disturbance (B = 0.68, $p = 0.007$) due to the psoriasis. Higher HAM-D scores were more strongly associated with being female (B = 3.42, $p = 0.031$), leading a sedentary lifestyle (B = 4.02, $p = 0.022$), and experiencing sleep disturbance caused by psoriasis as evaluated by the Psodisk subscale (B = 0.60, $p = 0.008$). A worse PCS score was associated with the presence of pain and sleep disturbance due to psoriasis (B = −2.03, $p = 0.008$; B = −1.46, $p = 0.025$), whereas a worse MCS score was linked to sleep disturbance (B = –1.57, $p = 0.010$) and Psodisk subscale peace of mind (B = −2.30, $p = 0.006$). Additionally, sleep disturbance also correlated with higher GSI scores (B = 3.91, $p = 0.012$).

4. Discussion

This study provides valuable insights into the sociodemographic characteristics, lifestyle factors, and psychological comorbidities of patients with psoriasis. Notably, a significant portion of the sample led a sedentary lifestyle (79.5%), and a considerable percentage were smokers (54.5%) and regular alcohol consumers (97.3%). These lifestyle factors may contribute to the overall health burden and quality of life in patients with psoriasis [59,60]. The prevalence of psychiatric comorbidities in our cohort was noteworthy, with 8% of patients having a personal history of psychiatric disorders and 10.7% receiving anxiolytic treatment at the time of recruitment. This aligns with previous studies highlighting the high prevalence of psychological issues in dermatological conditions like psoriasis [23,33]. Patients with psoriasis are frequently burdened with mental health issues due to the chronic and visible nature of their condition, which can significantly affect their social interactions and self-esteem [61]. Furthermore, female patients exhibited higher

levels of anxiety (assessed by HAM-A) and depression (assessed by HAM-D) compared to males, and those with a sedentary lifestyle showed significantly higher depression scores. These findings are consistent with existing literature that indicates gender and physical activity levels as critical determinants of mental health in chronic illness [18,61–65]. The higher prevalence of anxiety and depression in female patients may be attributed to both biological and social factors, including hormonal fluctuations and societal pressures [66,67]. An important biological factor to consider is the role of inflammation, which is a common denominator in both psoriasis and psychiatric disorders. Psoriasis is characterized by chronic systemic inflammation, which can affect various organs, including the brain [68,69]. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1 beta (IL-1β) are elevated in psoriasis and have been implicated in the pathophysiology of depression and anxiety [70,71]. These cytokines can cross the blood–brain barrier and influence neurotransmitter systems, leading to changes in mood and behavior. Furthermore, chronic inflammation can alter the hypothalamic–pituitary–adrenal (HPA) axis, leading to increased levels of cortisol, which is associated with both psoriasis severity and depressive symptoms [72]. Finally, an increase in inflammation can also result from unhealthy lifestyles such as physical inactivity, resulting in a complex interplay that may further contribute to the mental health challenges faced by patients with psoriasis [73]. It should be noted that treatment of psoriasis may involve biologics that affect blood cytokine levels (i.e., IL-12, IL-23, and TNF-α), with an overall reduction in inflammation [74]. It is conceivable that these therapies may also impact anxiety and depressive symptom severity, thereby potentially improving patients' mental health and well-being. However, this hypothesis is merely speculative, considering that the impact of biological therapies on psychiatric symptoms was not the objective of this study. Nonetheless, this could be the starting point for further studies, which should adopt a longitudinal design and should be carried out on larger samples.

Our correlation analysis indicated that both age and BMI negatively correlated with the physical and mental components of quality of life (PCS and MCS scores of SF-36), suggesting that older and overweight patients may experience greater impairments in both the physical and mental components of QoL. These findings underscore the importance of managing comorbid conditions such as obesity in patients with psoriasis, as these can exacerbate the overall disease burden [75]. Additionally, Psodisk subscales correlated significantly with psychopathological variables, reinforcing the impact of disease severity on mental health. This correlation emphasizes the need for comprehensive assessments that include both physical and psychological aspects of the psoriasis.

The multivariate analysis further substantiated these findings by confirming the correlations among gender and sedentary lifestyle behaviors and levels of anxiety and depressive symptoms and by identifying other independent variables associated with psychopathological outcomes. According to these analyses, disease duration of psoriasis was negatively associated with anxiety symptoms, indicating that longer illness duration might contribute to better coping mechanisms or adaptation over time. This adaptive response may be due to patients developing more effective strategies for managing their condition and its psychosocial impact over time [76]. However, this interpretation is merely speculative and requires further investigations to be confirmed.

Physical pain and sleep disturbances, as assessed by Psodisk, were significantly associated with both anxiety and depressive symptoms, as well as lower quality-of-life scores. This highlights the critical role of pain management and sleep quality in improving the overall well-being of patients diagnosed with psoriasis [77]. Pain is a common symptom in psoriasis that can severely limit daily activities and negatively impact mental health. Similarly, sleep disturbances are frequently reported in patients with psoriasis and are associated with higher levels of anxiety and depression [15]. In fact, previous research has shown that the prevalence of sleep disorders in these patients is significantly higher than in the general population, with conditions such as insomnia, obstructive sleep apnea, and restless legs syndrome being particularly common [77–79]. These sleep disorders not

only exacerbate the physical symptoms of psoriasis but also contribute to a vicious cycle of psychological distress [80]. Once again, the association between sleep disturbances and mental health issues in psoriasis can be partly explained by the role of systemic inflammation [77]. Pro-inflammatory cytokines, which are elevated in psoriasis, can disrupt sleep architecture, leading to poor sleep quality and increased daytime fatigue [81]. This disruption in sleep can further elevate inflammatory markers, creating a feedback loop that exacerbates dermatological and psychiatric symptoms.

Moreover, the burden of psoriasis, including the stress of managing a chronic and visible skin condition, can contribute to sleep disorders: anxiety about flare-ups, social stigma, and self-esteem issues can lead to hyperarousal, making it difficult for patients to fall and stay asleep. The chronic sleep deprivation that results can impair cognitive function, mood regulation, and overall mental health, further highlighting the importance of addressing sleep disturbances in this population. Addressing these symptoms through targeted interventions can substantially improve patient outcomes. In particular, cognitive–behavioral therapy for insomnia (CBT-I) has shown promise in improving sleep and reducing symptoms of depression and anxiety in various populations, and could be particularly beneficial for patients with psoriasis [82–84].

Furthermore, we found a significant association between the Psodisk item "peace of mind" and the MCS score of the SF-36 scale, which highlights the profound impact of psoriasis on patients' psychological stability. The "Peace of mind" Psodisk subscale assesses the psychological tranquility and emotional stability of patients, reflecting their overall mental state, encompassing aspects such as emotional well-being, role limitations due to emotional problems, and social functioning. Interventions aimed at enhancing patients' peace of mind, such as mindfulness-based therapies and stress management programs, could potentially improve the overall mental health and quality of life in this population [85,86].

Finally, these findings highlight the importance of a multidisciplinary approach in managing psoriasis. Dermatologists, mental health professionals, and primary care providers should collaborate to address the comprehensive needs of patients [87]. Integrating psychological support, lifestyle counseling, and psychiatric assessment into routine dermatological care could potentially mitigate the mental health challenges faced by these patients, leading to more holistic and effective treatment outcomes [18,88–92]. Additionally, the significant impact of sedentary lifestyle on depression scores suggests that promoting physical activity could be a beneficial component of psoriasis management. Regular exercise has been shown to reduce symptoms of depression and anxiety, improve cardiovascular health, and enhance overall quality of life [93,94]. Encouraging patients to engage in physical activities suited to their capabilities can be a practical step towards better mental health outcomes. Furthermore, the lack of significant differences in psychopathological scores based on smoking habits, alcohol consumption, and family history of psychiatric disorders does not undermine the importance of addressing these behaviors, as they still pose significant health risks and can potentially exacerbate other aspects of psoriasis [95,96].

The results of the present paper should be considered in light of several limitations. First, the observational design precludes any conclusions about the causal relationships between considered variables and psychological outcomes. Longitudinal studies are needed to determine the directionality and temporal sequence of these associations. Second, the use of self-reported measures may introduce response bias, as participants might underreport or overreport their symptoms based on their subjective perceptions, and future studies should consider incorporating objective measures. Third, the Hamilton rating scales for depression and anxiety (HAM-D and HAM-A) were originally designed to describe rather than quantify symptoms. Although these instruments have been widely employed for quantitative assessments in clinical research, their use for this purpose may not provide the most accurate representation of symptom severity, considering the availability of more specific and updated assessment instruments. However, given their extensively use in already published articles, the adoption of HAM-D and HAM-A can provide comparable

data. Nevertheless, further steps of the present research will include the use of more recent and updated assessment instruments for depressive and anxiety symptoms in order to balance this limitation. Fourth, the relatively limited number of patients and their heterogeneity concerning psoriasis symptoms and clinical subtype limit the generalizability of the findings. Larger samples would enhance the validity of the results. Additionally, the study was conducted in a single geographic region, which may not reflect the experiences of patients with psoriasis in different contexts. Comparative studies across different populations are necessary to confirm the generalizability of these findings. Lastly, another possible limitation of our study is that several other variables may have influenced patients' anxiety and depressive symptom severity as well as their quality of life. These include the presence of comorbidities, although in their stable phase, any stressful life events that occurred in the months prior to enrollment and the use of psychiatric and dermatological medications. Specifically, the use of anxiolytic or antidepressant medications may have influenced the average HAM-A and HAM-D scores in the overall sample. However, the impact of this confounding factor is likely to be minimal, given the widespread use of these medications [97–99]. Similarly, certain dermatological therapies commonly used for the treatment of psoriasis may contribute to the development of affective or anxiety symptoms in patients (i.e., corticosteroids, methotrexate, cyclosporine, and biological therapies). However, we attempted to mitigate this confounding effect by using assessment tools specifically designed for evaluating quality of life and symptoms related to psoriasis, such as Psodisk. Despite these efforts, given the cross-sectional design of the study and its real-world setting, we were not able to fully determine the extent to which these medications influence mental health outcomes. Future research will be essential to explore the implications of these treatments on the mental health of patients with psoriasis more comprehensively.

Despite these limitations, this study provides important insights into the complex interplay between physical and psychological health in individuals with psoriasis and underscores the need for comprehensive care approaches.

5. Conclusions

This study underscores the complex and multifaceted nature of psoriasis, which extends well beyond dermatological symptoms to encompass significant psychological, psychiatric, and quality-of-life impairments. Pain and sleep disturbances emerged as key factors influencing both anxiety and depressive symptoms in patients with psoriasis, as well as the overall quality of life. Inflammation appears to be a pivotal factor linking unhealthy lifestyles, psoriasis, psychiatric symptoms such as anxiety and depression, and sleep disturbances.

These insights emphasize the need for a comprehensive approach to psoriasis management that includes addressing psychiatric comorbidities and lifestyle modifications, particularly focusing on improving physical activity, pain management, and sleep quality. Future research should aim to explore targeted interventions that can alleviate these psychic burdens and enhance the quality of life for patients with psoriasis. Integrating psychiatric support and lifestyle counseling into routine dermatological care could potentially mitigate the mental health challenges faced by these patients, leading to more holistic and effective treatment outcomes.

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The Associations of Exposome Score with Various Domains of Psychopathology: A Network Analysis in a Non-Clinical Sample

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Abstract: Background: The intricate correlation between environmental exposures and mental health outcomes is increasingly acknowledged in psychiatric research. This study investigated the relationship between cumulative environmental risk factors, as represented by the exposome score (ES), and various domains of psychopathology within a non-clinical sample using a network analysis. Methods: We recruited 1100 participants (aged 18–35 years, 51.4% females) via a computer-assisted web interview, assessing psychopathological symptoms using standardized questionnaires. Environmental exposures, including season of birth, obstetric complications, advanced paternal age, childhood trauma, cannabis use, and urban upbringing, were self-reported to calculate the ES. Results: A network analysis revealed significant associations of the ES with psychotic-like experiences (PLEs) (weight = 0.113), manic (weight = 0.072), and attention-deficit/hyperactivity disorder symptoms (weight = 0.062). These connections did not differ significantly with respect to their weights. Depressive symptoms had the highest centrality and predictability. The mean predictability across all nodes included in the network was 0.344. Conclusions: These findings underscore the transdiagnostic nature of environmental exposures, aligning with previous research indicating broad associations between the ES and various facets of psychopathology. Our results suggest that the ES may not specifically correlate with PLEs but may indicate the risk of a broader psychopathology.

Keywords: psychosis; mood disorder; depression; transdiagnostic psychiatry; early intervention

1. Introduction

In the ever-evolving field of psychiatric research, there is a growing emphasis on unraveling the complex interplay between environmental exposures and mental health outcomes. Over the course of a lifetime, individuals encounter a myriad of environmental factors. These exposures, such as season of birth, obstetric complications, advanced paternal age at conception, growing up in an urban environment, and the experience of childhood trauma have the potential to heighten the risk of developing psychopathology, particularly in those with pre-existing vulnerabilities [1,2]. Moreover, the influence of chronic stress, especially during critical neurodevelopmental stages, is emerging as a powerful catalyst in shaping mental health outcomes [3,4]. There is a growing and active interest in unraveling the intricate relationship between mental disorders and environmental exposures, given their modifiable and potentially preventable nature.

Traditionally, psychiatric research has focused on examining the effects of individual environmental exposures on specific mental health outcomes [5]. Nonetheless, a paradigm shift is underway, acknowledging that these factors are not limited to specific phenotypes, with certain risk factors contributing to a spectrum of mental disorders. In addition to genetic susceptibility, various disorders may stem from different risk factors. Many environmental factors can affect various behavioral phenotypes. For example, cannabis abuse has been linked to elevated risks of psychosis spectrum disorders as well as anxiety, depression, and bipolar disorders [6]. Also, studies have indicated that individuals who experienced childhood trauma are more likely to develop non-specific psychopathology manifesting

in affective, anxiety, and psychotic symptoms that transcend traditional diagnostic categories. This aligns with findings from a recent umbrella review, which demonstrated that a history of childhood trauma is linked with various mental disorders [7]. Likewise, urbanicity, advanced paternal age, and obstetric complications have been identified to show transdiagnostic associations [8–12]. Environmental exposures are intricately entwined, showcasing both causative and non-causative associations, along with complex interactions. For instance, cannabis use, recognized as an environmental risk factor for psychosis, often co-occurs with other exposures including childhood adversity and urbanicity. Previous research has suggested that exposure to environmental risk factors increases connectivity across the symptom network [6]. These exposures show correlations and mutual interactions, while research also indicates a dose-response correlation between exposures and psychopathological outcomes, wherein a greater number or severity of exposures tends to correlate with progressively worse outcomes [13,14].

A novel exploration that aims to better understand the association between environmental risk factors and psychopathology is related to investigating cumulative measures that comprehensively encompass multiple risk factors. These measures are known as the exposome score (ES) or polyenviromic risk score (PERS) [15,16]. The ES, akin to risk scores in other medical disciplines, aims to include various environmental factors associated with mental disorders. Researchers have used various methods to explore the collective impact of various environmental exposures linked to mental disorders [13,17–19]. The predominant approach involves a straightforward total score of environmental risk loading, often derived by summing individual factors. However, this method fails to recognize the varying risk magnitudes associated with each exposure [20]. To address this limitation, prior research has turned to estimates from meta-analyses to formulate a weighted environmental sum score, which is a method that exerts conceptual parallels with the polygenic risk score [21]. A recent advancement in this field is the ES for schizophrenia, a cumulative environmental exposure score tailored to psychotic disorders. Previous studies have demonstrated the potential utility of these scores in predicting the risk of developing psychosis, with the ES explaining a greater amount of variance in psychosis risk than genetic factors alone [22]. It is crucial to note the complexity of constructing these scores, as each score represents a unique combination of environmental factors. The particular exposures incorporated into each score, along with their relative weights, may differ based on the population and circumstances. Beyond its associations with the extended psychosis phenotype, a higher ES for schizophrenia has shown links with poorer mental and physical outcomes.

To date, it remains unknown as to whether the ES is specifically associated with PLEs in non-help-seeking individuals. Some studies employing the ES suggest that the vulnerability, assessed through the exposome, is associated not only with psychotic spectrum disorders but also with a wider range of mental health problems and functional impairment [23]. This observation is consistent with the understanding that psychosis manifests along a continuum and overlaps with other symptom dimensions [17,24]. Additionally, reports indicating that psychosis expression may be preceded by a nonspecific prodrome with mixed psychopathology domains could also be relevant [25,26]. In our previous studies, initially, we focused on investigating the association between psychotic-like experiences and a broad spectrum of psychopathology. Subsequently, our aim was to explore whether the exposome score (ES) may also be linked to the extended psychosis phenotype and its individual symptoms. Specifically, we identified that the ES is associated with positive screening for psychosis using the Prodromal Questionnaire–16 (PQ–16) in a non-clinical sample [27]. With respect to single PQ–16 items, we found that the ES is associated not only with PLEs (i.e., "paranoid thoughts", "a lack of control over own ideas or thoughts", "thought echo", and "being distracted by distant sounds") but also items covering depressive and anxiety symptoms ("uninterested in things used to enjoy" and "feeling anxious when meeting people for the first time"). In the present study, we aimed

to further explore which domains of psychopathology are associated with the ES score in a community sample of non-help-seeking individuals.

2. Materials and Methods

2.1. Participants

Participants were recruited through the computer-assisted web interview conducted in March 2023 and available on the online survey platform dedicated to research purposes. Only registered users had access to the survey. The survey was based on two specific inclusion criteria: age between 18 and 35 years and a self-reported absence of prior psychiatric treatment. Recruitment procedures adhered to the sociodemographic composition of the Polish population in 2021, encompassing 51% males, 34% of participants aged 18–24 years, and 60% residing in urban areas (i.e., 32% living in cities with populations between 100,000 and 200,000 inhabitants, 9% living in cities with populations between 200,000 and 500,000: 7%, and cities with populations exceeding 500,000: 12%). Prior to responding to the survey, participants were apprised of its confidential and anonymous nature. Certain results obtained from this dataset were published previously [27,28]. This research received approval from the Bioethics Committee at Wroclaw Medical University, Wroclaw, Poland (approval number: 99/2023).

2.2. Assessment of Psychopathology

A detailed description of questionnaires used to assess psychopathological symptoms with corresponding measures of internal consistency is provided in Supplementary Table S1. In brief, we used the following questionnaires: (1) the Patient Health Questionnaire–9 (PHQ–9) for depressive symptoms [29]; (2) the Mood Disorder Questionnaire (MDQ) for manic symptoms [30,31]; (3) the Obsessional Compulsive Inventory-Revised (OCI-R) for obsessive-compulsive disorder (OCD) symptoms [32]; (4) the Generalized Anxiety Disorder–7 (GAD–7) for anxiety symptoms [33]; (5) the PQ–16 for PLEs [34] and (6) the Adult ADHD Self-Report Scale for DSM-5 (ASRS-5) for ADHD symptoms [35].

2.3. Assessment of the ES

The following exposures were assessed using self-reports: (1) winter season of birth; (2) obstetric complications; (3) advanced paternal age; (4) handedness; (5) a history of childhood trauma (emotional neglect, emotional abuse, bullying, and sexual abuse); (6) problematic cannabis use; and (7) urban upbringing (Table 1). To calculate the ES, we adhered to the methods proposed previously [16]. Specifically, all exposures were binarized and multiplied by the log odds derived from previous meta-analyses. Next, they were summed and divided by the number of exposures recorded in this study. The log odds were almost the same as those used in the study by Padmanabhan, Shah, Tandon, and Keshavan [16]. For the winter season of birth, the log odds from an updated meta-analysis were used [36]. Handedness was not included in the study by [16]. Therefore, the log odds from the meta-analysis by Hirnstein and Hugdahl [37] were used.

2.4. Statistics

Data were analyzed by using network analysis techniques implemented within the R software (version 4.1.3). Variables of interest had approximately normal distribution as absolute values of skewness and kurtosis were lower than 2 and 4, respectively. Variables included in the network covered symptom scores and covariates (age, gender, education, and employment status). The network was estimated using the Mixed Graphical Models (the *mgm* package) as we included continuous (symptom scores and age) and binary variables (education—higher vs. other than higher, gender, employment status—employed vs. unemployed) in the network [38]. To improve the interpretability of the network, the L1-penalized regression (LASSO) was used [39,40]. The LASSO shrinks partial correlations with low coefficients. The node centrality was estimated by calculating the node strength. The node strength is the sum of all edge weights connected to it. Also, the node pre-

dictabilities were estimated. The predictability provides information about the proportion of variance explained by nodes directly connected to it. Visualizations were carried out using the *qgraph* package [41].

The final stage of a network analysis was performed in the *bootnet* package [42]. It was used to evaluate bootstrapped differences in edge weights and node centralities together with network accuracy and stability. Case-drop bootstrapping, consisting of 1000 iterations, was performed to assess the stability of node strength. Additionally, non-parametric bootstrapping involving 1000 iterations was employed to evaluate the stability of edge weights. The network stability was explored by computing the correlation stability coefficient (CS-C), which should exceed 0.25.

Table 1. Components of the exposome score.

Exposure	Assessment	Odds Ratio [Log Odds Ratio]
Winter season of birth	Respondents were requested to report their month of birth, and then, based on the meteorological seasons in the Northern Hemisphere, individuals born between December and February were assigned to the winter season, as reported in the recent meta-analysis by Coury, Lombroso, Avila-Quintero, Taylor, Flores, Szejko, and Bloch [36].	1.05 [0.05] [36]
Obstetric complications	The history of obstetric complications was documented using the following questions: "Were you delivered by caesarean section due to perinatal complications?", "Was your birth weight less than 2500 g?", and "Were you delivered preterm, i.e., before the 37th week of pregnancy?". Possible responses were "yes", "no", and "I don't know". Respondents were categorized as having exposure to obstetric complications if their response to any of these questions was "yes". Responses of "I don't know" were coded as missing data.	2.00 [0.69] [11]
Advanced paternal age	Participants were asked to report the age of their father at the time of their birth. Advanced paternal age was defined as ≥35 years.	1.28 [0.25] for paternal age of 35–54 years and 2.22 [0.80] for ≥55 years [43]
Handedness	Participants were queried about their hand preference, i.e., whether they are right-handed, left-handed, or have mixed-handedness. Subsequently, in line with a prior meta-analysis [43], responses indicating left-handedness and mixed-handedness were collectively analyzed as non-right-handedness.	1.65 [0.50] [37]
Childhood trauma	Participants were screened for a history of emotional neglect, emotional abuse, bullying, and sexual abuse before the age of 17. Three questions from the Traumatic Experience Checklist (TEC) [44] were used to assess emotional neglect, abuse, and bullying: "When you were a child or a teenager, have you ever felt emotionally neglected (e.g., being left alone, insufficient affection) by your parents, brothers or sisters?"; "When you were a child or a teenager have you ever felt emotionally abused (e.g., being belittled, teased, called names, threatened verbally, or unjustly punished) by your parents, brothers or sisters?", and "When you were a child or teenager, did you experience psychological violence (e.g., nicknames, teasing) or physical abuse (e.g., jerking, beating) from your peers?". A history of sexual abuse was assessed using the following questions from the Childhood Experience of Care and Abuse (CECA.Q) [45,46]: "When you were a child or teenager did you have any unwanted sexual experiences?"; "Did anyone force you or persuade you to have sexual intercourse against your wishes before age 17?" and "Can you think of any upsetting sexual experiences before age 17 with a related adult or someone in authority e.g., teacher?". Participants who confirmed a history of any of these experiences were classified as having been exposed to sexual abuse.	Emotional neglect: 2.90 [1.06], emotional abuse: 3.40 [1.22], bullying: 2.39 [0.87], and sexual abuse: 2.38 [0.87] [47]
Problematic cannabis use	To identify problematic cannabis use, we applied 11 of the 16 questions of the Cannabis Problems Questionnaire (CPQ) [48], which refer to the past 12 months: "Have you tended to smoke more on your own than you used to?"; "Have you been neglecting yourself physically?"; "Have you felt depressed for more than a week?"; "Have you been so depressed you felt like doing away with yourself?"; "Have you given up recreational activities you once enjoyed for smoking?"; "Do you find it hard to get the same enjoyment from your usual interests?"; "Have you felt more antisocial after smoking?"; "Have you worried about getting out of touch with friends or family?"; "Have you been concerned about a lack of motivation?"; "Have you worried about feelings of personal isolation or detachment?" and "Do you usually have a smoke in the morning, to get yourself going?". Respondents who reported at least one of these consequences of cannabis use were identified as showing problematic cannabis use.	1.75 [0.56] [49]
Urban upbringing	Participants were asked to categorize their primary residence according to the following classifications: (1) rural; (2) a city of up to 100,000 inhabitants; (3) a city of 200,000–500,000 inhabitants; and (4) a city over 500,000 inhabitants. In the data analysis process, the responses were categorized into those reporting a rural or urban place of residence.	1.72 [0.54] [8]

3. Results

The sample characteristics are summarized in Table 2. There were 1100 participants (aged 27.1 ± 5.1 years, 48.6% males). Most frequently, they reported secondary education (50.3%) and full-time employment (51.3%).

Table 2. Sociodemographic and clinical characteristics of the sample.

	Mean ± SD or *n* (%)
Age, years	27.1 ± 5.1
Gender, males	535 (48.6)
Education	
Primary	61 (5.5)
Vocational	89 (8.1)
Secondary	553 (50.3)
Higher	397 (36.1)
Occupation	
Unemployed	164 (14.9)
Part–time	170 (15.5)
Student	202 (18.4)
Full–time	564 (51.3)
Urbanicity, urban	672 (61.1)
Winter season of birth	269 (24.5)
Advanced paternal age	223 (24.8) *
Obstetric complications	276 (31.9) **
Handedness, non-right	107 (9.7)
Emotional neglect	576 (52.4)
Emotional abuse	477 (43.4)
Bullying	593 (53.9)
Sexual abuse	233 (21.2)
CPQ, any cannabis-related problems	72 (6.5)
PQ–16	5.3 ± 4.0
GAD–7	7.6 ± 5.5
PHQ–9	9.4 ± 6.2
MDQ	5.5 ± 3.7
OCI–R	22.3 ± 14.7
ASRS-5	10.1 ± 4.3
ES	0.25 ± 0.17

Note: ASRS-5; the Adult ADHD Self–Report Scale for DSM-5; ES, the exposome score; GAD–7, the General Anxiety Disorder–7; MDQ, the Mood Disorder Questionnaire; OCI–R, the Obsessive-Compulsive Inventory–Revised; PHQ–9, the Patient Health Questionnaire–9; PQ–16, the Prodromal Questionnaire–16. * n = 200 (18.2%) with missing data ** n = 236 (21.5%) with missing data.

All nodes in the network were well-connected and no negative edges were found (Figure 1, Table 3). A total of 22 edges (out of 55 potential edges) had non-zero weights (40.0%). The ES node was directly connected to three nodes representing symptom scores, including PLEs (weight = 0.113), manic symptoms (weight = 0.072), and ADHD symptoms (weight = 0.062). These edges did not differ significantly with respect to their weights (Supplementary Figure S1). The highest strength centrality was obtained for the node representing depressive symptoms, while the lowest one was found for the ES (Supplementary Figure S2). The strength centrality of depressive symptoms was significantly higher compared to the strength centrality of the ES and manic symptoms, but not in comparison with other nodes (Supplementary Figure S3). The mean predictability of the whole network was 0.344. This means that on average the network explained 34.4% of the variance in the included variables (nodes). Apart from covariates, depressive symptoms had the highest predictability (0.646), while the ES had the lowest predictability (0.155) (Supplementary Table S2).

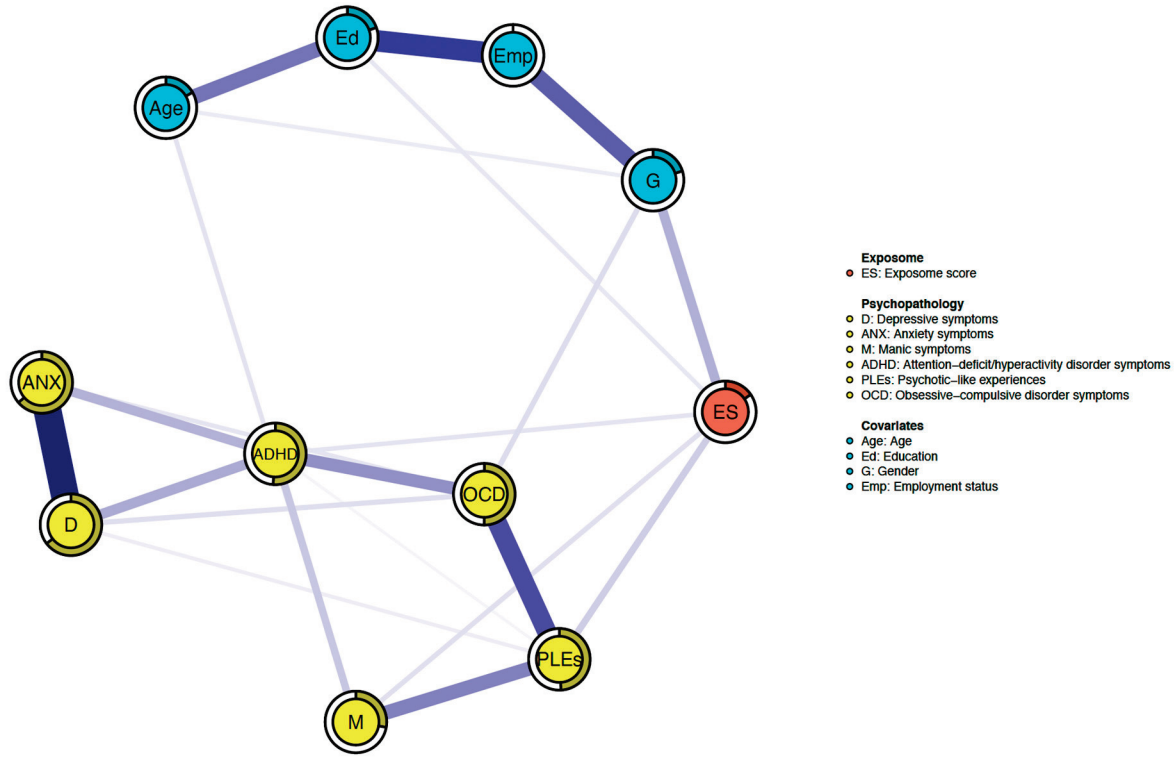

Figure 1. The network assessed in the present study. Specific variables are shown as nodes that are connected by edges. All edges show positive associations. Thicker edges refer to stronger associations. The filled parts of rings around nodes illustrated node predictability.

Table 3. Edge weights.

	ES	D	ANX	M	ADHD	PLEs	OCD	Age	Ed	G
D	0.000	-								
ANX	0.000	0.590	-							
M	0.072	0.000	0.000	-						
ADHD	0.062	0.191	0.175	0.128	-					
PLEs	0.113	0.046	0.000	0.279	0.027	-				
OCD	0.000	0.077	0.061	0.000	0.246	0.398	-			
Age	0.000	0.000	0.000	0.065	0.000	0.000	0.000	-		
Ed	0.057	0.000	0.000	0.000	0.000	0.000	0.000	0.304	-	
G	0.177	0.000	0.000	0.000	0.000	0.000	0.082	0.052	0.000	-
Emp	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.445	0.355

Note: ADHD, attention-deficit/hyperactivity disorder symptoms; ANX, anxiety symptoms; D, depressive symptoms; Ed, the level of education; Emp, employment status; ES, the exposome score; G, gender; M, manic symptoms; OCD, obsessive-compulsive disorder symptoms; PLEs, psychotic-like experiences.

Bootstrapping procedures demonstrated that the network analysis had sufficient stability and accuracy (Supplementary Figures S4 and S5). The CS-C values for the strength centralities and edges were 0.672 and 0.750, respectively.

4. Discussion

In this study, we sought to unravel the intricate correlation between the ES and diverse domains of psychopathology within a non-clinical sample. Building upon our prior findings [27], which linked the ES not only to PLEs but also to experiences representing anxiety and depressive symptoms, indicating the contributory role of ES in non-specific

psychopathology. The present analysis provides a deeper insight into specific domains of psychopathology. Our findings reveal significant associations between the ES and specific psychopathological domains, including PLEs, manic, and ADHD symptoms. These advancements contribute to a more nuanced comprehension of the ES's influence on shaping mental health outcomes. The results align with the evolving paradigm in psychiatric research, underscoring the transdiagnostic nature of environmental exposures.

Previous research indicates that the ES may not only be associated with an elevated risk of psychosis expression within the extended psychosis phenotype but also correlates with the severity of functional impairment [43]. Other studies have revealed a link between the ES and a broad spectrum of mental and physical health outcomes, encompassing conditions such as depression, anxiety, alcohol use disorder, as well as various somatic health impairments [44]. The study conducted by Pries et al. showed the strongest association of the ES with schizophrenia, followed by bipolar disorder and suicidal ideation [45]. These findings propose that environmental exposures are not exclusively linked to the psychosis spectrum phenotype but, instead, show a more widespread association with various facets of psychopathology. In our study, the ES node was directly connected to three nodes representing PLEs, manic, and ADHD symptoms. Such results imply the transdiagnostic and multidimensional nature of the ES. Despite differences in the nature of these symptoms, the edges connecting the ES node to symptom nodes did not differ significantly in terms of their weights. This suggests a relatively uniform influence of the ES on various domains of psychopathology. These results align with and expand upon the recently proposed conceptualization of psychopathology as a network comprising causally linked sets of symptoms in which symptoms reciprocally influence each other over time, culminating in the development of a more defined syndrome characterized by a specific pattern within a dynamic network for each syndrome [6]. The prior study utilized a network analysis of general population data to elucidate the association between environmental risk factors (specifically, cannabis use, trauma, and urban environment) and various dimensional measures of psychopathology (including anxiety, depression, OCD symptoms, and a composite measure of psychosis expression) [46]. The results unveiled specific pathways connecting environmental factors to symptoms, with cannabis use often playing a significant role in these pathways. Additionally, the analyses suggest that individuals exposed to environmental risk factors demonstrate stronger connections within symptom networks, implying that environmental exposures might play a role in fostering less resilient symptom networks. Moreover, environmental factors have been shown to heighten the probability of psychosis expression by increasing general psychopathology [47]. Environmental exposure leads to a more strongly connected and consequently more susceptible psychopathology network. Several studies within the general population have revealed that symptom domains are interconnected and do not occur independently, even prior to the onset of a specific disorder. Furthermore, these studies indicate that interactions between symptoms can forecast the progression to a more severe mental health outcome [48–50]. It has also been shown that exposure to environmental risk factors (including trauma, urban living, and cannabis use) enhances the connectivity between symptoms associated with affective dysregulation and the expression of psychosis in a dose-response manner [23]. This aligns with the theory that disturbances induced by the environment spread through the network of psychopathology, leading to an increased mixture of psychosis symptoms and a gradual expansion and strengthening of connectivity. This progression might ultimately result in the transition to a more severe, distinct clinical syndrome.

Centrality metrics play a crucial role in comprehending network analysis, offering insights into the importance of individual nodes within the network. The network approach facilitates the identification of central nodes, which are highly interconnected. In our study, the node representing depressive symptoms demonstrated the highest strength centrality and predictability, indicating its substantial influence and strong connections with other nodes. This aligns with findings from other studies where depressive symptoms were noted either as the most central or bridging symptoms within broader psychopathology [51–53].

Additionally, depressive symptoms exhibit robust associations, extending beyond mental health to include physical health outcomes and a general propensity for medical comorbidity [54]. Previous research suggests that central nodes are pivotal intervention targets due to their ability to have a more profound impact on altering other nodes [55]. Centrality measures arrange nodes based on their connections, while predictability, although similar in concept, offers absolute values indicating the percentage of variance explained by other variables in the network [56]. Nodes with high predictability and centrality are deemed key variables for potential interventions, suggesting that targeting depressive symptoms may have the most significant impact on associated psychopathological domains. Conversely, the ES node exhibited the lowest strength in centrality and predictability, implying a comparatively weaker direct influence on other nodes.

While our study provides valuable insights into the association between the ES and psychopathology, it is essential to acknowledge certain limitations. First, the cross-sectional nature of our data restricts our ability to establish causality. The observed relationships between the ES and specific psychopathological domains do not imply a directional influence, and longitudinal studies are warranted to elucidate the temporal dynamics of these associations. Also, the accuracy of data obtained using internet-based surveys might be limited. Moreover, the specific characteristics of our non-clinical sample may constrain the applicability of our results to other populations, including those with more severe psychopathology. Subsequent studies should delve into the enduring impacts of the ES on psychopathology over time and encompass a more extensive array of environmental exposures. Furthermore, depending on self-reported evaluations for both environmental risk factors and psychopathological symptoms introduces the risk of recall bias and subjective interpretation, particularly regarding obstetric complications. Nevertheless, in case of obstetric complications, our survey allowed participants to express uncertainty regarding their exposure history, and we subsequently excluded such cases from the data analysis. It is also noteworthy to highlight that standardized tools were not employed for assessing handedness. Regarding the CPQ, only specific items were utilized. Similarly, when documenting a history of childhood trauma, we utilized specific items from the CECA.Q and TEC. Moreover, the use of dichotomized risk factors within the ES might have led to the loss of information. It is worth mentioning that our study was conducted among a non-help-seeking population, mainly consisting of young adults, where some individuals, even with exposomic vulnerability, may not develop distinct mental health problems later in life. Also, the use of a non-clinical sample without assessment of psychopathology using validated diagnostic instruments may limit the generalizability of our results to clinical populations. Furthermore, various limitations related to the snowball method and sampling accuracy should be taken into consideration. It is essential to consider the potential overlap of psychopathological symptoms. For example, the symptoms assessed by the ASRS-5 could potentially reflect cognitive impairments associated with PLEs, mood, or OCD symptoms. Similarly, symptoms from the MDQ might overlap with those related to borderline personality disorder. Moreover, the assessment of environmental exposures and psychopathological symptoms is inherently complex, and the inclusion of additional relevant factors (such as ethnic minority, migration, and pregnancy complications) or refining exposure assessments may enhance the precision of future studies. In conclusion, while our study contributes valuable insights, future research should address these limitations to foster a more comprehensive understanding of the complex interplay between the exposome, psychopathology, and mental health outcomes.

In summary, our findings indicate that the ES may not be specifically associated with the occurrence of PLEs in non-help-seeking individuals. This observation might be informative for future studies on the ES, suggesting that risk stratification, based on cumulative measures, should rather focus on investigating broader mental health outcomes. This is of particular importance as the majority of environmental exposures show non-specific associations with distinct aspects of psychopathology. These findings also hold potential implications from the public health perspective suggesting that comprehensive interven-

tions focused on early-life vulnerabilities might improve outcomes of individuals at risk of developing psychopathology. Reducing the ES might be achieved by targeting modifiable risk factors, e.g., problematic cannabis use. In case of other exposures, e.g., a history of childhood trauma, therapeutic interventions might reduce their long-lasting effects.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/brainsci14030242/s1, Table S1: Questionnaires used to assess psychopathological symptoms; Table S2: Node predictabilities; Figure S1: Bootstrapped differences between edge weights in the network analyzing symptoms associated with the exposome score; Figure S2: Strength centralities; Figure S3: Bootstrapped differences in the strength centrality; Figure S4: Stability of the strength centrality index; Figure S5: Bootstrapped 95% confidence intervals of edge weights.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Bioethics Committee of Wroclaw Medical University, Wroclaw, Poland (approval number: 99/2023, issued on 1 February 2023).

Informed Consent Statement: The necessity to provide a written informed consent was waived by the Bioethics Committee at Wroclaw Medical University (Wroclaw, Poland) due to the survey's anonymous nature.

Data Availability Statement: Data that are the basis of the present study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions.

Conflicts of Interest: The authors declare no conflicts of interest.

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What Came First, Mania or Depression? Polarity at Onset in Bipolar I and II: Temperament and Clinical Course

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Abstract: (1) Background: Bipolar disorder (BD) is divided into type I (BD-I) and type II (BD-II). Polarity at onset (PO) is a proposal to specify the clinical course of BD, based on the type of the first episode at disorder onset—depressive (D-PO) or manic (M-PO). At the same time, affective temperaments represent preexisting variants of the spectrum of affective disorders. Our objectives were to investigate the hypothesis that temperament may exert an influence on PO, and that this factor can serve as an indicator of the forthcoming course of the disorder, carrying significant therapeutic implications. (2) Methods: We included 191 patients with BD and examined clinical variables and temperament; the latter was assessed using the short version of the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego—Auto-questionnaire (TEMPS-A-39-SV). We tested the associations between these variables and PO using standard univariate/bivariate methods followed by multivariate logistic regression models. (3) Results: 52.9% of the sample had D-PO and 47.1% had M-PO. D-PO and M-PO patients scored higher for dysthymic and hyperthymic temperaments, respectively ($p < 0.001$). Also, they differed in BD subtypes, age at first affective episode, illness duration, number of depressive episodes, seasonality, suicide risk, substance use, lithium, and benzodiazepine use ($p < 0.05$). Only BD-II and age at first depressive episode were predictors of D-PO, whereas BD-I, age at first manic/hypomanic episode, and hyperthymic temperament were predictors of M-PO ($p < 0.01$). (4) Conclusions: Our findings point to the importance of carefully assessing temperament and PO in patients with BD, to better predict the clinical course and tailor therapeutic interventions to individual patients' needs.

Keywords: bipolar disorder; polarity at onset; affective temperaments; manic/hypomanic polarity; depressive polarity

1. Introduction

Bipolar disorders (BD) are highly heterogeneous. The heterogeneity of BD has been demonstrated at both the clinical [1] and biological levels [2,3]; interindividual differences have been highlighted in patients with all types of BD. Accounting for heterogeneity allows us to stratify BD into more homogeneous subtypes and to enforce specific interventions and adapt treatment strategies to individual patient needs [4].

Polarity at disease onset (PO) has been suggested to underpin part of the clinical heterogeneity of BD. It refers to the predominant mood state at the beginning of the illness. It serves as a course specifier, indicating whether the initial episodes of the disorder were characterized by mania, hypomania (elevated mood), or depression. Previous studies showed that identifying the polarity at onset is valuable for understanding the trajectory and clinical expression of BD [5–8]. For instance, individuals with a depressive onset may

experience a different course and symptomatology compared to those with a manic or hypomanic onset. Accordingly, the type of episode (depressive or manic) that first occurs in the course of BD may distinguish groups of individuals who differ in the clinical outcome of the illness [5–8]. In addition, polarity at disease onset has also been shown to be a familial trait in BD, with concordance in kin pairs [9]. In a study involving 971 subjects from 507 families identified through sibling pairs with "type-I BD", the authors observed pairs that were concordant for mania at onset. This concordance occurred significantly more frequently than would be expected by chance [9].

Most past studies have explored the association between polarity at disease onset and clinical course, typically in samples comprising individuals diagnosed with "type-I BD" [5–7]. Several lifetime clinical features differed between patients with "type-I BD" according to the type of episode occurring at the onset of the illness. At the beginning of this millennium, Perugi et al. [6] examined polarity at disease onset in a large sample of individuals with "type-I BD". They found that depressive polarity at onset was the most common, accounting for 50% of cases. Overall, the trend in episode polarity over time mirrored the polarity observed at the beginning of the illness. Accordingly, depressive onset was associated with more depressive episodes than manic or hypomanic episodes. Individuals with a depressive onset also exhibited higher rates of rapid cycling and suicide attempts, yet were significantly less prone to the development of psychotic symptoms. The authors supported the existence of distinctive longitudinal patterns in "type-I BD" based on their findings, and these patterns appeared to be associated with the polarity observed at the disease onset. Some years later, Perlis et al. [7] specifically explored the hypothesis that the initial occurrence of a depressive episode rather than a manic episode in BD might indicate a subsequent course characterized by a higher burden of depressive symptoms. The study involved the retrospective analysis of data on the first mood episode polarity from 704 individuals with "type-I BD". Depressive onset was found to be more prevalent among women and those with an earlier onset of the illness. It was significantly linked to a higher number of lifetime depressive episodes and a greater proportion of time spent experiencing depression and anxiety in the year leading up to the study. The authors concluded that the polarity of the first mood episode could be a valuable factor in identifying subsets of patients with BD at risk for a more chronic course. Finally, Forty et al. [5] examined polarity at disease onset in a large, well-characterized sample of patients with "type-I BD". The authors confirmed that the lifetime clinical features significantly associated with a depressive episode at the beginning of the illness were an earlier age at onset, more frequent and more severe depressive episodes, and less prominent lifetime psychotic features.

Only one study examined the clinical profile of both BD subtypes using polarity at disease onset [8] and corroborated the clinical validity of this construct in predicting clinical outcome. Eduard Vieta's group in Barcelona conducted a 10-year follow-up prospective study, gathering data from 300 individuals diagnosed with "type-I BD" and "type-II BD". The sample was divided into two groups based on the polarity of the onset episode. The study revealed that 67% of the patients had a depressive onset. Those with a depressive onset exhibited a more chronic course compared to those with a manic onset, showing a higher number of total episodes and a longer duration of illness. Additionally, patients with a depressive onset experienced a greater frequency of depressive episodes, whereas those with a manic onset had more manic episodes. Depressive onset patients had a higher incidence of suicide attempts, a later onset of illness, fewer hospitalizations, and were less likely to develop psychotic symptoms. Interestingly, the authors discovered that the onset of depression was more common among patients diagnosed with "type-II BD".

Affective temperaments, as conceptualized by Agop Akiskal, represent enduring and stable patterns of emotional reactivity and regulation that influence an individual's overall mood disposition. Akiskal's model, derived from the broader field of temperament in psychology, focuses specifically on emotional traits related to mood disorders [10]. These temperaments, including hyperthymic, depressive, cyclothymic, irritable, and anxious, provide a framework for understanding the predisposition to various affective states.

For example, hyperthymic individuals may exhibit a persistent elevation in mood, while those with a depressive temperament may be prone to sustained periods of low mood. Akiskal's work has significantly contributed to the nuanced understanding of mood disorders, shedding light on the diverse ways individuals experience and express emotions, ultimately aiding in the identification, classification, and treatment of mood-related conditions. The concept of affective temperaments enriches the exploration of the interplay between inherent emotional traits and the development of mood disorders [11].

Interestingly, premorbid temperament types may play an important role in the clinical development of mood episodes, including the direction of affective episodes. As early as 1992, Akiskal proposed that the temperament's polarity appears to shape the phenomenology of affective episodes differentially [12]. Other investigations confirmed this initial speculation [13,14]. In particular, one study concentrated on the connection between temperament and the psychopathological features of mood episodes. It underscored that when temperaments align with the affective episode, the characteristics of the mood episode are more likely to display the same emotional tone [15]. For instance, euphoric mania may be more prevalent in individuals with a predominant hyperthymic temperament, while depressive characteristics may be more common in those with a prevalent depressive temperament [15]. Findings are consistent with the original hypothesis that the presence of different affective temperaments might influence the phenomenology of affective episodes.

Only one study investigated the relationship between polarity at onset and premorbid affective temperament. In a large sample of patients with "type-I BD" authors found a significant association between hyperthymic temperament and manic disease onset [16]. Nevertheless, until now, no investigation has investigated the influence of premorbid affective temperaments on the polarity of disease onset (and vice versa) in a sample encompassing both "type-I BD" and "type-II BD" patients. Affective temperaments may be variably associated with different polarities of disease onset in both subtypes of BD, subsequently influencing the clinical course of the illness.

The purpose of the present study is to bridge this knowledge gap by examining the relationship between the polarity at disease onset, temperament, and the clinical characteristics of the illness in a large cohort of individuals diagnosed with both "type-I BD" and "type-II BD." We hypothesize that the polarity observed at disease onset will serve as an indicator of the subsequent course of BD. Additionally, we expect that the mood polarities observed at the onset of the illness will align with the corresponding premorbid affective temperament in individuals with BD.

2. Materials and Methods

2.1. Participants

Outpatients with DSM-5 diagnoses of "type-I BD" (BD-I) and "type-II BD" (BD-II) were recruited at the Psychiatry Department of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome, Italy. Diagnosis was confirmed using the Structured Clinical Interview for DSM-5 [17]. Diagnostic interviews were conducted by trained assessors with demonstrated high interrater reliability (k = 0.87). By implementing stringent inclusion and exclusion criteria, the study aimed to ensure a representative and reliable sample for the investigation. In addition to a DSM-5 diagnosis of BD, inclusion criteria were as follows: (a) age 18–65 years; (b) at least 5 years of education; (c) fluency in Italian; (d) at least 6 months of stable pharmacotherapy for BD. Exclusion criteria were: (a) a history of psychosis unrelated to the primary mood disorder; (b) traumatic brain injury with loss of consciousness; (c) major medical or neurological conditions; (d) a Mini-Mental State Examination (MMSE) score [18] of less than 24 (since scores below this level indicate cognitive deterioration based on normative data from the Italian population); (e) current substance use disorder. Based on the above inclusion/exclusion criteria, we enrolled 191 patients in this study. The sample size was considered appropriate based on previous studies in the field [19,20].

The study conformed to the Principles of Human Rights, as adopted by the World Medical Association at the 18th WMA General Assembly in Helsinki, Finland, in June 1964 and subsequently amended at the 64th WMA General Assembly in Fortaleza, Brazil, in October 2013. All participants gave written informed consent to participate in the study after receiving a full explanation of the study procedures and objectives. Patients received no financial compensation for this study. The commitment to ethical standards, as reflected in adherence to the World Medical Association's principles, underscored the importance of safeguarding participant rights and well-being throughout the research process. The thoroughness of diagnostic procedures and ethical safeguards contributes to the robustness and reliability of the study's findings, enhancing the scientific and ethical integrity of the research endeavor. The study was approved by local ethics committees.

2.2. Assessment

A semi-structured interview, employed in prior studies [21], was utilized for comprehensive data collection on anamnestic characteristics and clinical information, with a specific focus on the polarity at disease onset (PO). Administered by an experienced psychiatrist, this interview adhered to DSM criteria and clinical assessments, steering clear of simplistic yes/no responses to ensure nuanced insights. Question wording was adaptable for clarity, and the final evaluation incorporated inputs not only from the patients but also from family members/close friends (who were consistently present for at least one visit) and relevant medical records.

All gathered data, spanning family history, psychiatric background, and current psychiatric status, were meticulously entered into preprinted medical records. Following established conventions [8], patients were classified as having a "depressive PO" (D-PO) if the initial episode was depressive, and as "manic/hypomanic PO" (M-PO) if the first-occurring episode was manic or hypomanic. The utilization of a hetero-administered interview approach, coupled with the inclusion of collateral information from various sources, contributes to the robustness and depth of the collected data, enhancing the validity of the study's findings.

Affective temperaments (cyclothymic, depressive, irritable, hyperthymic, and anxious) were assessed using the short, 39-item version of the validated Italian Temperament Evaluation of Memphis, Pisa, Paris and San Diego—Auto-questionnaire (TEMPS-A-SV) [22]. This instrument is widely used in research and has shown good psychometric properties and optimal factor structure [23]. The original TEMPS-A scale comprises a total of 110 items, with each of the five temperament dimensions represented by about 20 items each. For our study we used the shorter version, validated in Italian, known as the TEMPS-A Short Version (TEMPS-A-SV), which includes a subset of items from the full scale [22]. The TEMPS-A-SV is designed for a more time-efficient assessment while still capturing essential information about an individual's temperament. This shortened version consists of 39 items, providing a streamlined yet effective tool for evaluating the five temperament dimensions. The distribution of items across the dimensions in the TEMPS-A-SV is generally proportional to the full version, allowing for a quick but reliable analysis of cyclothymic, hyperthymic, depressive, irritable, and anxious traits. This abbreviated version is often employed in settings where a more concise evaluation is needed, making it a versatile option for both research and clinical purposes [22].

The test–retest reliability of the TEMPS-A ranged from 0.58 for the irritable, to 0.68 for the cyclothymic, to 0.69 for the dysthymic, and 0.70 for the hyperthymic temperament in the valedictory study [24]. The instrument showed an excellent internal consistency, with Cronbach's α ranging from 0.76 for the dysthymic to 0.88 for the cyclothymic temperament in the same study. In another study with the short version, Cronbach's α was 0.72 for the cyclothymic, 0.71 for the depressive, 0.69 for the irritable, 0.54 for the hyperthymic, and 0.62 for the anxious temperament, while for the entire construct it was 0.80 [25]. For the TEMPS-A-SV, Cronbach's α was 0.79 (95% Confidence Intervals (C.I.s) from 0.76 to 0.82) for the cyclothymic, 0.72 (95% C.I.s from 0.68 to 0.76) for the depressive, 0.72 (95% C.I.s from

0.68 to 0.76) for the irritable, 0.75 (95% C.I.s from 0.71 to 0.78) for the hyperthymic, and 0.71 (95% C.I.s from 0.66 to 0.75) for the anxious temperament [22]. Reliability estimates were 0.93 for the cyclothymic, 0.92 for the irritable and the depressive, 0.91 for the hyperthymic, and 0.87 for the anxious temperament [22].

2.3. Statistical Analyses

To meet our objectives, we divided our sample into two groups: patients with D-PO and patients who reported M-PO. Variables were reported as percentages or means ± SD as appropriate. We initially tested differences in sociodemographic and clinical characteristics across the two groups using standard univariate/bivariate comparisons of continuous measures (ANOVA) and categorical measures (contingency table/χ^2). The same type of analysis has been used to assess differences in TEMPS-A-SV mean values between the two groups. Mean differences were reported using Cohen's d as effect size measure.

In addition, we regressed all the factors that were significantly associated with D-PO and M-PO in bivariate analyses on PO, in a multivariate logistic regression with PO as the dependent outcome measure, together with age and sex, in order to consider demographic differences [26].

Where appropriate, we investigated possible multicollinearity between the variables of interest using the variance inflation factor (VIF) indicator obtained from linear regression analysis. Analyses were performed using the statistical routines of SPSS Statistics 24.0 for Windows (IBM Co., Armonk, NY, USA). All statistical tests used a significance level of $p < 0.05$.

3. Results

In the total group of patients, 101 (52.9%) had depressive polarity (D-PO) at onset and 90 (47.1%) had manic/hypomanic polarity (M-PO) at onset. The sociodemographic and clinical characteristics of the sample are shown in Table 1.

Table 1. Sociodemographic and clinical characteristics of the sample according to polarity onset (n = 191).

	Depression at Onset (n = 101)	**Mania at Onset (n = 90)**	***F* or χ^2**	**df**	***p***
Socio-demographic and lifestyle characteristics					
Age, y—mean ± SD	45.54 ± 13.21	42.42 ± 11.52	2.99	1	0.085
Gender, males—*n* (%)	41 (40.6)	49 (54.4)	3.66	1	0.056
Married partner—*n* (%)	50 (49.5)	39 (43.3)	0.73	1	0.393
Children—*n* (%)	56 (55.4)	40 (44.4)	2.30	1	0.129
Smoking, yes—*n* (%)	46 (45.5)	46 (51.1)	0.59	1	0.442
Substance use, lifetime—*n* (%)	23 (22.8)	33 (36.7)	4.43	1	**0.035** *
Clinical variables					
Diagnostic status—*n* (%)					
BD I	48 (47.5)	64 (71.1)	10.92	1	**0.001** **
BD II	53 (52.5)	26 (28.9)			
Age first depressive episode, y—mean ± SD	27.20 ± 11.86	30.77 ± 10.60	4.37	1	**0.038** *
Age first manic episode, y—mean ± SD	34.87 ± 13.56	29.74 ± 10.97	7.81	1	**0.006** **
Duration of illness, y—mean ± SD	17.30 ± 11.97	13.58 ± 9.98	5.36	1	**0.022** *
Past depressive episodes—mean ± SD	6.36 ± 6.21	3.63 ± 3.37	13.71	1	**<0.001** ***

Table 1. *Cont.*

	Depression at Onset (*n* = 101)	Mania at Onset (*n* = 90)	*F* or χ^2	df	*p*
	Clinical variables				
Past manic/hypomanic episodes—mean ± SD	5.53 ± 6.70	4.74 ± 4.41	0.90	1	0.343
Family history of psychiatric disorders—*n* (%)	72 (71.3)	62 (68.9)	0.13	1	0.718
Seasonality—*n* (%)	33 (32.7)	44 (48.9)	5.20	1	**0.023** *
Switch—*n* (%)	38 (37.6)	29 (32.2)	0.61	1	0.435
Hospitalizations—*n* (%)	53 (52.5)	59 (65.6)	3.36	1	0.067
Suicidality—*n* (%)	68 (67.3)	48 (53.3)	3.91	1	**0.048** *
	Medications use				
Antipsychotics—*n* (%)	64 (63.4)	56 (62.2)	0.27	1	0.870
Antiepileptics—*n* (%)	56 (55.4)	48 (53.3)	0.086	1	0.770
Lithium—*n* (%)	51 (50.5)	59 (65.6)	4.42	1	**0.036** *
Benzodiazepines—*n* (%)	53 (52.5)	26 (28.9)	10.92	1	**0.001** **

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; df, degrees of freedom; *p*, significance level; SD, standard deviation; *n*, number of observations; y, years.

3.1. Univariate and Bivariate Analyses

Univariate/bivariate analyses revealed that patients with D-PO and M-PO differed significantly in the following clinical characteristics: Bipolar Disorder subtypes, age at first depressive episode, age at first manic/hypomanic episode, illness duration, number of past depressive episodes, seasonality, lifetime suicide risk, lifetime substance use, use of lithium and benzodiazepines. Also, they differed in the presence of dysthymic and hyperthymic temperament (Table 2, Figure 1).

Specifically, patients with D-PO were more frequently diagnosed as "type-II BD" (d = 0.49), reported a younger age at first depressive episode (d = 0.32), longer duration of illness (d = 0.34), more past depressive episodes (d = 0.54), higher lifetime suicide risk (d = 0.30), more benzodiazepine use (d = 0.49), and higher scores for dysthymic temperament (d = 0.40).

Conversely, patients with M-PO were frequently diagnosed as "type-I BD" (d = 0.49), reported a younger age at first manic/hypomanic episode (d = 0.41), reported greater seasonality (d = 0.34), lifetime substance use (d = 0.31), higher lithium use (d = 0.31), and higher scores for hyperthymic temperament (d = 0.53).

Table 2. Differences in TEMPS-A-SV scores (mean ± SD) according to polarity at onset.

	Depression at Onset (*n* = 101)	Mania at Onset (*n* = 90)	*F* or χ^2	df	*p*
Cyclothymic	5.19 ± 3.67	4.58 ± 3.41	1.41	1	0.237
Dysthymic	3.60 ± 2.48	2.64 ± 2.37	7.43	1	**0.007** **
Irritable	1.66 ± 1.78	1.65 ± 1.83	0.00	1	0.996
Hyperthymic	2.92 ± 2.41	4.14 ± 2.14	13.65	1	**<0.001** ***
Anxious	1.45 ± 1.21	1.27 ± 1.17	0.96	1	0.329

** $p < 0.01$; *** $p < 0.001$; df, degrees of freedom; *p*, significance level; SD, standard deviation; TEMPS-A-SV, Temperament Evaluation of Memphis, Pisa, Paris and San Diego—Auto-questionnaire, 39 item.

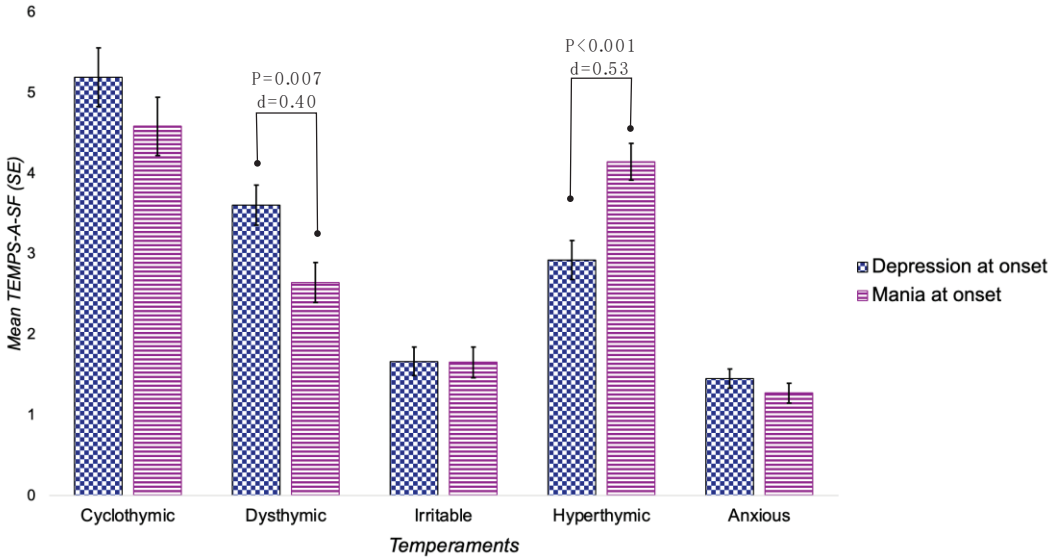

Figure 1. Histograms showing differences in TEMPS-A-SV scores (mean ± SE) according to polarity at onset. *p*, significance level; d, Cohen's d (effect size).

3.2. Multivariate Logistic Regression

Multivariate logistic regression revealed that "type-II BD" (Wald = 5.60; $p = 0.01$ OR: 3.39; 95% Confidence Interval [95%CI]: 1.23–9.35) and age at first depressive episode (Wald = 22.28; $p < 0.001$; OR: 0.41; 95%CI:0.29–0.60) were associated with D-PO, whereas "type-I BD" age at first manic/hypomanic episode (Wald = 21.72; $p < 0.001$, OR: 0.46; 95%CI: 0.33–0.64), and hyperthymic temperament (Wald = 8.12; $p = 0.004$; OR: 1.41; 95%CI: 1.11–1.79) were associated with M-PO (Table 3). The model explained 69% (Nagelkerke R^2) of the variance in PO. There was no significant multicollinearity, as indicated by the fact that the VIF of the variables of interest was <2.

Table 3. Multivariate logistic regression analyses.

	OR	95%CI	Wald	*p*
	D-PO			
Type-II BD	3.39	1.23–9.35	5.60	**0.01** *
Age at first depressive episode	0.41	0.29–0.60	22.28	**<0.001** ***
	M-PO			
Type-I DB	3.39	1.23–9.35	5.60	**0.01** *
Age at first manic/hypomanic episode	0.46	0.33–0.64	21.72	**<0.001** ***
Hyperthymic temperament	1.41	1.11–1.79	8.12	**0.004** **

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; df, degrees of freedom; *p*, significance level; SD, standard deviation; TEMPS-A-SV, Temperament Evaluation of Memphis, Pisa, Paris and San Diego—Auto-questionnaire, 39 item.

4. Discussion

This is the first study to examine the relationship between temperament and polarity at disease onset (PO) as a clinical course specifier of BD. The results confirmed our original hypothesis; we showed that PO can impact the clinical course of BD and is influenced by premorbid affective temperament. Specifically, temperament seems to align with the type of episode that initially occurs in bipolar disorder. Consistently, we observed a higher frequency of depressive onset (D-PO) in patients with a dysthymic temperament and a more frequent manic/hypomanic onset (M-PO) in patients with a hyperthymic temperament. Notably, multivariate analyses underscore hyperthymic temperament as a significant risk factor for M-PO.

These findings align with initial observations indicating a positive correlation between the number of manic episodes in BD and hyperthymic temperament, while depressive episodes were linked to dysthymic temperament [25]. Further studies have substantiated this relationship, particularly within the framework of the "predominant polarity" construct developed by Eduard Vieta's group [27]. This construct delineates the prevailing direction of mood episodes throughout an individual's illness history, indicating a predominance of either manic or hypomanic episodes, or depressive episodes. Different predominant polarities correlate with distinct clinical characteristics. With respect to temperamental traits, Azorin and colleagues noted that patients with predominantly manic recurrences exhibit a stronger hyperthymic temperament compared to those with depressive predominant polarity [28]. In parallel, earlier research has established a specific connection between the construct of predominant polarity and PO, suggesting that the direction of the first episode in the illness often aligns with the more frequently occurring episode direction [29,30]. In our study, we build upon these observations, indicating a potential association between temperament, PO, and the predominant polarity of the impending illness. This highlights a risk continuum from temperamental traits to the clinical course of BD.

Our data may also align with recent biological findings in BD. A recent review highlighted that polarity at onset is among the familial traits observed across generations of BD patients [31]. The study specified that individuals with BD were more likely to exhibit the same polarity of mood episodes (i.e., depressive, manic, or mixed) at the onset of illness as their affected relatives. In parallel, previous evidence has underscored that all temperament theories presume a biological basis for individual differences, with moderate genetic influences demonstrated in twin and adoption studies [32]. Given the enduring nature of temperament as a "trait" and its stability across the lifespan, the association we demonstrated with polarity at onset in patients with BD could serve as a link between phenotypic presentation and genetic vulnerability. However, further longitudinal studies are essential to elucidate and confirm this initial observation.

Our data confirmed that PO influences the clinical course of BD and suggest the existence of two distinct "phenotypes" of the disease: one with D-PO, dysthymic (depressive) temperament, "type-II BD" diagnosis, younger age at first depressive episode, longer duration of illness and higher suicide risk; the other with M-PO, hyperthymic temperament, "type-I BD" diagnosis, younger age at first manic/hypomanic episode, higher seasonality, more frequently treated with lithium. These results are in line with what emerged from a recent large study on the characterization of patients with BD, that confirmed the clinical relevance of disease onset phenotypes [33].

In our sample, depressive onset emerged as the most prevalent phenotype, constituting at least 50% of the initial presentations, a pattern consistent with prior research [5–8]. Clinical features associated with depressive onset (D-PO) align with the existing literature, encompassing a higher frequency of depressive episodes and an extended duration of illness [ibidem]. These findings echo earlier studies emphasizing that the clinical course of bipolar disorder (BD) tends to be less severe and recurrent in patients primarily experiencing mania/hypomania compared to those primarily presenting with depression [21,31]. They underscore the importance of early prevention strategies for patients presenting with depressive symptoms [32,34].

In line with previous reports [29,33,35], our study also identified an elevated risk of suicide in patients with D-PO. This observation may indirectly correlate with other studies where a dysthymic (depressive) temperament was identified as a risk factor for suicide, while a hyperthymic temperament was deemed protective [36]. The higher prevalence of benzodiazepine use in the D-PO group might be explained in relation to temperament, suggesting that the use of anxiolytics could be an attempt by patients to manage depressive or anxious temperamental traits, as previously proposed [37].

The second clinical phenotype identified in this study involved patients who initially presented with mania/hypomania. Results revealed that individuals with manic/hypomanic onset (M-PO) reported higher lifetime substance use and greater use of lithium. The former

is unsurprising, given the common occurrence of substance use during manic/hypomanic episodes [30], which also aligns with the prescription of lithium. Additionally, long-term responsiveness to lithium has been positively associated with the hyperthymic temperament and negatively associated with other temperament types [34]. Furthermore, our findings indicated that patients with M-PO reported higher seasonality than those with depressive onset (D-PO). This contrasts with previous research suggesting that patients with depressive onset are more susceptible to seasonal changes [38]. Nevertheless, our results are in line with recent data indicating that patients with BD-II exhibit less seasonality than those with BD-I [1]. In our sample, patients with BD-I predominantly had M-PO, while those with BD-II had D-PO [39], supporting the consistency of our results. Additional studies are required to further elucidate this point.

Our study showed a strong relationship between PO and BD subtypes, with D-PO associated with "type-II BD" and M-PO associated with "type-I BD". This is in line with Daban and colleagues, who specifically aimed to define the clinical profile of both "type-I BD" and "type-II BD" using PO [8], and with very recent data from Brancati and colleagues [36]. Our findings are consistent with those of authors showing that BP-I tends to have more manic episodes, whereas BP-II tends to be more chronic and depressive episodes predominate [29]. Multivariate analyses also showed that patients with D-PO are younger at their first depressive episode, while patients with M-PO are younger at their first manic/hypomanic episode. This is further strengthened by the finding that first depressive recurrences occur earlier in BD-II, whereas first (hypo)manic recurrences occur earlier in BD-I [40]; so it appears that the course of BD can be predicted by the direction of its polarity at the outset, with age being a moderator of the course. Furthermore, episodes at a lower age at the beginning of BD bear the same sign that could be expected from belonging to the BD-I or to the BDI-II diagnostic group. Interestingly, in our sample, the D-PO group reported their first manic episode on average 7.67 $\pm$ 1.7 years after their first depressive episode. These results confirm that the BD diagnosis must be considered even when patients present with a depressive episode that is not immediately followed by mania/hypomania. Previous studies have shown that the interval between the first depressive episode and mania/hypomania can be very long and varies greatly from patient to patient [41,42]. This variability could be explained by the delay in BD diagnosis, which is mainly due to the difficulty in recognizing mania/hypomania compared to depression, and its consequent treatment with antidepressants. The difficulty, rather than the ability of a given physician to diagnose each condition, is likely due to the tendency of patients to refer to the healthcare system. In fact, while patients feeling depressed are likely to consult a physician, those feeling elated are unlikely to do so. Accordingly, an average of 8 years elapses between a patient's first episode and a correct BD diagnosis [8]. On the other hand, in the M-PO group, the first depressive episode occurs on average 1.03 $\pm$ 0.37 years after the first manic episode. This seems to confirm the hypothesis of the primacy of mania proposed by Athanasios Koukopoulos, according to which depression is a consequence of mania [43–45]. "Mania is the fire and depression is its ashes", he used to state frequently. Koukopoulos' primacy of mania hypothesis received biological support [45] and has considerable implications for what concerns the use of antidepressant medications in the depressive phase of BD [46]. In fact, the current trend is to provide a basis of mood stabilization before adding an antidepressant for bipolar depression [47,48].

When it comes to treatment implications, we have to bear in mind that a depressive polarity onset coupled to depressive, irritable, cyclothymic, and anxious temperaments may expose patients to a switch to the opposite polarity when exposed to antidepressants, and that the latter should always be administered with mood stabilizers [48]. Conversely, in patients experiencing manic polarity onset, a combination of antipsychotic medications and mood stabilizers is frequently required to effectively address the symptoms present during the initial stages of the illness [49].

Before presenting our conclusions, we must point out some issues that might limit the generalizability of our results. The cross-sectional nature of our study limits our ability to

confirm our predictions. Further longitudinal studies are needed to extend our original speculations. In addition, the retrospective nature of the study may have led to uncontrolled recall bias. To minimize the risk of recall bias, we adopted a detailed semi-structured interview based not only on patient reports but also on information from family members and close friends (who were present for at least one visit) and on all available medical records. Finally, one of the defects of our approach was that we classified initial episodes as either depressive or manic/hypomanic and failed to categorize episodes with mixed features as mixed, but we rather pooled them along the manic ones. This represents an inherent limitation of polarity at onset (PO) as a course specifier, as outlined in the original construct [8].

5. Conclusions

Summarizing our evidence, we have shown that differences in temperament predisposition, especially in the hyperthymic affective temperament trait, influence the polarity of the first-occurring episode of BD. Using a large sample of patients with either "type-I BD" or "type-II BD", we confirmed our initial hypothesis that PO is congruent with the respective premorbid affective temperament. Accordingly, the systematic assessment of premorbid affective temperaments may play a crucial role in confirming whether the initial episodes of the disorder were characterized by mania, hypomania (elevated mood), or depression. These findings hold the potential to validate the subtyping of BD based on first-episode polarity and can contribute significantly to tailoring specific prevention and treatment strategies. Future studies could employ both polarity at onset and affective temperaments and be longitudinal in design.

In addition, our findings on the effects of PO on the clinical course of BD point to the need for improved prevention and treatment systems. In patients with depressive onset, who often present with a higher suicidal risk, different pharmacological treatments may be considered compared to those with manic/hypomanic onset, who tend to exhibit more pronounced seasonality and substance use. Tailoring treatments based on these distinct clinical characteristics can enhance the effectiveness and safety of pharmacological interventions, thereby addressing the specific needs of each patient subgroup and avoiding possible side effects. Furthermore, our study underscores the significance of simultaneously considering both "type-I BD" and "type-II BD". We highlight that these subtypes exhibit distinct clustering patterns based on polarity at disease onset, and accordingly they manifest varying clinical characteristics.

Neurobiological studies could further help delineate subtypes of patients according to PO, with the goal of refining early intervention strategies and better characterizing the heterogeneity of BD.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to data availability, all used data are available after request to the authors, because they are stored in protected datasets in our institution.

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brain sciences

MDPI

Article

Elevated Plasma Levels of Mature Brain-Derived Neurotrophic Factor in Major Depressive Disorder Patients with Higher Suicidal Ideation

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Abstract: Several pieces of evidence show that signaling via brain-derived neurotrophic factor (BDNF) and its receptor, tropomycin receptor kinase B (TrkB), as well as inflammation, play a crucial part in the pathophysiology of depression. The purpose of our study was to evaluate plasma levels of BDNF-TrkB signaling, which are inflammatory factors in major depressive disorder (MDD) patients, and assess their associations with clinical performance. This study recruited a total sample of 83 MDD patients and 93 healthy controls (CON). All the participants were tested with the Hamilton Depression Scale (HAMD), the Beck Scale for Suicide Ideation, and the NEO Five-Factor Inventory. The plasma level of selected BDNF-TrkB signaling components (mature BDNF (mBDNF), precursor BDNF (proBDNF), tyrosine kinase B (TrkB), and tissue plasminogen activator (tPA)) and selected inflammatory factors (interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)) were measured using an enzyme-linked immunosorbent assay (ELISA). Further, we performed correlation analysis to indicate the relationship between the plasma levels of the factors and clinical characteristics. Results: (i) A higher level of mBDNF and lower openness were observed in MDD patients with higher suicidal ideation than patients with lower suicidal ideation. (ii) In MDD patients, mBDNF was positively correlated with the sum score of the Beck Scale for Suicide Ideation (BSS). (iii) The levels of mBDNF, tPA, IL-1 β and IL-6 were significantly higher in all MDD subjects compared to the healthy controls, while the levels of TrkB and proBDNF were lower in MDD subjects. Conclusion: Our study provides novel insights regarding the potential role of mBDNF in the neurobiology of the association between depression and suicidal ideation and, in particular, the relationship between BDNF-TrkB signaling, inflammatory factors, and clinical characteristics in MDD.

Keywords: BDNF-TrkB signaling; inflammatory factors; suicidal ideation; Beck Scale; major depressive disorder

1. Introduction

Today, the total number of people suffering from major depressive disorder (MDD) is about to exceed 322 million globally [1]. The years of life lost due to disability (YLD) caused by depressive disorders has reached 43,099,000 (95% CI: 3,053,600–58,895,600), and the years of life lost due to depression have increased by 33.4% (95% CI: 31.0–35.8) compared to 1990 and by 14.3% (95% CI 13.1–15.6) compared to 2007 [2]. MDD is ranked by the World Health

Organization (WHO) as the single largest contributor to global disability [3]. MDD as a syndrome has a range of symptoms and varies greatly in its course, symptomatology, and clinical outcome, leading to difficulties in treatment and mechanistic study [4]. In addition, the WHO has estimated that the overall international suicide rate is 10.6/100,000/year, accounting for 1.5% of all deaths [5]. However, there is no single model or mechanism that could explain all aspects of MDD satisfactorily, including suicidal behavior, attempts, or ideation.

Brain-derived neurotrophic factor (BDNF) is the most well-studied neurotrophin and has been implicated in the pathogenesis of various psychiatric disorders, including MDD. Both mature BDNF (mBDNF) and its precursor, proBDNF, play key parts in neuronal survival, morphogenesis, and plasticity. Via differential engagement with their receptors, they work in a largely opposed manner [6,7]. Despite this, proBDNF could be converted to mBDNF via intracellular and extracellular proteases, and the plasminogen tPA (tissue plasminogen activator)/plasmin system is the most crucial protease involved in this process [8]. mBDNF exerts biological effects on neurons by binding to its receptor tyrosine kinase B (TrkB), which subsequently elicits various intracellular signaling pathways, including mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK), causing oxidative stress and inflammation in depression [9,10]. proBDNF binds with high affinity to the p75 pan-neurotrophin receptor and is then implicated in depression and anxiety [11,12]. Multiple pieces of evidence indicate that BDNF metabolism is deleteriously altered in MDD patients as well as in animal models. However, the changes in the role of BDNF in depression are still elusive. Indeed, several studies have reported decreased BDNF levels in MDD patients [13,14], while others have demonstrated that BDNF levels were higher in MDD patients [15,16]. In addition, there have also been studies that have shown no significant difference in BDNF levels between MDD patients and controls [17]. One reason for these diverging results may be that most of the abovementioned research failed to differentiate mBDNF and proBDNF, or, due to the limitations of the kits available at the time, they might have included both forms of BDNF [18]. A recent study reported lower levels of serum and exosomal BDNF and higher levels of proBDNF in MDD subjects compared to controls, which indicates that mBDNF and proBDNF have different serum expression profiles [19]. According to the above, the expression of BDNF in MDD patients requires more elaborate analyses that include MDD patients with different characteristics.

Over the past years, there has been increasing evidence indicating that abnormalities in immune-inflammatory pathways and the activation of cell-mediated immunity represent important pathophysiological pathways that could contribute to the development of MDD [20–22]. Additionally, mounting experimental and clinical research has provided support for the psycho-neuro-inflammatory hypothesis. Several studies based on animals have found elevated concentrations of pro-inflammatory cytokines—IL-6, IL-1β, and TNF-α (interleukin-6, interleukin-1β, and tumor necrosis factor-α, respectively)—as well as anti-inflammatory cytokines in both the central and peripheral nervous systems in various rodents' stress paradigms, namely the chronic mild stress (CMS) [23–26], social isolation [27,28], learned helplessness [29], olfactory bulbectomy (OB) [30], and social defeat [31,32] models of depression. Elsewhere, researchers have shown that a rapid antidepressant effect of ketamine is related to the downregulation of pro-inflammatory factors (IL-1β, IL-6, and TNF-α) in the hippocampus of rats [33]. Clinical studies have also found a significant association between numerous pro-inflammatory cytokines and depressive symptoms. MDD patients have been found to have increased concentrations of pro-inflammatory cytokines and acute-phase proteins, including IL-1, C-reactive protein (CRP), and monocyte chemoattractant protein-1, compared to non-depressed individuals [34–36]. Several meta-analyses have revealed elevated peripheral levels of IL-6 in MDD patients compared with controls, while the results for IL-1β and TNF-α differ among studies [37–40]. Taken together, the aforementioned results provide compelling evidence indicating the involvement of inflammatory factors in MDD.

However, there are currently no appropriate animal models to explain suicidal behavior. Hence, we started with MDD patients and the hypothesis that the expression levels of BDNF and immune factors in peripheral blood may be related to suicidal ideation in MDD patients. Additionally, the aim of the present study was to evaluate plasma levels of BDNF-TrkB signaling and inflammatory factors in medically stable, currently untreated MDD patients and assess their associations with clinical performance. We first suggested the correlation between mBDNF and suicidal ideation. The levels of pro-inflammatory factors (IL-1β, IL-6, and TNF-α) and factors involved in BDNF-TrkB signaling (mBDNF, proBDNF, TrkB, and tPA) in the peripheral blood of MDD and healthy controls were also examined to investigate the function of inflammation and BDNF signaling in MDD patients.

2. Materials and Methods

2.1. Subjects

In total, 83 unipolar MDD subjects were enrolled. All patients were admitted to the Department of Psychiatry, the First Affiliated Hospital, Zhejiang University School, for inpatient treatment. Their diagnoses were determined through the Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fifth revision (DSM-V) and were confirmed by two expert psychiatrists. Healthy controls (CON) were recruited by clinical referrals, newspaper advertisement, and bulletin board notices. Control subjects had no history of any DSM-V axis disorder, which was also confirmed by clinical interview. All subjects had to have been free of any psychotropic medication for at least three months and exhibit a stable status. The demographics, including age, sex, education, and illness duration, are presented in Table 1.

Table 1. Demographic and clinicopathological information of the included subjects.

Characteristic	MDD + HSI (*n* = 43)	MDD + LSI (*n* = 40)	CON (*n* = 93)	*p*
% Males (*n*)	37.2 (16)	35.0 (14)	43.0 (40)	0.638
Age (y), mean (SD)	26.44 (6.77)	27.98 (6.94)	27.58 (7.69)	0.566
Education (y), mean (SD)	14.21 (2.24)	14.88 (1.77)	14.92 (1.81)	0.194
Illness duration (m), mean (SD)	2.45 (2.92)	1.86 (2.05)		0.970
Relapse time (*n*)	1.53 (0.86)	1.42 (0.89)		0.321
Onset age (y)	24.35 (6.94)	25.97 (6.26)		0.272
HAMD-17 score, mean (SD)	24.53 (4.70)	23.48 (4.18)	2.28 (2.53)	<0.001 [ab]
Anxiety/somatization, mean (SD)	8.30 (1.94)	7.26 (1.90)	1.11 (1.31)	<0.001 [abc]
Cognitive disorder, mean (SD)	5.58 (1.43)	3.75 (1.72)	0.13 (0.37)	<0.001 [abc]
Psychomotor retardation, mean (SD)	7.49 (1.88)	7.58 (1.78)	046 (0.93)	<0.001 [ab]
Sleep disorder, mean (SD)	3.56 (1.59)	3.38 (1.58)	0.38 (0.90)	<0.001 [ab]
Weight, mean (SD)	0.65 (0.90)	0.48 (0.85)	0.05 (0.31)	<0.001 [ab]
Neuroticism, mean (SD)	41.12 (6.74)	42.10 (6.05)	27.02 (6.61)	<0.001 [ab]
Extraversion, mean (SD)	28.23 (7.62)	30.65 (6.74)	40.11 (6.44)	<0.001 [ab]
Conscientiousness, mean (SD)	38.14 (7.94)	38.80 (7.12)	43.56 (5.49)	<0.001 [ab]
Agreeableness, mean (SD)	40.56 (5.84)	42.15 (5.54)	43.28 (4.62)	0.023 [ab]
Openness, mean (SD)	35.05 (6.89)	38.03 (5.25)	39.19 (4.89)	0.001 [abc]

Abbreviations: HAMD-17, the 17-item Hamilton Depression Scale; HSI, high suicidal ideation; LSI, low suicidal ideation; m, month; MDD, major depressive disorder; *n*, number; SD, standard deviation; y, year. [a] Indicates a statistically significant difference ($p < 0.05$) between the CON and MDD + HSI groups. [b] Indicates a statistically significant difference ($p < 0.05$) between the CON and MDD + LSI groups. [c] Indicates a statistically significant difference ($p < 0.05$) between the MDD + HSI and MDD + LSI groups.

Subjects were excluded if they: (1) had a current pregnancy; (2) had another current psychosis or a history of bipolar disorder or psychotic symptoms that existed outside a major depressive episode; (3) had an eating disorder or post-traumatic stress disorder (PTSD) within one month of entering the study; (4) presented alcohol or drug dependence or abuse within six months of entering the study; (5) had a history of neurological disorders, such as cerebral trauma, seizure disorder, or MRI evidence of structural brain abnormalities; (6) were MDD patients who had received any form of treatment prior to the study; (7) had

medical illnesses that could be etiologically related to the ongoing depressive episode, such as acute infections, chronic inflammatory disorders, untreated hypothyroidism, uncontrolled hypertension, or diabetes; (8) refused to participate in the study. These criteria are also presented in Table 2.

Table 2. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
• MDD diagnosis	• Current pregnancy
• Free of any psychotropic medication for at least three months	• Other current psychosis or a history of bipolar disorder or psychotic symptoms
• In a stable state	• Eating disorder or post-traumatic stress disorder (PTSD)
	• Alcohol or drug dependence or abuse
	• Neurological disorder history
	• MDD patients who had received any form of treatment prior to the study
	• Medical illnesses that could be etiologically related to the ongoing depressive episode
	• Subject refused to participate in the study

2.2. Symptom Assessment

The depression status of all the subjects was quantified using the 17-item Hamilton Depression Scale (HAMD-17). The suicide item 3 was regarded as the rating for suicidal ideation (SI), which has been previously reported as an effective measure for suicidal ideation [41]. SI ratings ranged from 0 to 4, with scores ≥ 3 defined as a relatively high degree of SI (HSI) and scores < 3 as a relatively low degree of SI (LSI) [42]. Moreover, the HAMD-17 was divided into five structural factors (anxiety/somatization, cognitive disorders, psychomotor retardation, and sleep and weight disorders), which was performed to better assess the depression symptoms.

In addition, we used the Beck Scale for Suicide Ideation (BSS) to measure the current intensity of the patients' specific attitudes, behaviors, and plans that were connected to suicidal behavior for the past week [43]. Internal reliability, test-retest stability and validity for the BSS have been established [44]. The severity of suicidal ideation was evaluated by summing the ratings of the first 19 items. Items 20 (prior suicide attempts) and 21 (severity of the suicide attempt) were not included in the total score. The sum score of the BSS ranged from 0 to 38 points. In our study, the Chinese version of the BSS was used.

The NEO-Five Factor Inventory (NEO-FFI) was used to assess personality characteristics, which is a shortened version of the NEO Personality Inventory-Revised [45]. It consists of 60 items and measures the main Big Five domains: Neuroticism (easily upset, maladjusted), Extraversion (energetic, assertive, talkative), Conscientiousness (responsible, dependable, orderly), Agreeableness (good-natured, cooperative, trusting) and Openness (imaginative, independent-minded, intellectual) [45,46]. The statement of each subject is rated based on a 5-point Likert scale, ranging from "strongly disagree" to "strongly agree". Sum scores on each separate domain range from 12 to 60.

2.3. Measurements

All the subjects underwent a peripheral venous blood draw between 08:00 and 10:00 am. The samples were collected in anticoagulant-free tubes and immediately centrifuged for 20 min at a speed of 3000 r/min to obtain patients' plasma. Plasma samples were then separated and stored at −80 °C until future analysis. ELISA kits were used to measure plasma levels. The details of all the ELISA kits were as follows: mBDNF (DBD00—R&D Systems, Minneapolis, MN, USA); tPA (DTPA00—R&D Systems, Minneapolis, MN, USA); and IL-1β (ab214025—Abcam, Cambridge, MA, USA). Plasma proBDNF, TrkB, TNF-α, and IL-6 levels were estimated using a DuoSet human ELISA kit (proBDNF: DY3175; TrkB: DYC397; TNF-α: HSTA00E; IL-6: HS60DC—R&D Systems, Minneapolis, MN, USA) combined with a DuoSet ELISA Ancillary Reagent kit (DY008—R&D Systems, Minneapolis, MN, USA). Based on the manufacturers' instructions, we determined the concentration of factors in each sample. The results are exhibited in pg/mL. All the experiments were performed in duplicate.

2.4. Data Analysis

For normally distributed continuous variables, we present the data as mean ± standard deviation, while for non-normally distributed continuous variables, data are shown as median ± interquartile range. Comparisons between two groups were conducted using Students's *t*-tests or the Mann–Whitney U test according to variance analysis. Comparisons among three groups were first conducted with the Kruskal–Wallis (K-W) test. If a significant difference was obtained, a comparison between the two groups was then carried out using the Mann–Whitney U test. Correlation analysis was performed to discover the relationship between the plasma levels of the factors and the clinical characteristics. All statistical analyses included in the study were carried out using the Statistical Package for the Social Sciences (SPSS) version 22.0 with significance at a p value < 0.05.

2.5. Ethics

This study was carried out in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Our work was approved by the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. 2016029), and we obtained written informed consent from each subject or their family members (for the severe depression study) before their involvement in the study.

3. Results

3.1. Demographic and Clinical Characteristics

We divided all the subjects into three groups, namely healthy controls (CON), MDD with lower suicidal ideation (MDD + LSI), and MDD with higher suicidal ideation (MDD + HSI). All the demographic and clinical characteristics of the recruited subjects are exhibited in Table 1. There were no significant between-group differences regarding age, sex, and years of education or significant differences in illness duration, relapse time, and onset age between groups with high or low suicidal ideation.

HAMD-17 scores including the five structural factors were significantly different between the MDD and CON groups, with both MDD groups scoring higher than the CON groups. The scores for the "anxiety/somatization" and "cognitive disorder" structural factors were higher in the MDD + HSI group than the MDD + LSI group ($p = 0.026$ and $p < 0.001$). Higher neuroticism and lower extraversion, conscientiousness, agreeableness, and openness were observed in both MDD groups compared to the healthy controls (all $p < 0.023$). Further, lower openness was found in the MDD + HSI group compared with the MDD + LSI group ($p = 0.024$).

3.2. Increased mBDNF in MDD Patients with High and Low Suicidal Ideation

Table 3 shows the changes in different plasma peptides for the three groups. The levels of mBDNF, tPA, IL-1β, and IL-6 were significantly elevated in all MDD subjects compared to the healthy controls (Table 3, Figure 1). Meanwhile, the levels of TrkB and proBDNF were lower in the MDD subjects. There was no statistically significant difference in TNF-α levels among the three groups (Table 3, Figure 1). Further analysis revealed a significant difference in serum mBDNF levels between the MDD + HSI and MDD + LSI groups (8900.82 ± 5488.47 vs. 6157.71 ± 2965.86 pg/mL, respectively, $p = 0.010$, Figure 1). Moreover, we found a positive link between mBDNF and the Beck Scale sum score for MDD patients (rho = 0.299, $p = 0.006$, Figure 2).

Table 3. Plasma peptide levels (pg/mL) in MDD patients with high and low suicidal ideation and healthy controls.

Plasma Peptide	MDD + HSI (n = 43)	MDD + LSI (n = 40)	CON (n = 93)	p	ES (HSI vs. LSI)	ES (HSI vs. CON)	ES (LSI vs. CON)
mBDNF, mean (SD)	8900.82 (5488.47)	6157.71 (2965.86)	3508.85 (3590.37)	<0.001 [abc]	0.30	0.50	0.37
proBDNF, mean (SD)	2011.14 (2317.79)	1076.08 (1643.96)	3236.87 (2832.83)	<0.001 [ab]	0.23	−0.23	−0.42
TrkB, mean (SD)	5620.79 (1350.27)	5721.11 (1201.44)	6435.37 (1387.59)	<0.001 [ab]	−0.04	−0.29	−0.27
tpA, mean (SD)	1865.83 (945.97)	1986.40 (780.20)	1526.29 (767.85)	<0.001 [ab]	−0.07	0.19	0.28
IL-1β, mean (SD)	722.32 (341.67)	847.86 (877.17)	295.25 (125.54)	<0.001 [ab]	−0.09	0.64	0.40
IL-6, mean (SD)	783.01 (500.53)	996.71 (711.76)	712.08 (521.99)	0.021 [ab]	−0.17	0.07	0.22
TNF, mean (SD)	473.34 (216.04)	532.12 (196.36)	533.93 (286.75)	0.492	−0.14	-0.12	−0.00

Abbreviations: HSI, high suicidal ideation; LSI, low suicidal ideation; m, month; MDD, major depressive disorder; mBDNF, mature brain-derived neurotrophic factor; proBDNF, precursor brain-derived neurotrophic factor; SD, standard deviation; TNF, tumor necrosis factor; tpA, tissue plasminogen activator; TrkB, tropomyosin receptor kinase B. [a] Indicates a statistically significant difference ($p < 0.05$) between the CON and MDD + HSI groups. [b] Indicates a statistically significant difference ($p < 0.05$) between the CON and MDD + LSI groups. [c] Indicates a statistically significant difference ($p < 0.05$) between the MDD + HSI and MDD + LSI groups.

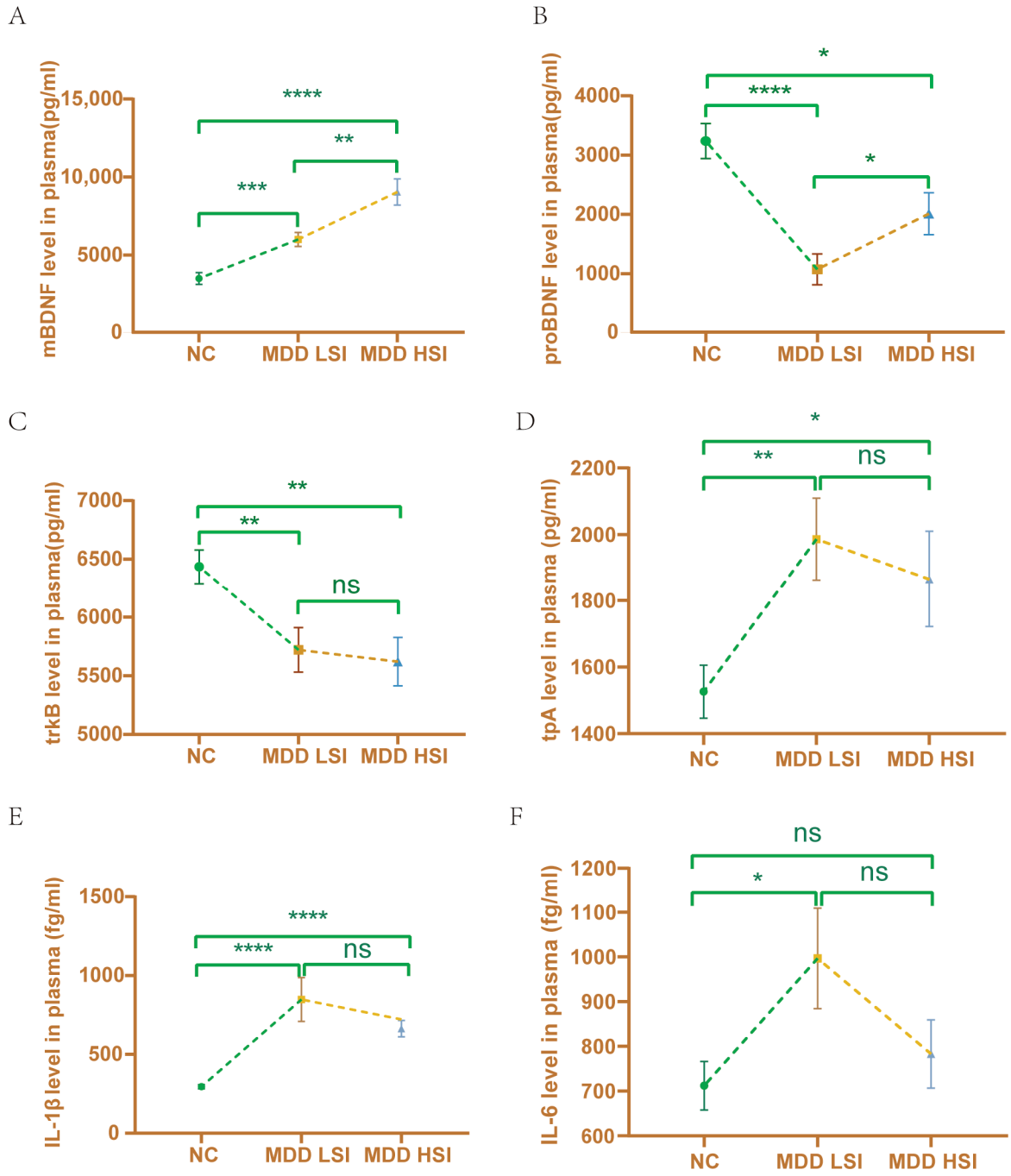

Figure 1. Changes in plasma peptide levels among patients with different suicidal ideation levels and healthy controls. (**A**) The levels of mBDNF were higher in MDD patients (7578.84 ± 4638.34 pg/mL) compared to controls (3508.85 ± 3590.37 pg/mL) (*** $p < 0.001$, ** $p < 0.01$, **** $p < 0.0001$), and there were significant differences between the plasma mBDNF levels in the MDD + HSI and MDD + LSI groups (8900.82 ± 5488.47 vs. 6157.71 ± 2965.86 pg/mL, * $p = 0.010$). (**B**,**C**) The levels of TrkB and proBDNF were lower in MDD subjects compared to healthy controls (5669.14 ± 1273.94 pg/mL vs. 6435.37 ± 1387.59 pg/mL, *** $p < 0.001$; 1560.51 ± 2063.48 pg/mL vs. 3236.87 ± 2832.83 pg/mL, * $p < 0.05$, ** $p < 0.01$,*** $p < 0.001$, **** $p < 0.0001$). (**D**–**F**) The levels of tPA, IL-1β, and IL-6 were significantly higher in all MDD subjects compared to healthy controls (1923.93 ± 866.90 pg/mL vs. 1526.29 ± 767.85 pg/mL, *** $p < 0.001$; 782.82 ± 655.53 fg/mL vs. 295.25 ± 126.54 fg/mL, *** $p < 0.001$; 886.00 ± 617.10 fg/mL vs. 712.08 ± 521.99 fg/mL, * $p < 0.05$, ** $p < 0.01$,*** $p < 0.001$, **** $p < 0.0001$).

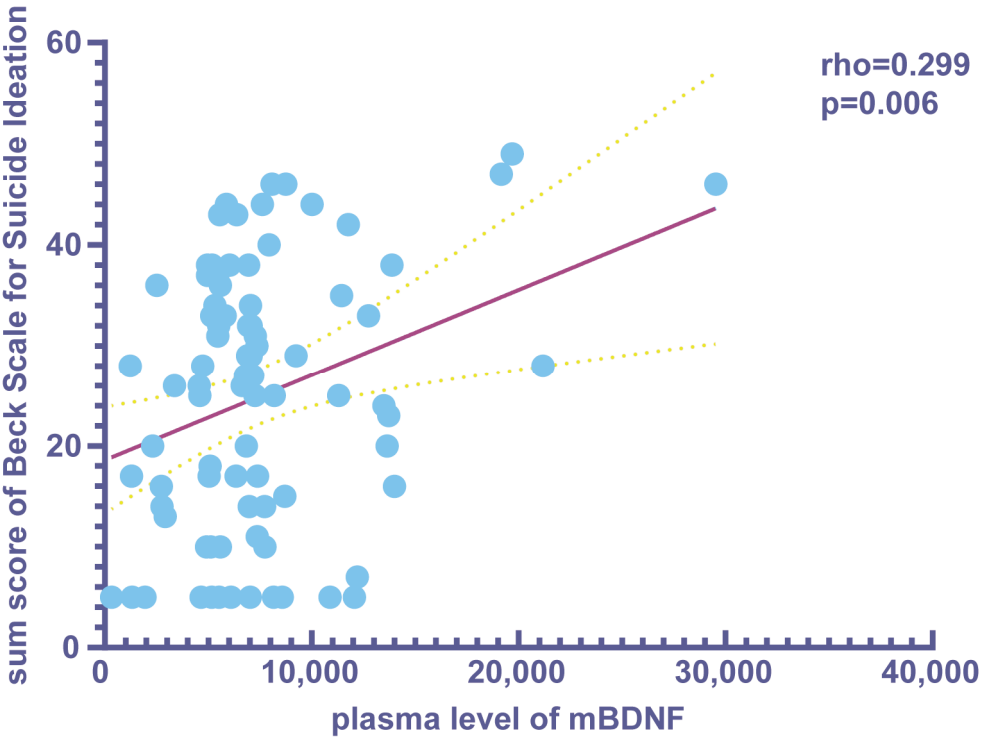

Figure 2. Correlations between plasma peptide levels and clinical characteristics in MDD patients: a positive correlation was found between mBDNF and the Beck Scale sum score for MDD patients.

4. Discussion

In the present study, we found that the mBDNF level was correlated with the level of suicidal ideation in MDD patients. For unmedicated subjects with MDD, the mBDNF levels were remarkably greater in those who had higher suicidal ideation than those with lower suicidal ideation. In MDD patients, the mBDNF level in the peripheral plasma was positively correlated with the Beck Scale scum score for suicide ideation. In addition, compared with control subjects, the plasma levels of mBDNF, tPA, and IL-1β were higher in MDD patients. However, the levels of TrkB and proBDNF were decreased in MDD patients.

Depression, which has high heterogeneity, features various clinical symptoms and drug sensitivities and could increase suicide risk independently. The lifetime prevalence of suicide in MDD patients is about 2–12% [47]. This shows that MDD is accompanied by a 20-fold elevated risk of suicide [48]. In addition, 15% of patients with MDD in the community have reported a suicide attempt at least once in their lifetime [49]. However, the etiology between suicide and MDD remains elusive and complex. Many risk factors have been regarded as stimulators of the risk of suicidal behavior (attempt or ideation), such as biological, psychological, and environmental factors.

Many studies have demonstrated that BDNF is implicated in the pathophysiology of MDD, and it is one of the main biomarkers proposed in association studies with suicide [50–52]. A recent study identified that the BNDF signaling pathway participates in resilience to stress [53]. Therefore, BDNF is a vital link in the pathogenesis of depression. In this study, the levels of plasma biological factors related to BDNF metabolism were analyzed, including mBDNF, proBDNF, TrkB, and tpA, in MDD patients with relatively high suicidal ideation compared to those with relatively low suicidal ideation and healthy controls. Previous studies have mainly focused on plasma/serum BDNF levels, but the results have differed. Several studies have shown that lower levels of BDNF are linked with a higher risk of suicide attempts and ideation or suicide behavior in MDD patients [54–56]. A recent meta-analysis showed that plasma but not serum BDNF levels were decreased in patients who had attempted suicide [57]. There were some mixed results reporting no

significant association between BDNF and suicide in MDD individuals [58–60]. However, in the present study, we found that high levels of mBDNF were related to high suicidal ideation. It has been reported that BDNF may undergo some mutation or methylation in MDD, which influences its expression and effects in real conditions [61,62]. Thus, the mutation of BDNF in MDD may be one of the reasons for these differences. Another reason for our study's data being inconsistent with those of most of the studies mentioned above may lie in the sample size and the standard of classification. Furthermore, our sample was composed of inpatients from a clinical ward whose suicidal ideations were evaluated immediately after drawing blood. Finally, the BDNF metabolism-related factors were measured near to the time of suicidal ideation and could be represented more effectively. In other studies, researchers have included patients with a lifetime history of suicide attempts, though BDNF measurements could not represent the levels at the time of the attempt [63]. Thus, the relationship between BDNF and suicide in MDD patients still requires deeper exploration.

However, some limitations existed in our study. First of all, our sample size was relatively small and thus could have limited statistical power to some extent. Second, the level of peripheral factors we measured could not exactly replicate the exact level of the factors in the brain. Taking BDNF as an example, peripheral BDNF has an indefinite relationship with BDNF levels in the central nervous system [55,57]. Third, other potential variables that could influence the levels of biomarkers such as exercise, genetic polymorphism, and smoking habits were not considered in this study, which could have caused bias [15,64,65]. In the future, repeating our study with a larger sample size and more detailed information on the participants would strength the findings. In addition, our study was a cross-sectional study, and therefore it was very difficult to indicate whether mBDNF associations with suicidal ideation were "state" or "trait" markers in the research sample.

In summary, this study first found a correlation between mBDNF levels and suicidal ideation. At the same time, the differences between mBDNF and proBDNF levels and their correlation with suicidal ideation in MDD patients were verified and analyzed, suggesting that serum BDNF levels may be used as a biomarker reflecting suicidal ideation in MDD patients to a certain extent. In addition, our findings also confirmed the presence of BDNF signaling-pathway-related factors (tPA, TrkB) and several major immune factor (IL-1β, IL-6, and TNF-α) abnormalities in the peripheral blood of MDD patients.

5. Conclusions

Overall, our data suggest that mature BDNF might be involved in the biological mechanisms of suicide ideation in MDD. Compared with healthy controls, the plasma levels of mBDNF, tPA, and IL-1β were higher in MDD patients, which indicates that inflammation is involved in the pathogenesis of depression. However, the levels of TrkB and proBDNF were decreased in MDD patients, indicating that multiple signaling pathways are implicated in MDD, with a complex pathology. In short, our study provides novel insights regarding the relationship between BDNF-TrkB signaling, inflammatory factors, and clinical characteristics in MDD, especially the possible role of mBDNF in the neurobiology of the connection between depression and suicidal ideation.

Author Contributions: M.H. was responsible for the concept and design of the study. H.L. and M.Z. performed most of the analyses, wrote most of the manuscript, and created most of the tables and figures. C.J., H.Z., Y.L., S.Z., P.X. and C.W. contributed to data acquisition and analysis. C.J., T.M. and Y.X. were in charge of the investigation of the participants. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was carried out in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Our work was approved by the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. 2016029).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

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Coping as a Mediator between Attachment and Depressive Symptomatology Either in Pregnancy or in the Early Postpartum Period: A Structural Equation Modelling Approach

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Abstract: Peripartum depression (PPD) is a major complication of pregnancy, and numerous risk factors have been associated with its onset, including dysfunctional coping strategies and insecure attachment styles, both during pregnancy and postpartum. The aim of our study was to investigate the role of coping strategies in mediating the relationship between women's attachment style and depressive symptomatology in pregnancy and one week after giving birth in a large sample of women (N = 1664). Our hypothesis was that the relationship between anxious and avoidant attachment and depressive symptomatology would be mediated by use of maladaptive coping strategies. The assessment instruments were Edinburgh Postnatal Depression Scale (EPDS), Brief Coping Orientation for Problem Experiences (COPE), and Experiences in Close Relationship Scale (ECR). The results indicated that the effect of insecure attachment styles (anxious and avoidant attachment) on antepartum depressive symptomatology was partially mediated by dysfunctional coping styles. Anxious attachment also has an indirect significant effect on postpartum depressive symptomatology through emotional coping; however, avoidant attachment does not seem to be significantly related to postpartum depressive symptoms. Our findings revealed that not only is it important to consider attachment in understanding peripartum depressive symptomatology, but also that coping plays an important role in these relationships. These findings would help a preventive coping-based intervention strategy to enhance the capacity of women with insecure attachment styles to use more adaptive coping during and after pregnancy.

Keywords: perinatal depression; attachment style; coping strategies; gender medicine; structural equation modelling

1. Introduction

Major depressive disorder with peripartum onset is the most common complication of childbearing. Estimates show that one in seven women can experience peripartum depression (PPD) occurring during pregnancy or after childbirth [1,2]. A wide range of factors have been consistently identified as important risk factors that interact to contribute to the development of depressive symptomatology, including genetic predisposition, and various environmental, social, and psychological factors including negative personality traits (e.g., neuroticism, insecure attachment styles) and ineffective coping strategies (e.g., denial, substance use) [3–5].

Coping is described as the cognitive and behavioral strategies that people may use to deal with stressful circumstances that are demanding, challenging, threatening, and/or have a potential for harm or loss [6]. Growing evidence suggests that maladaptive coping strategies (e.g., emotional coping, denial) may be risk factors for depressive mood during both antenatal [7,8] and postnatal period; while adaptive coping strategies (e.g., acceptance, humor) tend to be protective factors for PPD [3,8–10]. For instance, a recent large prospective study of 1626 women reported that maladaptive coping strategies such as substance use, self-distraction, and self-blame were positively associated with major postpartum depression [11]. Contrastingly, women who have positive coping styles that involve actively solving problems and positively interpreting situations were less likely to have perinatal depressive symptoms [12–15]. In recent years, research has also shown that coping with stressful conditions to ensure proper psychological adjustment does not operate in isolation. Rather, coping strategies appeared to mediate the relationship between personality traits and depressive symptomatology [11,12,16].

Preparation and transition to motherhood is considered a stressful experience that demands several adjustments to a new role and new responsibilities, which clearly triggers the attachment system throughout pregnancy and beyond [17]. The attachment system is an innate behavioral system that is biologically driven to promote survival through relational closeness. According to attachment theory, the infant's early experiences with caregivers determine internal working models of attachment (a set of mental representations of the self and others) which influence the individual's future attachment behaviors in intimate relationships, including adult romantic relationships and parenting [18–21]. When a caregiver is seen as being trustworthy and accessible, an infant establishes a secure attachment style. In contrast, in situations where the primary caregiver is perceived as being unavailable and/or unresponsive, an infant develops a negative internal working model and an insecure style of attachment [22]. Researchers have identified two types of insecure attachments in adults: anxious attachment and avoidance attachment. The nature of anxious attachment is distinguished by an overly active attachment mechanism that results in an ongoing quest for reassurance and consolation. On the other hand, avoidant attachment is defined by a less active attachment mechanism, leading to an ongoing suppression of needs related to psychological and social connections. This also promotes an excessive reliance on oneself and cultivates a negative disposition towards others [23]. Several studies have shown that insecure attachment styles are associated with depressive symptoms in adulthood [24–26]. Particularly, many previous studies have consistently shown that insecure attachment styles are strong and independent predictors of depression symptomatology either during pregnancy or in the period following birth (see for review [4,27]). For instance, Bianciardi et al. [5] found that insecure attachment styles were associated with depressive symptoms during both antenatal and early postpartum phases. However, many scholars have questioned the direct path between attachment and depression, and instead, they argue that early attachment experiences do influence later psychological distress through different intermediate mechanisms such as coping strategies [28–30]. Over the past few decades, research has provided extensive evidence suggesting that the coping strategies that individuals employ in stressful situations are determined, at least in part, by their attachment style [29,31]. Securely attached persons tend to rely on active coping styles (e.g., support-seeking coping strategies) and to maintain acceptable psychological well-being during stressful periods (e.g., [32–34]).

In contrast, individuals with avoidance or anxiety attachment styles have been found to appraise stressful events in threatening terms and report doubts about their coping abilities [35]. For instance, Schmidt et al. [36] found insecure attachment to be related to less flexible coping, with anxiously attached individuals showing more negative emotional coping (e.g., impulsivity and distortion) and avoidantly attached individuals showing more disengaging methods of coping (e.g., denial, tendency to avoid awareness of problems).

Despite many previous studies reporting a significant relationship between attachment styles and coping strategies, a mediational model to explore how coping might mediate the

link between attachment and perinatal depressive symptomatology has not been performed. Insights from attachment theory and behavioral neuroscience are not just theoretically interesting, but they have significant implications when applied to patients dealing with depressive disorders that occur during the perinatal period. Recognizing potential factors like coping mechanisms, which mediate the connection between attachment and depression, could enhance treatment results. This can be achieved by choosing therapies based on attachment that target either insecure attachment styles or the maladaptive coping methods linked to these styles.

Coping styles were originally divided into two high-order dimensions: problem-focused coping styles and emotion-focused coping styles [37]. However, there are many ways to group coping responses. An important distinction is between problem-focused (e.g., active coping, planning), emotion-focused coping (e.g., support seeking, emotion regulation), and disengagement coping, which includes maladaptive coping strategies such as avoidance, denial, and wishful thinking [38–41]. However, in the existing literature, uniformity is lacking in terms of how coping strategies are grouped to form higher-order factors. More research is necessary to ascertain the suitable factor structure, contingent upon the context [42]. Considering that higher-order strategies, including emotion-focused coping and maladaptive coping, have been found to consist of other lower-order coping strategies, it would be preferable to conduct individual factor analyses and determine the factor structure in the context of peripartum depressive symptomatology, instead of relying on previous factors that have already been defined [29]. Thus, in the present study, two steps are envisaged. First, we use exploratory and confirmatory factor analysis (CFA) to investigate the factor structure of the coping. Second, we examine the role of coping strategies in mediating the relationships between insecure attachment styles and depressive symptomatology in both the antepartum and postpartum periods. In this regard, structural equation modelling (SEM) analysis is a suitable statistical method to evaluate the extent to which a third intermediate or mediating variable (coping) explains the effect of a predictor (e.g., attachment insecurity) on an outcome (e.g., depressive symptoms) [43].

Depression is significant at each stage but most reported in the second half of pregnancy and early postnatal period [44,45] The present study aimed to examine the relationship of coping strategies, attachment styles, and symptoms of depression that occur in the late pregnancy period (third trimester) and within early postpartum period (day 1–7) as previously reported [45]. Based on the literature revised, we hypothesized that (a) both anxious and avoidant attachment scores, respectively, would be significantly associated with dysfunctional coping strategies; and (b) the relationship between anxious and avoidant attachment and perinatal depressive symptomatology would be mediated by the use of dysfunctional maladaptive coping strategies.

2. Materials and Methods

The data of this study were collected as part of a previous longitudinal study that assessed the prevalence and risk factors of perinatal depression among pregnant women attending, from July to November 2020, maternal health clinics in three major public hospitals (Ospedali Riuniti di Foggia, Ospedale Vito Fazi di Lecce, and Ospedale Di Venere di Bari) of the Regione Puglia (Italy) [46]. The inclusion criteria were being a woman over the age of 18 and in the third trimester of pregnancy. The exclusion criteria included intellectual disability and poor knowledge of language which undermined the possibility of the woman participating in the research protocol. All the participants were given verbal and written explanations of the purpose of the study, and their informed consent was obtained prior to their participation in the study. During the study period, 1664 eligible women were enrolled and assessed during the third trimester of pregnancy (t0). The same cohort was followed up one week after delivery (t1) [47,48]. Sociodemographic characteristics, attachment styles, and coping strategies were assessed during the first visit (t0). The characteristics of patients with and without depression were subjected to an analysis using descriptive analysis. T-test was applied for continuous data.

2.1. Edinburg Postnatal Depression Scale

The validated Italian version of the Edinburgh Postnatal Depression Scale (EPDS) [49,50] was administered twice, once during the antenatal visit and again during a postnatal follow-up. The EPDS was initially configured by Cox et al. [51] to detect the level of maternal depressive symptoms present in the first weeks after childbirth and, consequently, to identify women at psychopathological risk through a clinical interview. Subsequent studies have validated the EPDS for use in the perinatal period (during pregnancy and postpartum). The Edinburgh Postnatal Depression Scale (EPDS) is a tool comprising 10 items created specifically to screen for peripartum depressive symptomatology. Its use for the detection depressive symptoms in both antepartum and postpartum samples has been extensively adopted [52–54]. Items are scored from 0 to 3 while total scores range from 0 to 30 with higher scores reflecting a more severe form of depression. We administered the Italian language version of EPDS which constitutes a valid tool for detecting maternal antenatal and postnatal depressive symptomatology with acceptable internal consistency and test–retest reliability [49,55]. In numerous validation studies, cut-off points have varied. It is important to recognize that the optimal EPDS cut-off scores change considerably during different phases of the peripartum period [56,57]. Many international studies have reported an optimal cut off score of the $\geq$12/13 in late pregnancy [51,57,58]. However, as suggested by Dennis [59], a cut-off score $\geq$ 9 is normally used in order to identify patients with depressive symptomatology in the early post-partum period [48,59,60]. Therefore, in this paper, we choose to use EPDS cut-off scores of $\geq$12 and $\geq$9, respectively, in the assessment for antepartum depressive symptomatology and for depressive symptoms in the immediate postpartum period; our aim is to make the findings comparable with both local and international studies. The EPDS t0 and t1 showed internal consistency (Cronbach's alpha values were 0.78 and 0.79, respectively).

2.2. Experiences in Close Relationship Scale

The Experiences in Close Relationship Scale (ECR) is one of the most used self-report instruments for the assessment of adult attachment and has been widely adopted in previous studies assessing attachment as a risk factor for antenatal and postpartum depression [23,61,62]. The ECR comprises 36 items, and they are scored on a seven-point Likert scale, with 1 corresponding to "disagree strongly" and 7 corresponding to "agree strongly". It is composed of two subscales, namely attachment anxiety (concerning rejection or abandonment), and attachment avoidance (of intimacy and interdependency in close relationships) [60]. We employed the Italian version of the ECR [63], which was used in previous Italian studies on the relationship between attachment patterns and perinatal depression [64,65]. In the current study, the internal consistency was good (Cronbach's alpha 0.78).

2.3. Coping Orientation for Problem Experiences

Coping strategies were assessed with the brief Coping Orientation for Problem Experiences (COPE) which consists of 14 scales: active coping, planning, behavioral disengagement, self-distraction, seeking emotional support, seeking instrumental support, venting of emotions, positive reframing, humor, acceptance, denial, religion, substance use, and self-blame [42]. The model developed by Carver et al. [37] consists of three types of coping strategies: emotion-focused coping, problem-focused coping, and avoidant coping. Problem-focused coping strategies that are aimed at changing the stressful situation include active coping, seeking instrumental support, planning, and positive reframing. Emotion-focused coping strategies that are aiming to regulate emotions associated with the stressful situation include venting of emotions, seeking emotional support, humor, acceptance, self-blame, and religion. The third type of coping, avoidance-focused coping, which indicates physical or cognitive efforts to disengage from the stressors, includes self-distraction, denial, substance use, and behavioral disengagement [66,67]. We used the Italian language version developed by Conti [68]. This scale was previously used in a sample of Italian mothers to study the link between coping

and postpartum depressive symptoms [69]. The internal consistency of the total Brief COPE was high (Cronbach's was alpha 0.85).

2.4. Data Analysis

Statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS), version 26.0, and AMOS, version 22.0. The data were scanned for missing values and possible multivariate outliers via the Mahalanobis distance, with a criterion of $p < 0.001$ to remove the participants. The skewness and kurtosis were used to examine the distribution of the data. The linear association between attachment styles and stress coping strategies was examined by Pearson's correlation. We used logistic regression analysis to evaluate the relationship between independent variables including medications, medical condition during pregnancy, complications during pregnancy, and family history (FH) of psychiatric disorders on binary dependent variables (t0: EPDS $\geq$ 12 or t1: EPDS $\geq$ 9), respectively, in two different periods: pregnancy and postpartum.

Inflation variance (VIF) and tolerance factors were used to assess multiple alignment between variables. We conducted a second-order exploratory factor analysis (EFA) on the subscales of the Brief COPE in two different periods (pregnancy and postpartum) in order to reduce the number of factors and create a more specific model of coping strategies. A confirmatory factor analysis (CFA) was performed to validate the results of the EFA. Our main hypotheses were tested using structural equation modelling (SEM) to assess the mediating role of the different higher-order coping strategies in the relationship between attachment and perinatal depression at t0 and t1. Following the recommendations of Schreiber et al. [70], we used the criteria of the Comparative Fit Index, the Root Mean Square Error of Approximation (RMSEA), the Standardized Root Mean Square Residual (SRMR), and the minimum discrepancy per degree of freedom (CMIN/DF) to analyze the fit of the models. As recommended in SEM literature [71], alternative models were also tested to eliminate alternative explanations. To confirm the presence of mediation, bootstrapping, with 5000 bootstrap samples, was used to calculate the total, direct, and indirect effects of the predictors (attachment styles) on the outcome variables (perinatal depression). The total, direct, and indirect effects are reported as estimates with 95% confidence intervals. The level of statistical significance was set at $p < 0.05$.

3. Results

According to the EPDS score $\geq$ 12, 14.1% of the women (234/1664) suffered from depressive symptomatology in pregnancy, and according to the EPDS score $\geq$ 9, 18.5% (309/1664) in the postpartum period. Additionally, 19.4.6% (60/309) of women who had antepartum depressive symptoms were found to have postpartum depressive symptomatology. Missing values and cases found to be outliers were excluded from the analyses, leaving the antepartum total sample in 234 and the postpartum total sample in 287/1351 participants. The descriptive statistics of the study samples are illustrated in Table 1.

Differences between women with and without major depressive symptoms according to the EPDS scores in all analyzed variables in the antepartum and postpartum phase are reported in Table 2. Therefore, women with depression scored significantly higher in measurements of anxiety and avoidant attachment. Coping strategies of adaptive value, most frequently observed in women without depression, were those focused on acceptance of their situation, during both the prenatal and postnatal stages. The coping strategies that were most frequently associated with depression were denial, venting of emotion, self-blame, seeking emotional support, and behavioral disengagement.

The results of Pearson's correlations between attachment styles and coping strategies are reported in Table 3. The highest correlation was between avoidant attachment and anxious attachment. In the prenatal phase, anxious attachment was also positively correlated with seeking emotional support and dysfunctional coping strategies such as denial, self-blame, venting of emotion, and behavioral disengagement; avoidant attachment was positively correlated with seeking instrumental support, denial, behavioral disengagement,

and substance use. An examination of coping strategies during the postnatal stage also provides substantial insights. Anxious attachment was positively correlated with seeking emotional support, seeking instrumental support, venting of emotion, denial, behavioral disengagement, self-blame, religion, and substance use; avoidant attachment was correlated with behavioral disengagement, denial, and substance use.

Table 1. Characteristics of women with either antepartum or early postpartum depressive symptomatology.

	Antepartum (*N* = 234)	**Postpartum (*N* = 287)**
Age (mean, SD)	32.2 (5.9)	32.9 (5.2)
Educational Level (%)		
Primary school	1 (0.42)	1 (0.34)
Secondary school	37 (15.8)	34 (11.8)
Post-Secondary school	116 (49.5)	155 (54.0)
Higher education	79 (33.7)	96 (33.4)
Parity (primiparous) (%)	111 (47.4)	151 (52.6)
Marital status (%)		
Married or paired	230 (98.2)	286 (99.6)
Some medical condition during pregnancy (%)	64 (27.3)	85 (29.6)
Complication during pregnancy (%)	154 (65.8)	278 (96.8)
Family history of psychiatric problems (%)	147 (62.8)	141 (49.1)
Medications		
Corticosteroid	2 (0.85)	5 (1.74)
Insulin	21 (8.97)	25 (8.71)
Levothyroxine	26 (11.1)	38 (13.2)
Antihypertensives	1 (0.42)	10 (3.48)
Anticoagulants	8 (3.41)	10 (3.48)
Anxiolytics	13 (5.55)	13 (4.52)
Others	14 (5.98)	14 (4.87)

Table 2. Coping strategies in women with or without postpartum depressive symptomatology. Mean (SD).

	Antepartum w/Depressive	**Antepartum w/o Depressive**	**Postpartum w/Depressive**	**Postpartum w/o Depressive**
	Symptoms (N = 234)	Symptoms (N = 1430)	Symptoms (N = 287)	Symptoms (N = 1351)
Age	32.2 (5.95)	32.4 (5.43)	32.9 (5.17)	32.3 (5.54)
EPDS	14.4 (2.57)	5.17 (3.23) ***	11.7 (2.93)	3.98 (2.15) ***
Anxious Attachment	57.2 (21.6)	39.3 (16.7) ***	52.0 (21.0)	39.3 (16.8) ***
Avoidant Attachment	38.7 (18.0)	28.5 (12.1) ***	33.7 (15.1)	28.8 (12.7) ***
Coping Strategies				
Active Coping	6.38 (6.71)	6.71 (1.38) *	6.53 (1.34)	6.71 (1.38)
Seeking informational support	5.73 (1.60)	5.31 (1.59) **	5.52 (1.53)	5.34 (1.59)
Planning	6.12 (1.439)	6.45 (1.46) ***	6.29 (1.31)	6.44 (1.47)
Positive Reframing	5.73 (1.51)	6.20 (1.45) **	6.01 (1.31)	6.17 (1.48)
Venting of emotions	5.46 (1.509	4.84 (1.73) **	5.25 (1.43)	4.86 (1.75) ***
Seeking emotional support	5.58 (1.64)	4.84 (1.01) **	5.28 (1.61)	4.87 (1.63) ***
Humor	4.00 (1.53)	4.29 (1.33) *	4.61 (1.38)	4.29 (1.35)
Acceptance	6.06 (1.42)	6.27 (1.34) *	6.04 (1.27)	6.28 (1.35) **
Self-blame	5.76 (1.48)	4.95 (1.43) **	5.52 (1.42)	4.96 (1.44) ***
Religion	5.12 (2.05)	4.87 (2.00)	5.21 (1.91)	4.85 (2.01) **
Self-distraction	5.67 (1.54)	5.20 (1.61) **	5.51 (1.47)	5.22 (1.62) **
Denial	4.05 (1.69)	3.11 (1.33) **	3.68 (1.46)	3.14 (1.39) **
Substance use	2.21 (0.87)	2.05 (0.43) *	2.03 (0.21)	2.07 (0.52)
Behavioral disengagement	3.65 (1.57)	2.81 (1.16) **	3.27 (1.35)	2.83 (1.20) ***

EPDS = Edinburgh Postnatal Depression Scale. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

Table 3. Correlation coefficients between attachment styles and stress coping strategies.

	Antepartum		**Postpartum**	
	(*N* = 234)		**(*N* = 287)**	
	Anxious	**Avoidant**	**Anxious**	**Avoidant**
Anxious Attachment		0.463 **		0.373 **
Avoidant Attachment	0.463 **		3.73 **	
Active Coping	−0.002	−0.186 **	0.044	−0.073
Positive Reframing	−0.126	−0.120	−0.208 **	−0.199 **
Planning	−0.015	−0.032	−0.073	−0.149 *
Humor	−0.101	−0.046	−0.095	0.018
Acceptance	−0.129 *	−0.064	−0.168 *	−0.128 *
Seeking emotional support	0.228 *	−0.091	0.321 **	0.051
Seeking instrumental support	0.043	−0.201 **	0.167 **	−0.111
Behavioral disengagement	0.225 **	0.223 **	0.117 *	0.202 **
Self-distraction	0.023	−0.015	0.077	0.102
Self-blame	0.270 **	−0.078	0.209 **	0.090
Venting of emotions	0.188 **	−0.047	0.244 **	0.056
Denial	0.231 **	0.143 *	0.238 **	0.197 **
Religion	0.083	−0.103	0.125 *	0.003
Substance use	−2.22 **	0.135 *	0.158 *	0.169 **

* $p < 0.05$; ** $p < 0.01$ (two tailed).

Logistic regression analyses were used to examine the role of risk factors on depressive symptomatology. The first logistic regression showed that family history of psychiatric disorders was related to EPDS $\geq$ 12 during pregnancy ($\beta = 0.8216$, $p < 0.001$) and to EPDS $\geq$ 9 ($\beta = 0.7043$, $p < 0.001$) in the postpartum period. Furthermore, additional t-test analyses showed that significant differences in coping strategies between women with family history and women without family history of psychiatric disorders. Women with a FH of mental illness exhibited higher utilization of maladaptive avoidant coping strategies (i.e., behavioral disengagement, denial, self-distraction, and substance use) compared with women without FH of mental disorders during either pregnancy or post-partum period (all, $p < 0.05$).

3.1. Exploratory Factor Analysis

An EFA on the subscales of the Brief COPE was performed in two different periods (pregnancy and postpartum) using a principal component analysis and varimax rotation. Eigenvalues of 1.0 were used to determine the number of components extracted. The minimum factor loading was set to 0.50 [72]. The factor solution derived from the EFA in participants with antenatal depressive symptomatology yielded three distinct second-order factors, which accounted for 59.048 percent of variation in the data. No items showed cross-loadings of 0.50 or above on more than one factor. Barlett's test of Sphericity, which indicates whether the correlations in the data are sufficiently strong to use a dimension-reduction technique such as principal components analysis, was significant (χ^2 (55) = 657.564; $p < 0.001$) [73]. The Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy, which is a measure of the suitability of the data for factor analysis, was 0.719, which was well above the acceptable threshold of 0.50 [74,75]. According to the factor loading criteria, the subsequent factors comprised the following sub-categories: Factor 1, adaptive coping, includes the scales of active coping, planning, positive reframing, acceptance, and humor. Factor 2, emotional coping, includes the scales of seeking instrumental support,

seeking emotional support, venting of emotions, and self-blame. Factor 3, maladaptive coping, includes the scales of denial, behavioral disengagement, and substance use. No items cross-loaded on multiple factors with loadings greater than 0.50. Self-distraction and religion did not load above 0.3 in any of the three predicted factors. These scales were therefore left out of the analyses. Similar results were found when confirmatory factor analysis was conducted on participants with postpartum depressive symptomatology. The factor structure derived from the EFA yielded three distinct second-order factors, which accounted for 57.541 per cent of variation of the data. The Barlett's test of Sphericity was significant (χ^2 (66) = 450.237, $p < 0.001$). The KMO was 0.65. The resulting factors comprised the following sub-scales: Factor 1, adaptive coping, includes the scales of positive framing, acceptance, planning, and humor. Factor 2, emotional coping, includes the scales of seeking instrumental support, seeking emotional support, venting of emotions, and self-blame. Factor 3, maladaptive coping, includes the scales of denial and behavioral disengagement. No items cross-loaded on multiple factors with loadings greater than 0.50. Self-distraction and religion and active coping did not load above 0.3 in any of the three predicted factors. Therefore, these scales were excluded from the analyses.

3.2. Confirmatory Factor Analysis

In order to determine the reliability of the factor structure derived from the EFA, a CFA was used. An initial test of the three-factor model, derived from the EFA in participants with antepartum depression, indicated a less than acceptable fit with the following parameters: CMIN/DF = 3.027; CFI = 0.831, RMSEA = 0.098, SRMR = 0.082. The examination of the standardized residuals and modification indices suggested correlation of errors between planning and active coping; reframing and humor; venting and self-blame; instrumental support and self-blame; and denial and substance. This new model resulted in CMIN/DF = 2.388, CFI = 0.908, RMSEA = 0.07, and SRMR = 0.064, meeting all the fitting criteria. The definitive three-factor model reached a much better fit than the three-factor model that distinguishes problem-focused coping, emotion-focused coping, and avoidant coping [37]: CMIN/DF = 4.559, CFI = 0.63, RMSEA = 0.125, and SRMR = 0.114. Similar results were obtained testing the three-factor model derived from the EFA in participants with postpartum depressive symptoms. The initial test indicated a poor fit: CMIN/DF = 3.319, CFI = 0.804, RMSA = 0.086, SRMR = 0.078. Modification indices suggested adding covariances between seeking instrumental support and seeking emotion, seeking instrumental support and self-blame, humor and acceptance, and humor and positive reframing. The model reached an excellent fit index: CMIN/DF = 2.040, CFI = 0.95, RMSEA = 0.059, SRMR = 0.053. This definitive model showed a much better fit than the three-factor model that distinguishes problem-focused coping, emotion-focused coping, and dysfunctional coping: CMIN/DF = 3.632, CFI = 0.71, RMSEA = 0.106, and SRMR = 0.109.

3.3. SEM Analysis

Before undertaking the analysis, the assumptions of SEM including normal distribution and multiple alignment were examined. We assessed the distribution of all variables and transformed those variables that showed strong non-normality. Log transformation was used for EPDS postpartum and substance use scores. All the other variables were normally distributed [76]. There was no alignment between the variables (VIF amplitude was less than 10, and tolerance was higher than 0.1). To analyze the mediation effects of coping strategies on the relationship between attachment styles and peripartum depressive symptomatology, the three second-order factors established using the CFA were used in the structural equation modelling (SEM) analysis. Because of the complexity of the models, only the higher-order coping strategies were estimated as latent factors. The factor scores were utilized as manifest variables for all other constructs in the model. The logistic regression analyses used to examine the role of risk factors on depressive symptomatology showed a significant association between FH of psychiatric disorders and perinatal depressive symptomatology; thus, this control variable was included in the SEM models.

3.3.1. SEM Antepartum Depressive Symptomatology

The first model, which investigated the importance of coping strategies in mediating the relationship between attachment styles and antepartum depressive symptomatology, consisted of two independent variables (avoidance attachment and anxiety attachment), three intermediate variables (adaptive, emotional, and maladaptive coping), and the dependent variable (antepartum mood symptoms) based on EPDS score $\geq$ 12. The first model did not have any acceptable fit indices at this point (CMIN/DF = 7.81, CFI = 0.800, RMSEA = 0.097, SRMR = 0.103). Non-significant paths (attachment avoidant path to the maladaptive coping and the path of anxious attachment to ante-partum depressive symptomatology and to active coping) were eliminated stepwise to create a more parsimonious model. Then, based on modification indices, we allowed covariation of the error terms of instrumental support and blame, instrumental support and emotional support, substance use and denial, humor and reframing, and planning and active coping. This new model reached acceptable fit indices (CMIN/DF = 2.19, CFI = 0.894, RMSEA = 0.071, SRMR = 0.065) [72,77]. All regressions were statistically significant ($p < 0.01$). A diagrammatic representation of the structural models is presented in Figure 1. Results showed that anxious attachment was positively associated with both maladaptive coping and emotive coping strategies. Avoidant attachment was associated with ante-partum depressive symptomatology and less emotive and active coping strategies. Emotional and maladaptive coping strategies were positively associated with antepartum depressive symptoms, while active coping strategies were negatively associated with antepartum depressive symptoms. To further confirm the specificity of coping strategies as mediators of these relations, based on existing literature findings [78], an alternative model was also tested whereby antepartum depressive symptomatology was included as the mediator variable and coping strategies as the outcome variables. This model was nonsignificant (CMIN/DF = 3.224, CFI = 78.1, RMSEA = 0.098, SRMR = 0.0874). In summary, structural equation modelling identified a significant mediational effect of emotional and maladaptive coping strategies on the relation between anxiety attachment and antepartum depressive symptomatology. Results showed a significant mediational effect of emotional coping strategies on the relationship between avoidant attachment and ante-partum depressive symptoms. Results from bootstrapping analysis confirmed a mediating effect of emotional and maladaptive coping strategies on the relationships between anxious attachment and ante-partum depressive symptomatology (two-tailed significance bias-corrected, $p = 0.005$; 95% confidence interval 0.01 to 0.04). Moreover, results confirmed a mediating effect of emotional coping strategies on the relationships between avoidant attachment and antepartum depressive symptomatology (95% confidence interval -0.03 to -0.04; two-tailed significance bias-corrected, $p = 0.002$).

3.3.2. SEM Postpartum Depressive Symptomatology

The second model, which investigated the mediating role of coping strategies between attachment styles and postpartum depressive symptomatology, consisted of two independent variables (avoidance attachment and anxiety attachment), three intermediate coping factors (adaptive, emotional, and passive coping), and the dependent variable (postpartum mood symptoms) based on EPDS score $\geq$ 9. An initial test of the model resulted in poor model fit (CMIN/DF = 3.598, CFI = 0.805, RMSEA = 0.095, SRMR = 0.073). In order to obtain a satisfactory model fit, all nonsignificant pathways were sequentially removed from the initial model. This was done to evaluate a simpler, more parsimonious model that contained fewer pathways. The investigation of modification indices suggested adding covariances between humor and acceptance, humor and planning, blame and venting, and seeking instrumental support and seeking emotional support. Results of the final model revealed a satisfactory fit (CMIN/DF = 2.676, CFI = 0.874, RMSEA = 0.077, SRMR = 0.650). All regressions were statistically significant ($p < 0.01$). Figure 2 shows the path coefficients. Anxious attachment style was positively associated with emotive coping and maladaptive coping and negatively associated with active coping. Avoidant

attachment style was associated with maladaptive coping. The relationships between emotional coping, active coping, and postpartum depressive symptomatology were comparable to those found in the previous antepartum model. Results showed that emotional coping strategies were positively associated, and active coping strategies were negatively associated with post-partum depressive symptoms, respectively. Maladaptive coping was not associated with post-partum depressive symptoms, indicating that it did not serve any significant mediating role in the relationship between attachment styles and post-partum depression. The alternative model with post-partum depression and coping strategies swapped (with post-partum as mediator and coping strategies as the dependent variables) was nonsignificant (CMIN = 3.821, CFI = 0.784, RMSA = 0.099, SRMR = 0.945). In summary, structural equation modelling identified a significant mediational effect of emotional coping and less active coping strategies on the relationship between anxiety attachment and post-partum depressive symptomatology. Results from bootstrapping analysis confirmed a mediating effect of emotional and active coping strategies on the relationships between anxious attachment and post-partum depressive symptoms (95% confidence interval 0.0 to 0.01; two-tailed significance bias-corrected, $p = 0.005$).

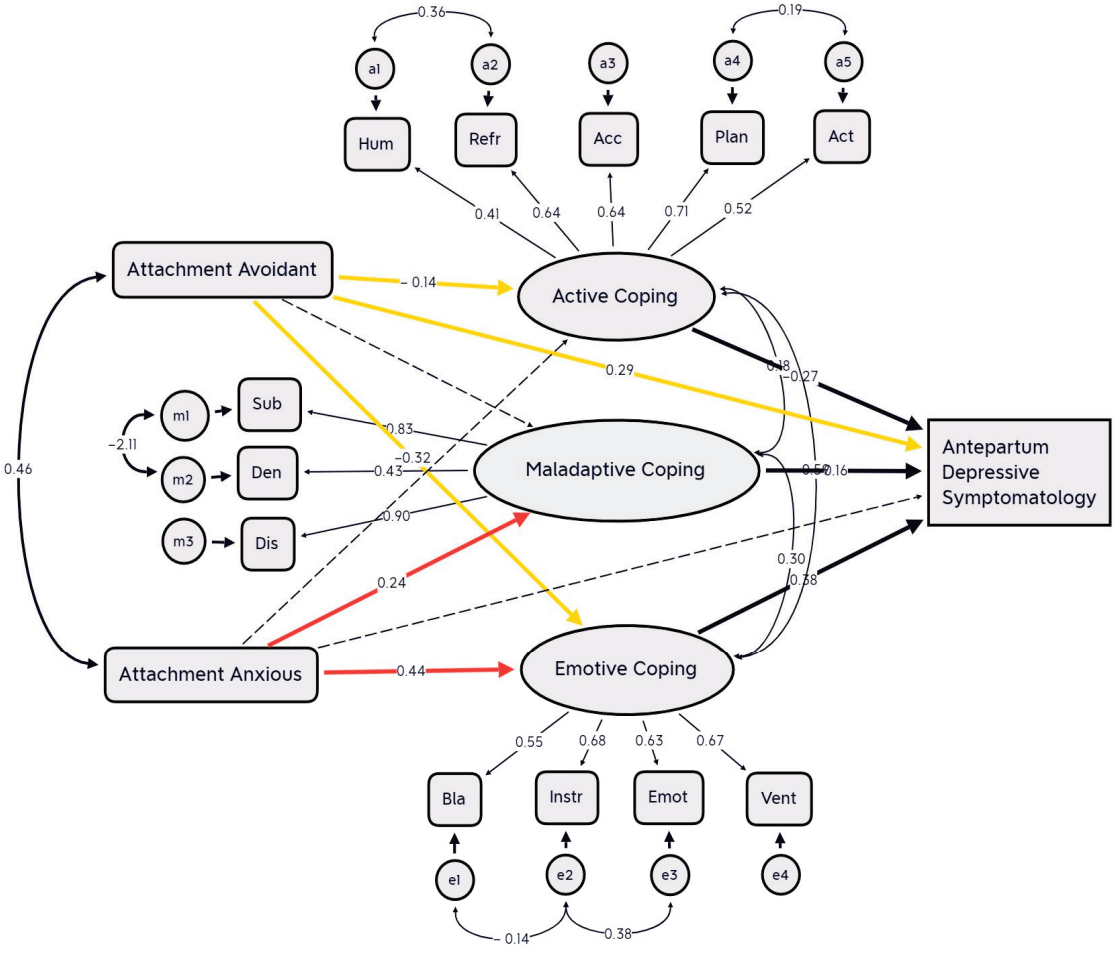

Figure 1. Path analysis model of the mediating role of coping in the relationship between attachment styles and antepartum depressive symptomatology. Values represent standardized path coefficients, factor loadings, and covariance estimates for the tested model. Solid lines represent significant effects ($p < 0.05$), and dashed lines represent non-significant effects ($p < 0.05$). The colored and bold lines represent significant pathways. Hum = humor; Refr = reframing; Acc = acceptance; Plan = planning; Act = active coping; Sub = substance use; Den = denial; Dis = behavioral disengagement; Bla = self-blame; Instr = seeking instrumental support; Emot = seeking emotional support; Vent = venting of emotions.

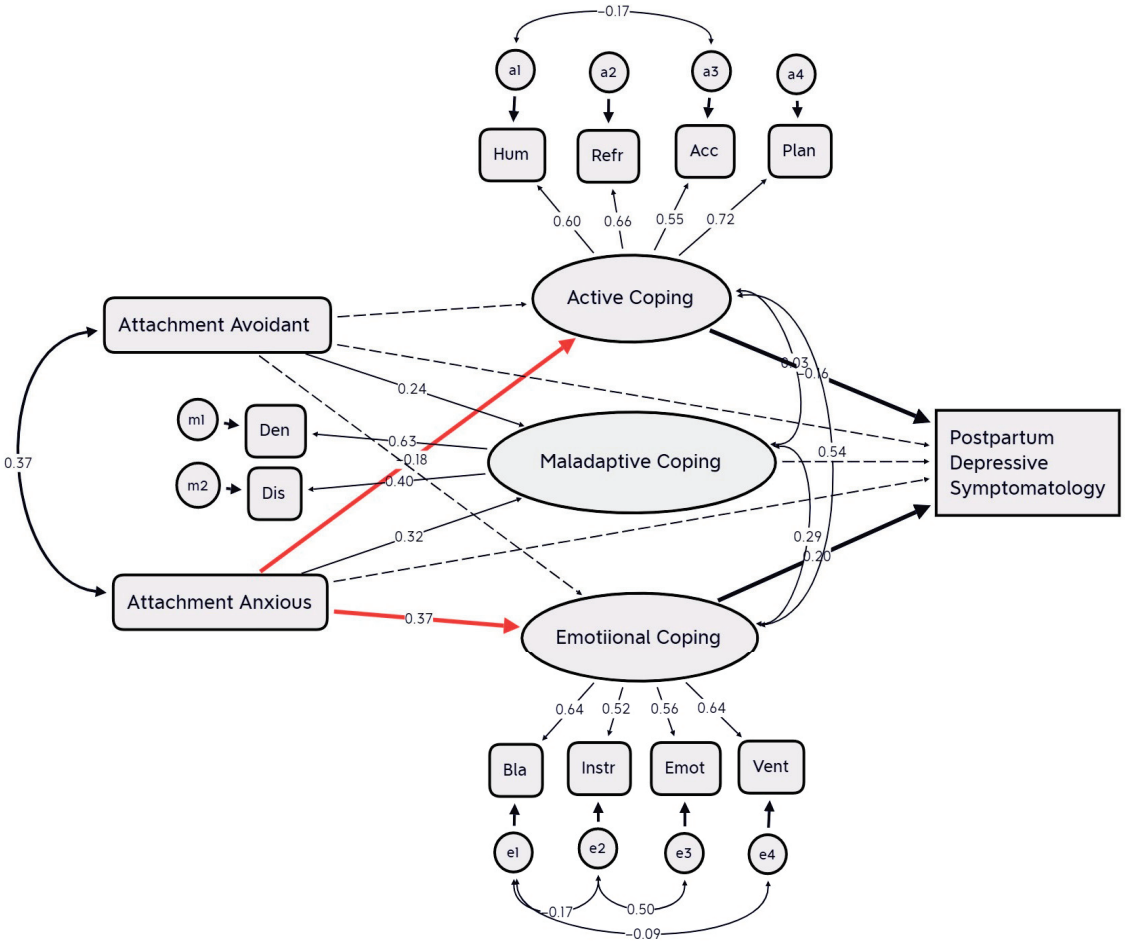

Figure 2. Path analysis model of the mediating role of coping in the relationship between attachment styles and postpartum depressive symptomatology. Values represent standardized path coefficients, factor loadings, and covariance estimates for the tested model. Solid lines represent significant effects ($p < 0.05$), and dashed lines represent non-significant effects ($p < 0.05$). The colored and bold lines represent significant pathways. Hum = humor; Refr = reframing; Acc = acceptance; Plan = planning; Act = active coping; Den = denial; Dis = behavioral disengagement; Bla = self-blame; Instr = seeking instrumental support; Emot = seeking emotional support; Vent = venting of emotions.

4. Discussion

This study was the first to test a model in which the relationship between attachment styles and depressive symptomatology is mediated by coping strategies in both antepartum and postpartum periods. The main result of the study is that attachment characteristics had a greater predictive power on depressive symptoms when its direct and indirect statistical effects are taken into consideration. As expected, based on evidence [4,26,27,79], preliminary analyses showed strong correlations between independent variables (avoidance attachment and anxiety attachment), intermediate variables (coping strategies), and the dependent variables (perinatal depression outcomes), laying the groundwork for mediation analysis [80]. First, results supported a three-factor structure of the coping strategies using the Brief COPE questionnaire, with the identification of three groups of coping strategies (i.e., active coping, maladaptive coping, and emotional coping) in both antepartum and postpartum samples [42]. In accordance with the studies by Carver [42] and Farley et al. [81], concerning the Brief COPE, the higher-order factor that we denominated emotional coping encompassed seeking emotional and instrumental support. Second, we examined the role of these three high-order factors of coping in mediating the relationship between attachment dimensions and antenatal or postnatal

depressive symptoms. The results of SEM analyses revealed that the hypothesized models of this study had a good fit in the study samples. Despite the fact that previous studies have consistently found linear associations between dimensions of insecure attachment styles and peripartum depressive symptomatology [5], here we show that coping strategies play a significant role in mediating the effect of anxious and avoidant attachment styles on depressive symptomatology. Moreover, we show that different dimensions of attachment styles and dysfunctional coping strategies were associated with either antepartum or postpartum depressive symptoms. In line with previous studies, the results indicated that, besides the direct effect of avoidant attachment on antepartum symptoms, the effect of insecure attachment styles (anxious and avoidant attachment) on antepartum depressive symptomatology was partially mediated by emotional coping styles. Anxious attachment also has an indirect significant effect on postpartum depression through emotional coping; notwithstanding, it seems that avoidant attachment is not significantly associated with postpartum depressive symptoms [82–85].

5. Antepartum Depressive Symptomatology

The results of mediational analyses revealed that anxious attachment style was significantly associated with antepartum depressive symptomatology through emotional and maladaptive coping strategies. These findings are consistent with prior studies that suggest the connection between anxious attachment and psychological distress, encompassing depressive symptoms, is not a straightforward relationship; instead, coping has an important function in mediating this relationship [28,30]. Regarding relations between anxious attachment and coping strategies, the present study shows that anxiously attached individuals use more ineffective maladaptive coping strategies (i.e., behavioral disengagement, denial, substance use) and emotional coping strategies (i.e., seeking instrumental support, seeking emotional support, venting of emotions, self-blame) compared to the effective ones. The findings are consistent with previous studies showing that those individuals with anxious attachment use emotion-focused and maladaptive coping strategies more frequently when dealing with stresses [82–84]. As emotion-focused coping strategies are most often used when the individuals perceive the stressor as something that cannot be altered and must be endured, we assume that women with anxious attachment utilized these strategies to lessen the emotional distress associated with the pregnancy and post-partum [6]. Additionally, as people with attachment anxiety reported high levels of alienation and tend to be withdrawn, these individuals might also rely to a greater extent on a variety of coping strategies, including dysfunctional coping such as maladaptive coping strategies [85].

Avoidant attachment style showed both a direct effect on antenatal depressive symptoms and an indirect effect through emotional coping. Our findings are consistent with those of a previous study showing that attachment avoidance has a direct effect on measures of psychological distress as well as an indirect effect via ineffective problem coping styles [30]. Early studies reported that attachment avoidance does not significantly predict distress when attachment anxiety was controlled for [28,29]. However, our results, consistent with previous research [30], showed that attachment avoidance predicted antenatal depressive symptomatology even when controlling for the other attachment dimension. In considering the relationship between attachment and coping, the findings of the present study indicate a negative correlation between avoidant attachment style and emotional coping. As several emotional coping strategies (e.g., self-blame and venting of emotions) are intended to relieve the psychological distress without necessarily engaging with and relying on others for support, the observed negative correlation was unexpected [37]. However, those with attachment avoidance are inclined to a lesser recognition of distress and skeptical of trust in relationships. Thus, as previous research as demonstrated, the negative correlation between emotional coping and attachment avoidance could be attributable to the negative correlation between attachment avoidance and perceived stress as well as to the difficulty in expressing their feelings to others [86,87].

6. Postpartum Depressive Symptomatology

Our findings indicate that emotional coping and less use of active coping strategies mediate the relations between anxious attachment and postpartum depressive symptomatology, while the effects of avoidant attachment were not significant. The results are consistent with previous studies [4,5] showing that anxious style was found to be associated with postpartum depressive symptomatology more frequently than avoidant style of attachment. Similarly, in the relevant literature, significant and positive correlations exist between anxious attachment and perceived stress. However, it seems that avoidant attachment is not significantly related to stress symptoms [88–91]. This is in line with the observations, as discussed above, that persons with attachment avoidance tend not to acknowledge their distress [83,92]. The fact that avoidant attachment style had a significant and direct effect on antepartum depressive symptoms but did not have any significant effect on postpartum depressive symptomatology may be indicative of the heterogeneous nature of the avoidant attachment style which encompasses both a positive and negative sense of self. It is also possible that those with avoidant attachment experiencing a greater level of perceived stress during postpartum period reported greater utilization of avoidant coping strategies to distance themselves from actively processing and/or resolving the distress. Indeed, it is noteworthy that avoidant attachment style was strongly correlated with maladaptive coping, including self-distraction, behavioral disengagement, and denial. Given that prior research has demonstrated a significant association between maladaptive coping and perinatal depressive symptomatology [3,11], it was expected that these coping strategies would mediate the relationship between avoidant attachment and post-partum depressive symptomatology. One possible reason for this inconsistency is that structural equation modelling used in the present study is potentially more powerful and less susceptible to bias than the regression methods used in other studies. These results may also be due to a stronger conceptualization and measurement of coping strategies.

The findings regarding anxious attachment are in line with the results reported in the literature, showing a strong association between anxious attachment styles with postnatal depressive symptoms [4,5]. We extended these original observations by providing evidence that anxious attachment has an indirect significant effect on postpartum depressive symptoms through ineffective coping strategies (e.g., emotional coping). These results confirm analyses reported in other earlier studies revealing patterns of the relationship between anxious attachment styles and ways of coping with difficult situations [28,30].

There are several shortcomings in this study that are noteworthy. First, data were collected through self-assessment questionnaires, which might reduce the validity of the results. Even so, the questionnaires we used in the current study were reliable and commonly used research instruments. Moreover, although a validated measure was used to assess attachment styles, the study could have been strengthened by using multiple attachment measures to operationalize insecure attachment styles. Second, although there has not yet been an Italian validation study for the use of EPDS in pregnancy, we used EPDS to assess antenatal depressive symptomatology. However, according to previous Italian studies, which investigated the prevalence and determinants of antenatal depression among Italian mothers, we used a cut-off > 12 [54,93,94]. Another limitation of the study was the absence of a clinical interview; thus, we could not directly compare EPDS scores with the clinical diagnosis of major depression. Third, the limitations imposed by the cross-sectional design of this study curtailed its capacity to comprehensively analyze the association between attachment styles and perinatal depression outcomes as mediated by coping strategies. Longitudinal studies could provide a more rigorous evaluation of these associations. Fourth, even though the results are derived from SEM, which is a more intricate model than those typically utilized in existing literature, they are still based on correlational data. Hence, it prevents us from forming any definitive conclusions about the cause-and-effect relationships between the variables. Fifth, our data collection was made in the first months of the first wave of the COVID-19 pandemic. Several previous studies specifically exploring the impact of COVID-19 on maternity, during the first severe wave

of the COVID-19 pandemic (2020), reported a significant higher prevalence and levels of depressive symptomatology in Italian mothers during the pandemic than previously reported in literature [69,95]. However, results have been inconsistent, and other findings did not show significant differences in depression and anxiety symptoms between women who gave birth before and during the pandemic period after the implementation of COVID-19 restrictions and threats, suggesting that reproductive experience alters the female brain in adaptive ways [96]. We cannot rule out the possibility that our findings have been influenced by high levels of perceived stress among pregnant women during COVID-19. Unfortunately, we did not measure pandemic-related stress symptoms. However, it should be noted that women were likely to use avoidant coping strategies like substance abuse and self-distraction for dealing with the stressful COVID-19-related situation [69]. Instead, in our sample, women with insecure attachment styles chose emotional coping strategies more frequently. More research is needed to clarify the impact of COVID-19 on coping strategies and depressive symptomatology during and after pregnancy.

Finally, our results, in line with previous research, revealed a significant association between family history of any psychiatric illness and maternal peripartum depressive symptomatology [97]. Additionally, we found a significative difference in maladaptive coping strategies between women with family history of mental illness compared with women without. These findings might suggest that risk for peripartum depressive symptomatology may be importantly influenced by the interaction between family history of mental illness and maladaptive coping strategies. However, our results showed that coping strategies play a significant role in mediating the effect of attachment styles on depressive symptomatology even when controlling for the family history of psychiatric disorders. Further research is needed to explore the potential implications of the relationship between FH, coping, and perinatal depressive symptomatology for developing targeted interventions and support strategies for women with family history of mental disorders.

7. Conclusions

Despite these limitations, our findings suggest that insecure attachment styles associated with a greater use of ineffective coping strategies can meaningfully predict perinatal depressive symptomatology. Particularly, our results suggest that different patterns of attachment and related coping strategies were associated with depressive symptoms during different phases of the peripartum period. We found a significant indirect effect between attachment anxiety and maternal depressive symptoms via emotional and maladaptive coping strategies during pregnancy and via emotional coping strategies during the early postpartum period. Avoidant attachment style showed both a direct effect and an indirect effect through emotional coping on antenatal depressive symptoms, whereas no significant effects involving ineffective coping strategies on the pathway from attachment avoidance to depressive symptomatology were found during the postpartum period. The implications of these findings suggest that a better understanding of dynamics of women's attachment and chosen coping strategies symptoms in different stages of the peripartum period may be useful in identifying and addressing risk factors associated with maternal depressive symptomatology. Further research would allow an exploration of the relationships between attachment and stress reactions as mediated by coping strategies. This would help a preventive coping-based intervention strategy to enhance the capacity of women with insecure attachment styles (especially anxious attachment) to use more adaptive coping during and after pregnancy.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are openly available in FigShare at https://doi.org/10.6084/m9.figshare.23100746, accessed on 23 May 2023.

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brain sciences

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Review

Insights into the Effect of Light Pollution on Mental Health: Focus on Affective Disorders—A Narrative Review

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Abstract: The presence of artificial light at night has emerged as an anthropogenic stressor in recent years. Various sources of light pollution have been shown to affect circadian physiology with serious consequences for metabolic pathways, possibly disrupting pineal melatonin production with multiple adverse health effects. The suppression of melatonin at night may also affect human mental health and contribute to the development or exacerbation of psychiatric disorders in vulnerable individuals. Due to the high burden of circadian disruption in affective disorders, it has been hypothesized that light pollution impacts mental health, mainly affecting mood regulation. Hence, the aim of this review was to critically summarize the evidence on the effects of light pollution on mood symptoms, with a particular focus on the role of circadian rhythms in mediating this relationship. We conducted a narrative review of the literature in the PubMed, Scopus, and Web of Science datasets. After the screening process, eighteen papers were eligible for inclusion. The results clearly indicate a link between light pollution and the development of affective symptoms, with a central role of sleep disturbances in the emergence of mood alterations. Risk perception also represents a crucial topic, possibly modulating the development of affective symptoms in response to light pollution. The results of this review should encourage a multidisciplinary approach to the design of healthier environments, including lighting conditions among the key determinants of human mental health.

Keywords: light pollution; artificial light at night; urbanization; mental health; circadian rhythms; mood disorders; psychopathology

1. Introduction

For the first time in human history, the majority of the population worldwide lives in urban areas. Indeed, more than 50% of people throughout the world live in cities, and this is expected to increase by 2050 (to around 70%), with urban areas reaching 500,000 inhabitants or more [1]. As previously demonstrated, living in an urban environment significantly increases the exposure to several risk factors, such as different sources of pollutants (e.g., air, noise, light pollution), with a subsequent significant impact on human health [2]. The different sources of pollution contribute to the development of psychological distress and a higher risk for psychiatric disorder onset or exacerbation. In particular, affective

disorders generally show a higher prevalence in urban centers. An increase of 21% has been reported for anxiety disorders and more than 39% [3,4] for mood disorders. Studies with different experimental designs have also suggested a higher risk of schizophrenia among urban inhabitants [5–7]. The physiological mechanisms behind these observations have largely been explored in an attempt to identify putative biological links between the urban environment and mental health. To this purpose, previous research has documented the role of changes in brain function based on neuroimaging techniques [8]. In particular, urban living and social stress appeared to be associated with increased activation of the amygdala and the anterior perigenual cingulate cortex [9]. More recently, research has addressed epigenetic regulation in preclinical and clinical settings, showing the influence of these mechanisms on the development of specific behavioral phenotypes [10–12]. The term "light pollution" was first used in the 19th century, although the initial attempts to describe and analyze this phenomenon were made by observing the effects of artificial light at night on bird migration. Indeed, not only does light pollution affect the well-being of humans but it also plays a significant role in exacerbating ecological crises worldwide by causing severe damage to both plant and animal populations [13]. The awareness of the problem of light pollution among scientists has increased considerably and, as a result, the number of available satellite images has increased. About 83% of the world's population lives in areas that are highly polluted by artificial light [14]. The greatest intensity of this phenomenon can be detected in urban centers, especially those with high population density. Artificial light at night (ALAN) is suspected of having negative effects on humans, animals, plants, and the balance of ecosystems. ALAN can affect the health and well-being of urban residents, as demonstrated by the increasing number of studies on the effects of light pollution on human health [15]. The light–dark cycle plays a significant role in the regulation of human circadian rhythms. Circadian rhythms are endogenous daily variations in physical, mental, and behavioral activity, which can synchronize with geophysical time showing entrainability. The suprachiasmatic nucleus (SCN), located in the anterior hypothalamus, acts as a master pacemaker, ensuring the best adaptation to both external and internal environments by constantly adapting to the feedback it receives [16]. The secretion of melatonin, a hormone associated with the control of circadian rhythms, is regulated by the conditions of external illumination; melatonin is released in the evening and suppressed by exposure to morning light [17]. The production of this hormone by the pineal gland is regulated by information stimulating the retinal photoreceptors, which are sensitive to different wavelengths [18]. There is evidence of a significant suppression of melatonin secretion after two hours of exposure to monochromatic light at 460 nm late in the evening [14,19]. Under the same conditions, with a wavelength of 550 nm, such effects were not observed. A strong inhibitory effect applies to short wavelengths and color temperature of about 6500 K; indeed, the use of light below 3000 K and the reduction of the blue spectral color is recommended [18]. Inappropriate spectral characteristics also exacerbate skyglow. In particular, 4000 K white LED is 2.5 times more polluting than low-temperature lighting, assuming the same photopic flow and upward emission function [14,15,19]. Light pollution is an emerging issue, and in some countries, there is still a lack of legislation regulating emissions. This may lead to poor choices of infrastructure and lighting fixtures that are harmful to the environment and towards human health. Exposure to ALAN is estimated to have increased by 3–6% annually in recent decades and continues to expand further in space, time, and intensity with more than 2% annual growth in radiance and extent [18]. Increased awareness of the risks that light pollution can pose to psychophysical health would also help to implement preventive behaviors, such as individual initiatives to use eye masks or lower blinds in the evening. However, increased environmental awareness can also lead to concerns about the future [20]. This concern about environmental issues affecting human health is referred to as "eco-anxiety," which is the anxiety people experience about environmental conditions [21,22]. The negative effects of eco-anxiety that have been found in different countries have contributed to a deeper understanding of the relationship between environmental issues and individual behavior [22]. As for the specific influence

of light pollution on human health, the physiological effects of exposure to ALAN can both be direct and indirect. Direct physiological effects involve the disruption of circadian rhythms and, in particular, the release of melatonin, a hormone that regulates changes in physiological processes, e.g., body mass, metabolic rate, hormone synthesis, and immunity, as a function of day length [19]. Melatonin has also been demonstrated to exert anxiolytic effects in animal experiments and several clinical conditions. Therefore, ensuring sufficient melatonin production by reducing ALAN and maintaining a regular sleep schedule may represent an endogenous anxiolytic system itself [23]. Based on the above, ALAN may contribute to the development or worsening of obesity and metabolic disorders [24], and is associated with an increased risk of developing breast cancer in women, prostate cancer in men, and pancreatic cancer in both [25–28]. Although the mechanisms are still unclear, changes in the physiological release and suppression of melatonin are likely to be involved in the development of these conditions [14]. ALAN may also have indirect effects on other physiological processes. For example, components of the immune system have circadian clocks and are therefore likely to be vulnerable to the effects of ALAN. The weakening of the immune system caused by external light pollution may make the human body more susceptible to viral infections [29]. Furthermore, it is discussed to what extent ALAN, which can cause sleep deprivation, may also have further indirect effects on cardiovascular and endocrine functions [30]. Indeed, the disruption of the physiological exposure to natural light, e.g., as a consequence of blue light from electronic devices (such as tablets, PCs, smartphones), has been shown to have negative effects on sleep in particular, with a decrease in sleep quality and sleep duration [31]. Despite the above evidence, more research is needed on the effects of light pollution on mental health in terms of affective symptoms and disorders. Moreover, a better understanding of the role that circadian disruption may play in the development of such conditions would be of help to clinicians in order to implement prevention and treatment strategies.

This review aims to identify possible effects of light pollution on mental health, with a particular interest in affective symptoms and disorders. Indeed, the effects of light pollution on human health are less well documented than those of other pollutants. Our hypothesis is that artificial light may affect mental health by contributing to the development of affective symptoms and disorders through alterations in circadian rhythms.

2. Materials and Methods

A literature search in the online databases PubMed, Scopus, and Web of Science was performed up to May 31st, 2024, using various combinations of the following keywords: "light pollution", "artificial light at night", "mental health", "affective disord*", "mood disord*", "anxiety disord*", "circadian rhythm*", "sleep disturb*", "sleep disord*". We included original research on human samples evaluating the relationship between light pollution and mental health, particularly studies reporting results on affective disorders and affective symptoms, being considered as a possible effect of exposure to artificial light. Studies assessing the effects of light pollution on affective symptoms/affective disorders as secondary outcomes were considered as well. As we hypothesize that circadian disruption is the main mediator of this association, we also included studies that examined the association between light pollution and circadian rhythms. We also included research evaluating risk perception concerning exposure to light pollution to investigate whether this might be another mediator of the emergence of affective symptoms. We excluded reviews, perspective manuscripts, commentaries, letters to the editor, and case reports. Articles published in languages other than English were also excluded. Studies that focused on biological data without clinical measures and studies on animal samples were excluded, as were studies on plants and other organisms.

3. Results

3.1. Literature Search Results and Study Description

After duplicate removal, literature screening, and hand screening of relevant references, 18 papers were included in the present narrative review. The selected studies variably investigate the role of indoor and outdoor light at night. Data were mainly collected in countries with higher levels of environmental pollution. The studies were grouped according to three main areas of evidence emerging from the literature research: sleep (nine studies), mood disorders and related behaviors (six studies), and risk perception regarding light pollution (three studies). The latter was considered because a survey of people's attitudes towards this issue is fundamental for the development of appropriate prevention strategies in the field of environmental health, as it may also mediate the emergence of new forms of psychopathology [21]. The data extraction of the included papers is reported in Table 1.

3.2. Light Pollution, Sleep, and Circadian Disruption

Sleep quality is a crucial determinant of wellbeing, linked not only to individual factors but also to the environment in which the person lives. For this reason, the role of light pollution as a possible moderator of the occurrence of sleep disturbances as an effect of urbanization processes may be crucial. There are currently few studies quantifying the effects of light pollution on overall sleep quality. Research attempted to measure the effect of artificial light on sleep quality by studying both indoor sources of artificial light and outdoor light pollution, e.g., by comparing subjects living in rural areas with those living in urban areas or exposed to different levels of ALAN. To measure the quality of sleep, most studies that were included in this review used the Pittsburgh Sleep Quality Index (PSQI) test [32], but subjective measures, e.g., surveys, were also used.

The possible association between artificial light and poor quality of sleep was confirmed by eight studies [33–40]. One study found small effect sizes, despite evidence of a negative correlation between night-time light exposure and sleep outcomes, suggesting that the effects of ALAN on sleep are more likely to be idiosyncratic [41]. As for outdoor ALAN, a comparative cross-sectional study [37] of adults living in rural and urban areas, where nighttime radiance measurement was considered as a measure of light pollution, found a poorer sleep quality in the urban population compared with the rural population exposed to the same levels of light pollution. Two of the above-mentioned studies [33,36] specifically investigated the effects of indoor night light on sleep. Indeed, artificial lighting is common in bedrooms and individuals often fall asleep with lights on—deliberately or unintentionally—or with the television light on. Similarly, children who are afraid of the dark may ask their parents to keep their lights on during sleep. In particular, one of the included studies investigated the effect of light on sleep quality and brain activity by performing two whole-night polysomnography (PSG) sessions, one with lights off and one with lights on [36]. Lights-on sleep was associated with increased stage 1 sleep, decreased slow-wave sleep, and increased arousal index. Spectral analysis revealed that theta power during REM sleep and slow oscillation, delta, and spindle power during NREM sleep were decreased in lights-on sleep conditions.

Vulnerable age groups were considered as well. In particular, a Chinese population-based cross-sectional study [34] explored the associations between ALAN exposure and sleep disturbances in children; sleep disturbances were measured by the Chinese version of the Sleep Disturbance Scale for Children (SDSC) [42]. Findings from this study suggested that sleep disturbances were more common among children living in areas with high levels of ALAN coming from outdoor sources, and that this exposure is associated with increased odds of sleep disturbances, shorter sleep duration, and longer sleep latency. The associations were stronger in children younger than 12 years, possibly because early childhood is a period when children are more sensitive to light-induced melatonin inhibition, and the sensitivity decreases with age [34]. Area-level outdoor ALAN, as derived from satellite imagery data, was associated with less favorable sleep patterns, mood, and anxiety

disorders in adolescents, as found in a cross-sectional study conducted in the US [38]. In this study, area-level outdoor ALAN was also associated with mood disorders for both bipolar and major depressive disorder/dysthymia, while associations with anxiety disorders were driven by specific phobias. In a population of students aged 20–22 years old, an intervention aimed at reducing exposure to night-time artificial light, with a particular focus on blue light emitted by smartphones, led to a significant improvement in sleep quality with a large effect size [39]. In older subjects (age $\geq$ 60), increasing exposure to ALAN seemed to be associated with increased prescription of hypnotic drugs and daily dose intake (zolpidem and triazolam), as demonstrated by a study conducted in South Korea [35]. Exposure to pre-awake light was also strongly associated with sleep disturbance in elderly subjects in a Japanese cross-sectional study [33]. Long-term exposure to outdoor ALAN was confirmed to increase the risk of poor sleep quality in Chinese veterans in a large study using mixed-effect logistic regression models [40]. The odds of reporting poor sleep quality were higher among participants who suffered from depression.

3.3. Light Pollution and Mood Disorders: Depressive, Hypomanic/Manic Symptoms, and Suicidal Behaviors

It has largely been demonstrated that individuals who experience seasonal changes in the length of the day, suffer from jet lag, or work regularly at night are more likely to develop depressive symptoms and mood changes, but it is not known whether outdoor ALAN affects the incidence of depressive disorders, bipolar disorders (BD), under-threshold mood symptoms, or suicide risk in the general population.

3.3.1. Light Pollution, Depressive Symptoms, and Suicidal Behaviors

The studies included in this review suggest that outdoor ALAN is associated with an increased prevalence of depressive symptoms and suicidal behaviors. In two studies [35,43], depressive symptoms were measured using self-administered scales, specifically the Center for Epidemiologic Studies Depression Scale (CES-D) [44] and the Patient Health Questionnaire(9 items) (PHQ-9) [45], while suicidal behavior was defined using an operational criterion as the experience of suicidal ideation or attempt. ALAN exposure assessments were based on earth-observing satellites. Using a large population sample, a study conducted in South Korea found that outdoor ALAN was significantly associated with depressive symptoms and suicidal behaviors [46]. In particular, adults living in areas exposed to higher outdoor ALAN levels showed increased odds of depressive symptoms and suicidal behaviors compared with those living in areas exposed to lower levels. In a study from the Netherlands [43], a statistically significant rise in depressive symptoms was observed with increasing levels of outdoor ALAN in the immediate residential environment, according to an unadjusted model. After adjusting for individual-level and environmental correlates, the association remained significant. A Japanese cross-sectional analysis also provided data on bedroom artificial levels during nighttime as a marker of indoor light pollution, revealing that higher levels were significantly associated with depressive symptoms, measured by the short version of the Geriatric Depression Scale (GDS-15) [33,47]. To explain neurobiological mechanisms through which ALAN may contribute to mood disorders, the disruption of circadian rhythmicity was demonstrated to be critical for mood disorders, including depression, as blue wavelengths at night can also suppress melatonin levels and their production [48]. A large Biobank-based study explored the association between night-time light emission and depressive symptoms, together with its association with urban features, e.g., air pollution, low green space, and poverty [49]. Higher light emission during night-time was associated with higher severity of depressive symptoms, together with higher levels of air pollution, economic and neighborhood deprivation, and higher household poverty. A prospective study evaluated the effects of different sources of artificial light, both indoors and outdoors, on sleep quality in pregnant women referred to nine maternity clinics in Malaysia [50]. Although it was not possible to draw causality from the results of this study, sleep quality and light exposure

were shown to affect psychological well-being, with a specific association with anxiety and depressive symptoms.

3.3.2. Light Pollution and Bipolar Disorders

Sleep–wake cycle disruptions and artificial light pollution may also trigger affective episodes in BD. Indeed, BD is associated with the alteration of several circadian rhythms including sleep–wake cycles, energy levels, and physical and social activities [51]. Accordingly, levels of light exposure during early life have been shown to influence later clinical features, such as the age at onset of BD [52]. Lighting conditions may influence the development of affective episodes or exacerbations of clinical symptoms. Particularly, the role of sleep deprivation in inducing mania has already been established. It has also been hypothesized that the blockade of nocturnal production of melatonin caused by ALAN may play a role in the pathogenesis of BD, as a consequence of melatonin's balancing effect on steroid hormones [53]. There are two studies on indoor ALAN exposure in subjects with BD [54,55], which highlighted the possible contribution of light pollution to the exacerbation of manic symptoms and the recurrence of manic/hypomanic episodes.

3.4. Risk Perception Related to the Effects of Light Pollution on Health

3.4.1. Risk Perception of Light Pollution, Sleep Disturbances, and Affective Symptoms

In an Irish study, risk perception of the effects of light pollution among residents was significantly influenced by location, underlining the importance of assessing experiences and attitudes in a wide variety of geographical environments [56]. Indeed, participants in this study confirmed that light entering the bedroom had a detrimental impact on sleep. Moreover, they suggested that light pollution may be a relevant factor to consider when implementing environmental strategies for improving overall sleep health [56]. A cross-sectional study, also conducted in an Irish non-clinical sample, examined how participants perceived ALAN exposure in their sleeping environment and how subjective perceptions of light pollution, as well as objectively measured household illumination levels, might be associated with measures of psychological distress, investigated through the General Health Questionnaire (GHQ) [57]; cognitive failures, studied using the Cognitive Failures Questionnaire (CFQ) [58]; and sleep duration quality and chronotype, measured with the PSQI and the Munich chronotype Questionnaire (MCTQ) [50]. Among respondents, those who perceived outdoor ALAN reported poorer sleep quality, more severe cognitive impairment; higher GHQ scores, particularly for somatic symptoms; anxiety/insomnia symptoms; and depression, when compared to those who did not perceive external ALAN entering the sleep environment [23,59]. To note, authors underlined a mismatch between the levels of ALAN and the subjective perception of ALAN presence in the bedroom during sleep, which meant that the perceived disruptive effect of ALAN on sleep appeared to be, to some extent, altered. Concerning these findings, it should be highlighted that poor sleepers and those with greater psychological distress could be hyper-aware of their sleep quality and thus show a sleep-related attentional bias to specific aspects of their sleep environment. Also, poor sleepers have a higher sensitivity towards light and are subsequently more vulnerable to sleep alterations. Finally, in this study, the perception of light entering the bedroom from indoor sources was not associated with differences in GHQ scores and showed smaller associations with CFQ and PSQI scores than external ALAN did.

Table 1. Overview of studies included in the narrative review.

Circadian Rhythms Disruption							
Reference	**Country**	**Design**	**Sample**	**Mental Health Outcome**	**Assessment Measure**	**Light Exposure (Measure Unit)**	**Main Findings**
Cho et al. [36]	Korea	Cross-sectional study	10 healthy young adults (21–34 years old)	Sleep quality and brain activity during sleep	PSQI PSG	Indoor LAN: fluorescent lamp (40 lux, 30 cm long), approximately 1 m away from participants' eyes	Increased stage 1 sleep, decreased slow-wave sleep, and increased arousal index during lights-on sleep. Theta power (4–8 Hz) during REM sleep, and slow oscillation (0.5–1 Hz), delta (1–4 Hz), and spindle (10–16 Hz) power during NREM sleep decreased in lights-on sleep.
Lahiri et al. [37]	India	Comparative cross-sectional study	263 participants from urban and 249 participants from rural areas (18–60 years old)	Sleep quality	PSQI 10-item PSS	Outdoor ALAN: nighttime radiance (1 radiance unit = 10^{-9} W/cm^2/sr)	Poorer sleep quality with higher nighttime radiance exposure. For urban participants, adjusted coefficient of 12.84 (95% CI: 12.31, 13.37) for exposure of >40.0 nW/cm^2/sr.
Min & Min [35]	South Korea	Population-based cohort study	52,027 older adults from the NHIS-NSC cohort (≥60 years old)	Insomnia	Hypnotic drugs prescription (zolpidem and triazolam)	Outdoor ALAN: satellite mapping of artificial light; light pollution levels (nanowatts/cm^2/sr)	Regression coefficients for prescription days and daily defined doses of hypnotic drugs were significantly higher among people living in areas with higher outdoor artificial nighttime light.
Obayashi et al. [33]	Japan	Cross-sectional study	2947 adults (≥40 years old)	Sleep quality (PSQI) Depressive symptoms	PSQI GDS-15	Bedroom LAN (median intensity 1.0 lux)	Higher risk for sleep disturbances and depressive symptoms in groups with median LAN intensities ≥ 3 and ≥10 lux (sleep disturbances: OR 1.25, 95% CI 1.05–1.48, $p = 0.011$ for 3 lux; OR 1.29 95% CI 1.02–1.64; $p = 0.034$ for 10 lux; depressive symptoms: OR 1.30, 95% CI 1.05–1.61; $p = 0.017$ for 3 lux; OR 1.33, 95% CI 1.003–1.77; $p = 0.047$ for 10 lux).

Table 1. *Cont.*

Circadian Rhythms Disruption							
Reference	**Country**	**Design**	**Sample**	**Mental Health Outcome**	**Assessment Measure**	**Light exposure (Measure Unit)**	**Main Findings**
Paksarian et al. [38]	USA	Population-based, cross-sectional study	10,123 adolescents; 6483 for behavior disorder outcomes (13–18 years old)	Sleep patterns. Past-year mood, anxiety, behavior, and substance use disorders	Modified version of the CIDI (v. 3.0 according to DSM-IV criteria). Self-reported habitual sleep patterns. Parent-reported information included in behavior disorder diagnoses	Outdoor ALAN, transformed into units of radiance ($nW/cm^2/sr$)	Higher ALAN levels associated with later weeknight bedtime. Adolescents in the highest ALAN quartile went to bed 29 (95% CI, 15–43) minutes later and reported 11 (95% CI, 19–2) fewer minutes of sleep than those in the lowest quartile. Positive association between ALAN and prevalence of past-year mood and anxiety disorders: each median absolute deviation increase in ALAN associated with 1.07 (95% CI, 1.00–1.14) times the odds of mood disorders and 1.10 (95% CI, 1.05–1.16) times the odds of anxiety disorders. Association with BD (OR 1.19 [95% CI, 1.05–1.35]) at further analyses.
Patel [41]	USA	Cross-sectional study	282,403 MMSA inhabitants. County level: 2823 inhabitants (≥18 years old)	Low/insufficient sleep	MMSA: self-reports of sleep hours and insufficient sleep. County level: prevalence of insufficient sleep	Outdoor ALAN ($nW/cm^2/sr$)	MMSA level: 10-unit increase in nighttime light associated with 5.59 min per day estimated decline in sleep and increase of 13.77% of the odds of reporting insufficient sleep (<7 h). County level: 10-unit increase in nighttime light associated with increase of 2.19% of the prevalence of insufficient sleep.
Randjelovic [39]	Serbia	Interventional study	30 young adults (university students) (20–22 years old)	Sleep quality	PSQI	Blue light emission from LED blacklight screens	Reduction of total PSQI score from 6.83 ± 2.73 to 3.93 ± 1.68 after the intervention ($p < 0.0001$; d = 1.02).

Table 1. *Cont.*

Circadian Rhythms Disruption							
Reference	**Country**	**Design**	**Sample**	**Mental Health Outcome**	**Assessment Measure**	**Light exposure (Measure Unit)**	**Main Findings**
Sun [40]	China	Cross-sectional study	7258 veterans (≥60 years old)	Sleep quality	PSQI	3-year outdoor ALAN exposure ($nW/cm^2/sr$)	ALAN exposure above the threshold associated with poorer sleep quality, with OR 1.15 (CI 95% 0.97–1.36) and 1.45 (CI 95% 1.17–1.78) at the 75th and 95th percentiles of ALAN against the threshold. Association of ALAN exposure with poor sleep quality more pronounced in veterans with depression.
Wang et al. [34]	China	Population-based cross-sectional study	20,994 children and adolescents (2–18 years old)	Sleep disorders	SDSC (Chinese version)	Outdoor ALAN exposure from 0.02 to 113.48 $nW/cm^2/sr$ within 500 m of each participant's residential address	Higher quintiles of outdoor ALAN exposure associated with an increase in sleep disturbances (total sleep scores) of 0.81 (95% CI 0.66–0.96) in Q2, 0.83 (95% CI 0.68–0.97) in Q3, 0.62 (95% CI 0.46–0.77) in Q4, and 0.53 (95% CI, 0.36–0.70) in Q5. Higher quintiles of exposure associated with OR for sleep disorder of 1.34 (95% CI 1.23–1.45) in Q2, 1.43 (95% CI 1.32–1.55) in Q3 1.31 (95% CI, 1.21–1.43) in Q4, and 1.25 (95% CI, 1.14–1.38) in Q5.
Mood symptoms							
Esaki et al. [55]	Japan	Cross-sectional study	184 subjects with BD (18–75 years)	Manic symptoms in BD patients	YMRS	Indoor ALAN bedroom light exposure (from bedtime to rising time assessed for 7 consecutive days using a portable photometer)	Prevalence of hypomanic states significantly higher in participants with an average light intensity at night exposure of ≥3 lux (36.7% versus 21.9%; $p = 0.02$), with significantly higher OR (2.15, 95% CI 1.09–4.22, $p = 0.02$) at the multivariable logistic regression analysis adjusted for BD type, depressive symptoms, sleep duration, and daytime physical activity.

Table 1. *Cont.*

Circadian Rhythms Disruption							
Reference	**Country**	**Design**	**Sample**	**Mental Health Outcome**	**Assessment Measure**	**Light exposure (Measure Unit)**	**Main Findings**
Esaki et al. [54]	Japan	Longitudinal study	172 subjects with BD (18–75 years)	Mood episode relapses in BD patients	Manic or hypomanic episodes (with or without mixed features) or depressive episodes according to the DSM-5 criteria	Indoor ALAN bedroom light exposure (from bedtime to rising time assessed for 7 consecutive days using a portable photometer)	Risk for manic/hypomanic relapses significantly higher with an average nighttime illuminance $\geq$ 3 lux (HR 2.54, 95% CI 1.33–4.84); significant relationship even at the multivariable model adjusted for a propensity score in relation to nighttime light (HR 2.17, 95% CI 1.04–4.52). No significant association between nighttime light and depressive relapses.
Helbich et al. [43]	The Nether-lands	Cross-sectional survey	10,482 adults (18–65 years)	Depressive symptoms	PHQ-9	Outdoor ALAN satellite-based measures of radiances for exposure assessments ($nW/cm^2/s$)	Significantly higher PHQ-9 scores among people in the second to fifth ALAN quintile (β_{Q2} = 0.503, 95% CI 0.207–0.798, β_{Q3} = 0.587 95% CI 0.291–0.884, β_{Q4} = 0.921, 95% CI: 0.623–1.218, β_{Q5} = 1.322, 95% CI 1.023–1.620). ALAN risk estimates adjusted for individual and area-level confounders still significant for the 100 m buffer.
Liao [49]	United King-dom	Cohort study (secondary analysis of baseline data)	200,393 adults	Depressive and anxiety symptoms; sleep patterns	Diagnostic category in the UKBB. Self-reports for sleep patterns	Five-year mean NLE value	Higher NLE associated with higher depressed mood, higher tiredness/lethargy, and obesity. As for other determinants of mental health, association between higher NLE and higher air pollution, less green space, higher economic and neighborhood deprivation, and higher household poverty. Economic deprivation, household poverty, and waist circumference acting as bridge factors between key urban features and mental health symptoms.

Table 1. *Cont.*

Circadian Rhythms Disruption							
Reference	**Country**	**Design**	**Sample**	**Mental Health Outcome**	**Assessment Measure**	**Light exposure (Measure Unit)**	**Main Findings**
Min & Min [46]	Korea	Population-based, cross-sectional study	113–119 participants for the assessment of depressive symptoms and 152–159 participants for the assessment of suicidal behavior; data from KCHS (≥20 years old)	Depressive symptoms and suicidal behavior	CES-D (Korean version). Questions about attempted suicide or contemplated dying over the preceding 12 months	Outdoor ALAN satellite data from the National Center for Environmental Information (from 0 to 63 $nW/cm^2/sr$. Spatial resolution: 50–100 m and detection limit 10^{-9} $W/cm^2/sr$)	Higher likelihood of depressive symptoms and suicidal behaviors in participants living in areas with highest ALAN levels (OR 1.29, 95% CI: 1.15–1.46 and OR = 1.27, 95% CI: 1.16–1.39, respectively).
Ng [50]	Malaysia	Prospective study	169 pregnant women (20–48 years old)	Depressive symptoms, anxiety, and stress. Sleep quality	DASS-21 PSQI (second and third trimesters)	Light exposure (H-LEA)	Higher lux level exposed from 10 pm to < 1 am associated with increased stress ($\beta = 0.212$, $p = 0.037$) and depression ($\beta = 0.228$, $p = 0.024$) in the third trimester. Poor sleep quality and higher light exposure at night attributed to greater stress and depression symptoms in the third trimester. Adverse effect of poor sleep quality on anxiety ($\beta = 0.243$, $p = 0.002$) and depression levels ($\beta = 0.259$, $p = 0.001$) in the second trimester.

Table 1. *Cont.*

Circadian Rhythms Disruption							
Reference	**Country**	**Design**	**Sample**	**Mental Health Outcome**	**Assessment Measure**	**Light exposure (Measure Unit)**	**Main Findings**
Risk perception							
Cleary-Gaffney et al. [23]	Ireland	Cross-sectional study	552 adults (≥18 years old)	Citizens' perceptions of ALAN exposure and its impact on psychological distress, cognitive failures, sleep quality, and chronotype	Light at night questionnaire. GHQ, CFQ, PSQI, MCTQ, MSI	ALAN exposure in the sleeping environment	Perception of external ALAN in the sleeping environment associated with poorer sleep quality, cognitive impairment, and greater psychological distress. Internal lighting passing into the sleeping environment associated with poorer sleep quality but not with psychological wellbeing. Habitual use of light-emitting devices associated with poorer psychological wellbeing but not with sleep quality and timing. No associations between the perception of external ALAN and MSI scores.
Coogan et al. [56]	Ireland	Cross-sectional survey	462 adults (age ≥ 18 years old)	Citizens' perceptions of light pollution and its impact	12-item questionnaire on light pollution	Outdoor ALAN perceptions of recent increase in light at night, the impact of light at night on sleep, changes in the timing of bird song, changes in the night time behavior of animals and changes in the number of bats seen	Perception of brighter night skies in urban settings, with public lighting reported as the main source of light at night. Neighbors' domestic lighting reported as the most common source of ALAN for rural settings. Respondents from rural settings more likely to report sleep impairment due to ALAN.

Table 1. *Cont.*

Circadian Rhythms Disruption							
Reference	**Country**	**Design**	**Sample**	**Mental Health Outcome**	**Assessment Measure**	**Light exposure (Measure Unit)**	**Main Findings**
Kim et al. [60]	Korea	Cross-sectional survey	1096 research subjects (20–50 years old)	Citizens' perceptions of light pollution and its impact and social amplification of risk	Survey on environmental and health risk factors, considering psychometric variables that influence risk perception	Outdoor ALAN (light trespass, over-illumination, glare, and light clutter)	Among the 11 environmental risk factors examined in the study, highest rank for light pollution variables reported for glare (5.78 points, fifth position), while over-illumination (5.17 points), light trespass (5.11 points), and light clutter (4.80 points) ranked ninth, tenth, and eleventh. Influence of all psychometric variables except for controllability on risk perception.

Notes: ALAN = Artificial light at night: BD = Bipolar Disorder; CES-D = Center for Epidemiologic Studies Depression Scale; CFQ = Cognitive Failures Questionnaire; CI = Confidence interval; CIDI = Composite International Diagnostic Interview; DASS-21 = Depression, Anxiety, and Stress Scale; GDS-15 = short version of the Geriatric Depression Scale; GHQ = General Health Questionnaire; H-LEA = Harvard Light Exposure Assessment; HR = Hazard ratio; KCHS = Korean Community Health Survey; LAN = Light at night; MCTQ = Munich Chronotype Questionnaire; MMSA = metropolitan and micropolitan statistical area; MSI = Melatonin-suppression index; NHIS = The National Health Insurance Service; NHIS-NSC = NHIS-National Sample Cohort; NLE = Night-time light emission; OR = Odds ratio; PHQ-9 = Patient Health Questionnaire (9 items); PSG = polysomnography; PSQI = Pittsburgh Sleep Quality Index; PSS = Perceived Stress Scale; SDSC = Sleep Disturbance Scale for Children; UKBB = United Kingdom BioBank; YMRS = Young Mania Rating Scale.

3.4.2. Factors Influencing Risk Perception of Light Pollution

A study conducted in Korea [60] used a survey where participants were asked to rate the risk perception level of the selected types of light pollution (light trespass, over-illumination, glare, and light clutter) together with other environmental factors that could represent a major threat to human health. The following factors were selected as indices possibly influencing risk perception: personal knowledge, risk awareness, controllability, impact of the risk on future generations, familiarity with the risk, fatal consequences of the risk, attribution of responsibility, and trust in government. The variables that demonstrated a possible explanatory role were the information obtained from the media and the recall of media criticism. Risk perception of each light pollution type and other environmental risk factors were compared. Among the considered environmental risk factors, glares were significantly more represented than lighting, light trespass, and light pollution. The results also showed that risk perception was considerably influenced by the acquisition of information from the media [60], confirming that media attention towards urbanization-related issues may affect people's worries about environmental threats and their behavior to reduce them. The recall of media criticism of each type of light pollution led to a statistically significant increase in risk perception [61].

4. Discussion

The results of this narrative review point towards an association between light pollution and mental health issues. In particular, increased exposure to light pollution—both indoors and outdoors—appears to have a negative effect on the quality of sleep in populations of different ages, including vulnerable populations, such as adolescents and elderly people. As hypothesized, increased exposure to indoor and outdoor ALAN appears to be associated with the emergence of mood symptoms and with the exacerbation of pre-existing disorders, as demonstrated for BD. The relationship between artificial light exposure and mood disturbances is likely to be mediated by specific biological pathways. In particular, crucial consequences of light pollution that are potentially involved in mood regulation appear to be the decrease in melatonin secretion and disturbances of circadian rhythms [62,63]. Indeed, these latter features play a crucial role in the pathophysiology of mood disorders, both depressive and bipolar [64–67], and also represent clinical symptoms that significantly impact the phenomenology of these conditions during acute episodes and inter-episodic phases [66,68–71]. Subsequently, inappropriate or persistent ALAN exposure may desynchronize biological rhythms and exacerbate mood disorders. Furthermore, ALAN has been demonstrated to increase neuroinflammation (for review, see Ref. [72]), a mechanism that has been strongly implicated in the development of psychiatric disorders, particularly mood disorders [73,74]. It is important to note that neuroinflammatory mechanisms are also believed to contribute to the effects of other pollutants, e.g., air pollutants, on the central nervous system, possibly driving the worsening of psychiatric symptoms after short-term exposure [75,76].

Based on the above, novel treatment strategies were also proposed based on the significant role of circadian alterations in the development of mood disorders. In particular, interpersonal and social rhythm therapy (IPSRT) is a psychological strategy that targets biological rhythm disruptions in people with mood disorders [77–79]. Interestingly, specific IPSRT protocols targeting vulnerable populations, particularly adolescents, even in at-risk stages, were also developed [78,80,81]. Further non-pharmacological approaches, e.g., psychoeducational approaches, also cover the area of circadian rhythms, discussing with patients the possibility of resynchronizing circadian cycles as a crucial point in the treatment of mood symptoms [82–84]. This may be of crucial importance due to the susceptibility of this age group to the effects of environmental factors disrupting biological rhythms, particularly ALAN, which can be emitted by a wide range of electronic devices, such as smartphones [39]. Since integrated approaches are of utmost importance in the field of early intervention, youths suffering from mood symptoms, or even during at-risk stages, should always be proposed to undergo such treatments [85]. Research on vulnerable

populations should not be limited to youths, since data from this review also show specific susceptibility in older adults. This is of particular interest since poor sleep quality has been demonstrated to significantly worsen the quality of life in elderly populations, also mediating the onset of mood disorders, particularly depression [40,86]. Subsequently, in this population, the exposure to sources of light pollution should be systematically evaluated as well, and psychoeducational interventions should be further developed, together with environmental strategies aimed at risk reduction.

This narrative review also evidenced that risk perception concerning ALAN could influence the emergence of psychological distress in response to this specific exposure. This is a controversial issue since it has been largely argued that the perception of risk related to environmental stressors may even lead to the development of new forms of psychopathology and should thus be evaluated in all exposed subjects [21,61]. To note, eco-anxiety might to some extent also have moderated the effects of light pollution on the development of affective symptoms. Indeed, this novel psychological feature was shown to be associated with the development of depression, especially in vulnerable populations [87]. Further research is expected to clarify the possible impact of light pollution in the development of eco-anxiety, as well as the relationship of this feature with mood symptoms in people exposed to ALAN. On the other hand, low-risk perception of light pollution, which could be due to insufficient interest in environmental determinants of health and to underestimation of artificial light consequences on human health, may lead to a number of unhealthy habits [88]. As it is predicted that light pollution could pose a growing, serious potential risk in the future [89], it is necessary to develop strategies to inform the public about the risks of light pollution. Therefore, an effective communication strategy should be implemented, e.g., by improving the dissemination of information through the Internet and social media.

The main strength of the studies here included, especially those on mood disorders, is the representative number of participants enriched with individual-level register and environmental data. At the same time, some limitations should be underlined. First, the analyses were mainly based on self-reported depressive symptoms, which represents a multi-faceted issue. Indeed, patient-reported outcomes are a main goal in the field of mental health and self-administered scales allow for reporting symptoms that may not be objectively observed by clinicians. On the other hand, these measures may have introduced some biases into the analyses because any symptoms would deserve to be further discussed with clinicians. It should also be pointed out that different sources of pollutants contribute to the complexity of the urban environment, which is a major threat to human mental health and may also include a number of social stressors [90]. To note, light pollution and artificial lighting have also been advocated as having social effects that should be considered an integral part of this complexity [89]. Another limitation of the included studies is that individual sleeping habits were not considered in most cases and altered sleep hygiene was not specifically assessed. This could represent a further bias, as it is not always possible to distinguish between changes in people's sleep habits and the effects of light pollution. Several studies included adults of different ages, which could also have introduced some bias since sleep habits sensitively change during the lifespan. Similarly, research was conducted at different latitudes where times of sunrise and sunset highly vary, as well as light quality and intensity. This could have significantly affected the duration of ALAN exposure and limited the generalizability of findings. Finally, most of the included literature focused on population samples rather than clinical ones. The latter would require further interest in the near future, also in consideration of the results of this review. On the basis of the revised literature, it is crucial to perform studies with robust designs and with particular interest in longitudinal data collection. As for vulnerable populations, there is a need for interventional studies specifically aimed at understanding what preventive strategies can be put in place to avoid the onset of clear-cut psychopathology in the event of exposure to environmental stressors. Finally, a wide range of urbanicity-related factors should always be considered when assessing human health, particularly mental health, in the urban

environment. Together with this, identifying social variables and attitudes that affect the risk perception of any type of pollution represents a priority for the implementation of appropriate prevention strategies.

5. Conclusions

In this present narrative review, we summarized the possible detrimental effects of light pollution on mental health, with evidence of the role of artificial light at night in the development of circadian disruptions and mood symptoms, together with the exacerbation of mood disorders. Light pollution should be considered among the determinants of mental health in the context of the urban environment. Research into mood disorders in the post-modern era should not underestimate the effects of urbanization and should thus be aware of the detrimental effects of various sources of pollutants on the development and exacerbation of these conditions. This relationship is complex and should take into account factors such as individual exposure and risk perception. Although future studies are expected to further clarify and characterize the effects of light pollution on mood disorders and the moderators of this association, the results of this review suggest how building more livable cities that protect public health should include eco-friendly lighting, alongside other factors, according to the principles of sustainability. Furthermore, raising people's awareness of risk factors and harmful habits related to light-dependent circadian rhythms should be a public health priority.

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brain sciences

MDPI

Review

Can Brain-Derived Neurotrophic Factor Be Considered a Biomarker for Bipolar Disorder? An Analysis of the Current Evidence

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Abstract: Brain-derived neurotrophic factor (BDNF) plays a key role in brain development, contributing to neuronal survival and neuroplasticity. Previous works have found that BDNF is involved in several neurological or psychiatric diseases. In this review, we aimed to collect all available data on BDNF and bipolar disorder (BD) and assess if BDNF could be considered a biomarker for BD. We searched the most relevant medical databases and included studies reporting original data on BDNF circulating levels or Val66Met polymorphism. Only articles including a direct comparison with healthy controls (HC) and patients diagnosed with BD according to international classification systems were included. Of the 2430 identified articles, 29 were included in the present review. Results of the present review show a reduction in BDNF circulating levels during acute phases of BD compared to HC, which increase after effective therapy of the disorders. The Val66Met polymorphism was related to features usually associated with worse outcomes. High heterogeneity has been observed regarding sample size, clinical differences of included patients, and data analysis approaches, reducing comparisons among studies. Although more studies are needed, BDNF seems to be a promising biomarker for BD.

Keywords: brain-derived neurotrophic factor; BDNF; bipolar disorder

1. Introduction

Bipolar disorder (BD) is a severe mental disorder with a reported prevalence in the general population of 2.4% [1,2]. People suffering from BD report a worsening of social functioning in terms of work-related problems, a high college drop-out rate, and interpersonal difficulties [3–5], as well as increased comorbidity with physical disorders and mortality compared to the general population [6–9]. In 2019, BD resulted in 8.50 million global disability-adjusted life years (DALYs), equivalent to 0.3% of DALY, contributing to 6.8% of DALYs for aggregate mental disorders [1]. Moreover, BD is associated with a significant economic burden [10], with an estimated total annual national economic expenditure of more than USD 195 billion in the US alone, with approximately 25% attributed to direct medical costs [10] and the remaining to loss of productivity.

Bipolar disorder is a multifactorial disease, with a complex interaction between biological and environmental factors, both contributing to the definition of the pathophysiology of BD [11–13]. Nevertheless, studies are still far from identifying biological mechanisms underlying the etiopathogenesis of BD and other mental disorders [14,15].

In the past few decades, research has been focused on the correlation between BD and neuro- and systemic inflammation [16]; in particular, the role of pro-inflammatory

cytokines, immuno-modulators, and growth factors in influencing the episodic course of the disorder has been investigated [17].

Neuroinflammation is characterized by an increased number of circulating proinflammatory cytokines, increased immune cell entry into the central nervous system through the blood–brain barrier, microglial activation, and degeneration of the encephalic tissue [18]. Different brain insults can cause microglial activation, with the release of interleukin-1β (IL-1β) and activation of astrocytes, starting the pro-inflammatory cascade [19].

Many studies have shown higher levels of inflammatory markers both in the bloodstream and in cerebro-spinal fluid (CSF) in BD patients [20]. Consistent findings have been reported through the analysis of brain tissue samples of deceased BD patients [21] and with neuroimaging studies. In a positron emission tomography (PET) study, Haarman et al. (2014) [22] found a significantly increased binding potential, an indirect marker of neuroinflammation, in BD patients when compared with healthy controls (HC). Chronic neuroinflammation can lead to several modifications in brain tissue, particularly the reduction in circulating brain-derived neurotrophic factor (BDNF) [23]. BDNF is a growth factor synthesized mostly in the brain in response to neuronal activity; it is produced as pro-BDNF, a precursor that can be activated in mature BDNF (m-BDNF) by extracellular metalloproteinases or intracellular endoproteases.

BDNF explicates its function mostly by the activation of the TrkB receptor. During intrauterine life, BDNF signaling guides the differentiation from progenitors into mature brain cells [24], but it keeps its role in activating neurogenesis even in adult life [25]. BDNF plays a key role in the regulation of neuronal transmission and synaptic plasticity, operating on both the presynaptic side, acting on the neurotransmitters' release, and the postsynaptic side, modulating receptors' expression [26]. BDNF can also be found in the bloodstream, since it is also produced by other tissues and cells, such as cardiomyocytes and platelets [27]. Many studies have reported that changes in BDNF serum levels may reflect modifications in the brain's BDNF production and/or clearance [28].

Recent data suggest a correlation between BDNF signaling deficits and some major brain diseases, including psychiatric disorders such as schizophrenia, major depressive disorder (MDD), and BD [29–31]. A significant decrease in circulating BDNF levels in BD patients compared to healthy controls, especially during acute episodes of the illness, has been found [32], suggesting its possible mediating role in affective disorders.

Moreover, a large body of literature has investigated the possible influence on BDNF activity of the rs6265 polymorphism, a single-nucleotide polymorphism (SNP) in the BDNF gene. The rs6265 polymorphism is a common functional nonsynonymous SNP, a coding mutation that changes the protein sequence, in which the amino acid valine (Val) is replaced with methionine (Met) in the BDNF protein, resulting in a less efficient BDNF secretion. Due to the important role played by BDNF in the nervous system, this SNP has been extensively studied in the pathogenesis of several psychiatric disorders, including mood disorders [33,34].

The role of BDNF in influencing both the clinical presentation and outcome of BD has been recently investigated, with conflicting results [35,36], which can be due to differences in study methodologies and sample heterogeneity regarding age and mood fluctuation. In fact, the levels of BDNF can vary in the different phases of the disorder and with the age of patients [37,38].

In this narrative review, we aim to review the current literature on the role of BDNF in BD and to investigate if it can be considered a reliable predictive biomarker for BD. To our knowledge, this is the first review to investigate both BDNF circulating levels and BDNF Val66Met polymorphism.

2. Materials and Methods

We searched the most relevant medical databases, including PubMed, Scopus, and Web of Science, until 11 April 2023, using as keywords "BDNF" or "brain derived neurotrophic factor" or "Neuroinflammation" or "Neurogenesis" or "inflammat*" matched

with "bipolar" or "BD" or "depressive episode" or "mood" or "affective" and with "euthymia" or "stability" or "acute phase" or "affective episode" or "manic episode" or "mixed state" or "mixed episode" or "depressive episode". Studies were included if they reported original data on BDNF circulating levels or Val66Met polymorphism in patients with BD and if they were written in English.

All articles published until April 2023 were considered. Studies including other sub-samples or other outcomes (i.e., MDD patients; other circulating factors, such as pro-inflammatory cytokines) were included only in case it was possible to extrapolate data regarding the association among BDNF circulating levels or Val66Met polymorphism and BD. We considered only articles including a direct comparison with healthy controls, and patients diagnosed with bipolar disorder whose diagnosis was made according to international classification systems, including clinical interviews that applied the criteria of the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases. We obtained full reports of potentially relevant studies. Data on study design, sample characteristics, detected biomarkers, and main findings were independently extracted by five authors (A.B., G.C., G.D.F., M.V.L., C.T.).

We identified 2430 papers, and 984 of them were excluded because of duplicates. After screening for eligibility according to inclusion criteria, 29 papers were finally included in our review (Figure 1).

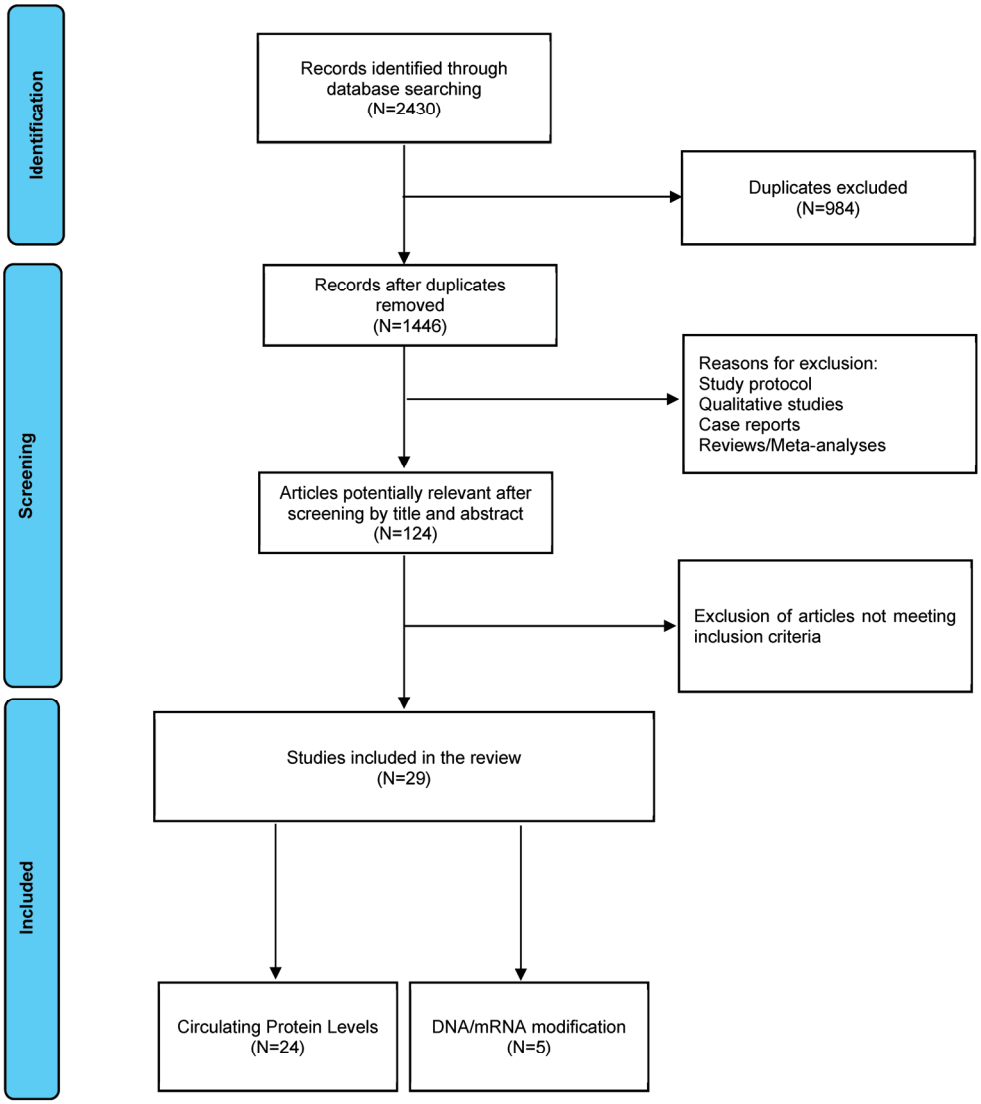

Figure 1. PRISMA flow diagram of selection of studies included in the review.

Due to the methodological heterogeneity between studies, papers were subsequently grouped into two sub-categories: "BDNF/DNA modifications and circulating mRNA levels" and "Circulating BDNF protein levels".

3. Results

Of the 29 papers included in the review, 5 were included in the "BDNF/DNA modification and circulating mRNA levels" group and 24 in the "Circulating BDNF protein levels" group.

About one-third of studies (9 out of 29) adopted a prospective design, and the remaining 21 studies were cross-sectional. None of the studies included in the review were randomized control trials (RCTs). Sample sizes ranged from 1446 [39] to 20 [40] participants.

3.1. BDNF/DNA Modifications and Circulating mRNA Levels

The five studies included in this group are reported in Table 1. All articles used real-time (RT)-PCR as a main tool. PCR is a biological technique developed in 1985 [41] to amplify a segment of DNA or RNA [42]. RT-PCR, also known as quantitative PCR, is used for simultaneous amplification and quantification of a specific DNA or RNA segment [43].

Two studies investigating BDNF mRNA levels adopted a prospective design. Li et al. (2014) [44] carried out a large prospective study involving 203 patients with a BD episode and 167 HC in whom both BDNF mRNA and BDNF serum levels were measured in a 3-year bi-annual follow-up. The authors found that BD patients had lower BDNF levels at baseline compared with healthy controls. Longer follow-ups could be useful to identify those patients experiencing a first manic or hypomanic episode in the following years.

In the second longitudinal study, Cinar RK et al. (2016) [45] assessed and compared BDNF mRNA levels in a sample of 20 BD patients during a manic episode with HC. BDNF mRNA levels were downregulated during acute manic episodes and increased in remission phases, being still lower than the levels of controls.

All other studies adopted a cross-sectional design. Soeiro-De-Souza et al. (2012) [46] and Nassan et al. (2015) [47] reported a correlation between the Val66Met polymorphism and a decrease in creativity during a manic phase; moreover, Nassan et al. (2015) [47] found that this genetic variation is more represented in early-onset BD.

Both studies have some limitations. The Soeiro-De-Souza study [46] would have had a higher impact with a larger sample and an additional measure of creativity; in the Nassan study [47], the retrospective classification of early onset BD might represent an important assessment bias.

Finally, Dell'Osso et al. (2014) [48] carried out an epigenetic study on BDNF gene promoter methylation. Methylation is a form of epigenetic gene silencing, consisting of gene inactivation [49]. They found higher BDNF gene promoter methylation levels in BD patients compared to HC and higher methylation levels during depressive phases compared with manic phases or mixed states.

3.2. Circulating BDNF Protein Levels

In total, 24 studies were included in this section (Table 2); most of them (17 out of 24) adopted a cross-sectional design, while the other 8 studies had a prospective design. All the studies measured circulating BDNF protein levels by ELISA, a quantitative analytical method used to measure the concentration of specific molecules. ELISA is based on the use of enzymes to show an antigen–antibody binding reaction, measured as a macroscopic color change. This technique allows us to assess very small quantities of molecules in biological fluids [50].

3.3. Acute Episodes of BD vs. HC

Seventeen studies have investigated the circulating levels of BDNF in BD patients during acute episodes compared with HC, and most of them have shown decreased BDNF circulating levels in BD patients during acute episodes when compared with HC. Only

Barbosa et al. (2010) [51] and Poletti et al. (2017) [52] showed higher BDNF circulating levels in BD patients during acute episodes, while Binici et al. (2016) [53], Ameele et al. (2017) [54], and Skibinska et al. (2021) [55] observed no significant difference in BDNF circulating levels between acute episodes of BD patients and HC. Most studies [44,56–60] have investigated BDNF serum levels during a depressive episode, while Tramontina et al. (2009) [40], Machado-Vieira et al. (2007) [61], and Oliveira et al. (2009) [59] have included BD patients in a manic phase; only Piccinni et al. (2014) [60] have included 19 mixed state patients, while Tunca et al. (2014) [62] and Yoshimura et al. (2006) [63] included both manic and depressive episodes.

3.4. Euthymic Patients vs. HC

Monteleone et al. (2008) [64], Nuernberg et al. (2016) [65], Aas et al. (2018) [39], and Mansur et al. (2016) [66] showed a significant decrease in BDNF serum levels in BD patients compared to HC, while Dias et al. (2009) [67], Chou et al. (2012) [68], and Rosa et al. (2014) [69] did not find any significant difference between patients and healthy controls.

3.5. Acute Episodes vs. Euthymia

Two studies [62,70] showed a significant decrease in BDNF serum levels during acute episodes compared with euthymic phases. Similar results were reported by Zhao et al. (2017) [71], who found a lower ratio of mature BDNF to precursor BDNF in BD patients compared to HC. Moreover, Tramontina et al. (2009) [40] and Nuernberg et al. (2016) [65] have highlighted a significant increase in BDNF levels after effective treatment. On the contrary, Ameele et al. (2017) [54] and Jacoby et al. (2016) [72] found no significant difference between euthymic and acute phases of BD. When assessing the levels of BDNF in the different acute phases of BD, Yoshiumura et al. (2006) [63] observed that depressed BD patients have lower BDNF circulating levels compared to manic patients.

3.6. Other Findings

Cunha et al. (2006) [70] and Machado-Vieira et al. (2007) [61] found a negative correlation between BDNF levels and symptom severity. Teng et al. (2021) [57] observed a positive correlation between BDNF levels and cognitive functions in a sample of 45 BD II patients matched with 40 HC. On the other hand, Barbosa et al. (2010) [51] did not find any correlation between BDNF levels and clinical parameters, and Chou et al. (2021) [68] showed no correlation between BDNF levels and cognition in a sample of euthymic BD patients compared with HC.

Aas et al. (2018) [39] showed lower BDNF circulating levels in a large sample of acute and stable BD (n = 254) and psychotic patients (n = 254) compared to 603 HC. Interestingly, patients with a history of childhood trauma had the lowest BDNF circulating levels. On the other hand, Skibinska et al. (2021) [55] demonstrated elevated BDNF levels in patients with a family history of affective disorders.

Contrary to most findings, Barbosa et al. (2010) [51] found a higher concentration of BDNF in BD patients with a long history of disease (10 years or more), which might be due to the brain response to chronic damage or the influence on BDNF levels of the prolonged use of drugs.

As for the effect of medication on BDNF levels, Tunca et al. (2014) [62] showed a positive correlation between BDNF levels and lithium concentration in a sample of 96 BD patients, while Yoshimura et al. (2006) [63] observed no effect on BDNF levels after risperidone administration in a sample of 18 BDI patients. Oliveira et al. (2009) [59] observed significantly lower BDNF serum levels in both drug-free and treated patients during acute episodes when compared to HC. No difference between drug-free and treated patients was found.

Table 1. Studies on BDNF/DNA modifications and circulating mRNA levels.

	Study and Country	Study Design	Sample	Study Aim(s)	Main Findings
1	Dell'Osso, 2014, Italy [48]	Cross-sectional	144 patients (43 MDD; 61 BD I; 50 BD II); 44 HC	To investigate differences in BDNF promoter gene methylation in patients with mood disorders	Higher methylation levels in BD II (compared to BD I) and MDD patients (compared to controls). Lower methylation levels in patients during mania/mixed episodes compared to the depressive phase.
2	Li et al. 2014, China [44]	Longitudinal	203 patients with a first major depressive episode 167 HC	To explore whether BDNF levels can differentiate between MDD and bipolar disorder in the first depressive episode	At baseline, lower BDNF mRNA levels and plasma levels in BD and MDD patients compared to HC. Lower BDNF levels in the BD group compared to the MDD group. The best model for predicting BD during a first depressive episode was a combination of BDNF mRNA levels with plasma BDNF levels.
3	Nassan et al. 2015, Washington [47]	Cross-sectional	82 BD pediatric and adolescent patients 855 BD adult 764 HC	Association of BDNF Val66Met SNP with EO-BD through a case–control candidate gene study	No significant evidence of association of the minor Met allele of Val66Met with BD. Significant evidence of an association between EO-BD and Val66Met.
4	Çinar et al. 2016, Turkey [45]	Longitudinal	20 BD 20 HC	To assess the BDNF mRNA expressions in BD patients and HC	Downregulation of BDNF mRNA in mania compared to HC. In remission, increased BNDF mRNA levels, but still lower than those of the controls.
5	Soeiro-De-Souza, 2012, Brazil and USA [46]	Cross-sectional	66 BD (41 manic and 25 depressed patients) 78 HC	To determine if the Val allele is associated with increased creativity in BD	Higher BWAS scores in manic patients with the Val allele (Met−). This relationship was not observed in depressed patients or HC. No association between BDNF Met allele status and cognitive function in any of the groups.

BDNF: brain-derived neurotrophic factor; MDD: major depressive disorder; BD: bipolar disorder; EO-BD: early-onset bipolar disorder; HC: healthy controls; mRNA: messenger RNA; SNP: single-nucleotide polymorphism; Met: methionine; Val: valine; BWAS: Barron Welsh Art Scale; Val66Met: substitution of an amino acid valine with a methionine.

Table 2. Studies on circulating BDNF protein levels.

	Study and Country	Study Design	Sample	Study Aim(s)	Main Findings
1	Aas et al. 2018, Norway [39]	Cross-sectional	254 BD patients; 589 psychotic patients; 603 HC	To assess BDNF serum levels and to investigate if childhood trauma can affect BDNF levels	Reduced BDNF levels in patients with severe mental disorders. The most substantial reduction was observed in patients reporting childhood sexual abuse.
2	Ameele et al. 2017, Belgium [54]	Prospective case–control study	67 BD patients (35 during a depressive and 32 during a manic episode) 30 HC	To evaluate mood-specific changes in BDNF and their association with inflammatory activity	No differences in the levels of BDNF levels between BD patients and HC.
3	Barbosa et al. 2010, Brazil [51]	Cross-sectional	53 BD (34 manic and 19 euthymic) patients 38 HC	To assess BDNF levels in BD patients and their association with clinical and demographic factors	Significantly increased plasma BDNF levels in patients with mania and euthymia compared to controls, without any correlation with clinical parameters. Higher BDNF concentration in BD patients with 10 or more years of disease was found.
4	Fernandes et al. 2009, Brazil [58]	Cross-sectional	40 BD patients 10 MDD patients 30 HC	To investigate serum BDNF levels as a potential diagnostic biomarker in bipolar and unipolar depression	Lower serum BDNF levels in depressed BD patients compared to MDD patients and controls were found.
5	Binici et al. 2016, Turkey [53]	Cross-sectional	25 BD patients 17 HC	To assess BDNF serum levels in euthymic adolescents with BD type I	No difference in BDNF levels between patients and healthy controls was found.
6	Chou et al., 2021, Taiwan [68]	Cross-sectional	23 euthymic BD type I patients 33 HC	To examine the cognitive performance in euthymic BD I patients and to assess if cognitive deficits correlate with BDNF levels	No association between impaired cognition and BDNF was found.
7	Cunha et al. 2005, Brazil [70]	Cross-sectional	85 BD (32 euthymic, 21 Depressed and 32 Manic) patients 32 HC	To investigate serum BDNF levels in manic, depressed, and euthymic BD patients and in matched healthy controls	Decreased serum BDNF levels in BD patients during manic and depressive episodes compared with euthymic BD patients and HC. Negative correlation between serum BDNF levels and severity of manic and depressive symptoms was found.

Table 2. *Cont.*

	Study and Country	Study Design	Sample	Study Aim(s)	Main Findings
8	Dias et al. 2009, Spain [67]	Cross-sectional	65 BD patients 50 HC	To investigate serum BDNF levels in BD patients compared with HC	No significant difference in serum BDNF levels in BD type I euthymic patients compared to healthy controls.
9	Jacoby et al. 2016, Denmark [72]	Longitudinal	60 BD-I patients 35 HC	To investigate whether neurotrophins and inflammatory markers vary with mood states	BDNF and the other inflammatory markers did not vary according to affective state in adjusted mixed models.
10	Machado-Vieira et al. 2007, Brazil [61]	Cross-sectional	60 BD patients 30 HC	To investigate whether BDNF levels are altered during manic phases of the disorder	Significantly decreased BDNF levels in manic patients compared to HC. Negative correlation between the severity of manic episodes and BDNF plasma levels.
11	Mansur et al., 2016, Brasile/Canada [66]	Cross-sectional	57 BD patients 26 HC	To assess the relationship between BDNF levels and indices of illness course	Lower levels of BDNF in the BD population.
12	Monteleone et al, 2008, Italy [64]	Cross-sectional	35 MDD patients 17 BD I patients 11 BD II patients 22 HC	To assess BDNF circulating levels in mood disorders; to exclude the possibility that comorbid psychiatric disorders exerted an effect on BDNF levels	Serum BDNF levels were reduced in both euthymic and depressed MDD patients as well as in euthymic patients with BD-I and BD-II. The reduction in circulating BDNF was not affected by drug treatments. Comorbid Axis I mental disorders did not influence circulating BDNF in affective patients.
13	Nuernberg et al., 2016, Brazil [65]	Longitudinal	236 patients with BD, MDD, SZ 100 HC	To evaluate BDNF levels at admission and discharge and compare them with HC To compare BDNF levels in the different SMI patients	BDNF levels persistently lower compared to HC were found.
14	Oliveira et al., 2009, Brazil [59]	Cross-sectional	22 BD unmedicated patients, 22 BD medicated patients, 22 HC	To assess whether drug-free patients have different levels of circulating serum BDNF compared to medicated BD patients and controls	Serum BDNF is decreased in drug-free and drug-treated BD subjects during manic and depressive episodes compared with HC. Similar serum BDNF levels in drug-free and medicated BD patients.

Table 2. *Cont.*

	Study and Country	Study Design	Sample	Study Aim(s)	Main Findings
15	Piccinni et al. 2014, Italy [60]	Cross-sectional	18 depressed patients (16 BD patients, 2 MDD patients) 19 BD patients with mixed episode 15 HC	To assess BDNF plasma levels in patients with mixed episodes, and compare them with those with a depressed episode and HC	Lower BDNF levels in depressed patients compared to patients with mixed episodes, although the difference was not statistically significant.
16	Poletti et al. 2016, Italy [52]	Cross-sectional	36 BD patients 17 HC	To assess BDNF serum levels in BD patients and HC	Significantly higher serum BDNF levels in BD patients compared with HC were found.
17	Rosa et al. 2014, UK and Spain [69]	Cross-sectional	50 BD I patients 50 HC	To assess BDNF levels in BD I patients compared with HC	Similar levels of plasma BDNF levels in bipolar patients and healthy controls were found.
18	Shahyad et al. 2023, Iran [56]	Cross-sectional	30 BD patients 30 MDD patients 30 HC	To assess the discriminatory properties of BDNF levels for the differential diagnosis of BD and MDD	Lowest BDNF levels in BD compared to MDD or HC.
19	Skibinska et al. 2021, Poland [55]	Longitudinal	27 BD patients 52 MDD patients 31 HC	To assess serum levels of BDNF, proBDNF, mBDFN, and rBDNF	No significant difference in BDNF among patients and controls was found. Higher levels of BDNF in patients with a family history of affective disorders were found.
20	Teng et al, 2021, Cina [57]	Cross-Sectional	45 BD II patients 40 MDD patients 40 HC	To assess the role of BDNF in clinical and cognitive outcomes in medication-naïve patients with BD II and MDD patients	Decreased serum BDNF in MDD and BD II patients with a current depressive episode, compared to HC. BDNF and cognitive deficits are both of low efficiency in distinguishing BD II from MDD.
21	Tramontina et al, 2009, Brazil [40]	Longitudinal	10 BD I patients 10 HC	To assess changes in BDNF serum levels of BD patients during and after treatment of an acute episode	Decreased BDNF levels in BD patients during mania compared to HC. This difference was no longer significant after treatment. A sharp increase in BDNF levels after effective treatment was found. No correlation between BDNF levels either in acute episodes or after treatment with clinical scales was found.
22	Tunca et al, 2014, Turkey [62]	Cross-Sectional	96 BD patients (37 euthymic, 33 manic, 26 depressed) 61 HC	To assess BDNF levels across different episodes in bipolar disorders	Significantly lower BDNF levels during mania and depression compared to euthymic patients and HC. Positive correlation between BDNF levels and lithium levels.

Table 2. *Cont.*

	Study and Country	Study Design	Sample	Study Aim(s)	Main Findings
23	Yoshimura et al, 2006, Japan [63]	Longitudinal	18 BD I patients (12 manic, 6 depressive) 20 HC	To investigate the efficacy of risperidone treatment for both acute manic and depressive episodes in BD	Decreased plasma levels of BDNF in depressed patients compared with manic patients or healthy controls. The administration of risperidone did not alter plasma BDNF levels.
24	Zhao et al, 2017, China [71]	Longitudinal	24 BD patients 37 MDD patients 44 HC	To investigate the role of mature BDNF (mBDNF) and its precursor (proBDNF) in distinguishing bipolar depression (BP) from MDD during acute depressive episode	Lower plasma mBDNF levels and mBDNF/proBDNF ratio in BP compared with MDD. The M/P ratio was restored to normal levels after antidepressant treatment in the MDD group.

BDNF: brain-derived neurotrophic factor; MDD: major depressive disorder; BD: bipolar disorder; HC: healthy controls; SZ: schizophrenia; SMI: severe mental illness; proBDNF: BDNF precursor; mBDNF: mature BDNF; rBDNF: mBDNF/proBDNF ratio; M/P ratio: mBDNF/proBDNF ratio.

4. Discussion

In the past decade, the role of BDNF in the course of BD has been investigated in several studies to gain a better understanding of the neurobiology of the disorder. Despite the large amount of available data, the pathophysiology of BD remains largely unknown [73]. Research on biological and social risk factors for severe mental disorders, particularly for BD, is far from being exhaustive [74,75]. In fact, available studies are highly heterogeneous, in terms of sample characteristics, mood states, and biological techniques.

The majority of studies included adult patients (18–65 years), while others also included adolescents [53]. Moreover, most studies recruited chronic and medicated patients, and only a few included first-onset drug-naive patients [44,45,57,59,61]. Finally, regarding sample selection, some studies included patients during acute or euthymic phases, and others enrolled BD patients regardless of mood state.

Overall, the results of our work show a reduction in BDNF circulating levels during acute phases of BD, which increase after effective therapy. When directly compared, the levels of BDNF were significantly lower in acute phases of BD compared to euthymic patients. This finding is particularly relevant considering that BDNF induces neuronal growth and survival and synaptic long-term potentiation (LTP) [26,76], inhibits the apoptosis cascade (by activating the phospholipase C-gamma), induces its own mRNA transcription (by enhancing phosphatidylinositol 3-Phosphate, PI3K), and modulates gene regulation.

The finding that BDNF levels are reduced in BD vs. healthy controls, and that they are reduced during acute phases vs. euthymia, can potentially link the BDNF levels to the pathophysiology of BD. In fact, the relationship between BDNF, BD, and neuroinflammation is well established. Guan et al. (2006) [77] induced an inflammatory response by administering lipopolysaccharide (LPS) to mice. Interestingly, the authors found a reduced BDNF mRNA in the hippocampus 4 h after the administration, and decreased BDNF circulating levels 7 h after the LPS administration. Studies carried out on patients treated with interferon alpha (INF-α) showed decreased BDNF circulating levels and increased levels of pro-inflammatory cytokines, such as IL-1 and IL-2, in association with the development of depressive symptoms [78]. Further to this, the acute phases of BD seem to be related to neuroinflammation, with microglial activation and immune cell clusters in the brain [79]. During chronic inflammation, pro-inflammatory cytokines bind microglia, with the release of neurotoxic molecules and a decrease in BDNF signaling [37]. Nevertheless, only a few studies have investigated both BDNF levels and neuroinflammation in samples of BD [80]. The relationship between BDNF, neuroinflammation, and mood episodes should be further investigated in order to improve the knowledge of the pathogenesis of BD.

The majority of studies included in the DNA/mRNA section of our review showed a correlation between BDNF signaling downregulation and BD. In fact, lower circulating BDNF mRNA levels have been found in patients compared to HC. Furthermore, Cinar RK et al. (2016) [45] observed a significant increase in BDNF mRNA levels during the remission period compared with the acute phase. This result can be explained by the fact that mRNA molecules store genetic information that will be decoded and translated into proteins [81]; therefore, decreased mRNA levels reported during acute phases of the disorder can be considered an indirect sign of BDNF levels downregulation. These findings highlight that BDNF may be a biomarker of BD and that its proteolytic conversion may be important in the pathophysiology of BD.

Only one study reported a significant correlation between childhood trauma and BDNF levels [39]. This result, although it requires further investigation, is of particular relevance, since childhood trauma has been reported as one of the most significant risk factors for the development of severe mental disorders and is associated with negative outcomes [82,83], and with a stable dysregulation of other biological pathways, including that of calcium metabolisms—which includes parathormone, vitamin D, and serum levels of calcium—and the hypothalamic–pituitary–adrenal axis [84]. Available research does not allow us to infer the causal relationship between BDNF levels and childhood trauma,

but it is possible to hypothesize that low BDNF levels could lead to a reduced resilience to childhood trauma, thus linking trauma to psychopathology.

Another relevant finding is the higher methylation in BDNF gene promoter found in BD patients [48]. Since methylation is a form of epigenetic silencing [85], its presence can be considered an indirect sign of BDNF downregulation.

Only two studies have investigated the Val66Met mutation, also known as the rs6265 SNP. This polymorphism does not seem to alter BDNF biological activity, but it can impair activity-dependent release, resulting in reduced BDNF circulating levels [86]. A correlation between the polymorphism and features that are usually associated with a worse outcome has been found, in line with the hypothesis that the downregulation of BDNF signaling can be associated with a more severe BD course.

Among all articles included in our work, only Zhao et al. (2017) [71] and Skibinska et al. (2021) [55] focused on mature and pro BDNF. While Skibinska et al. found no significant differences, Zhao et al. found decreased mBDNF levels and a lower M/P ratio in BD compared to HC. Interestingly, in a 2013 work, Södersten et al. [87] observed higher mBDNF levels and M/P ratio in mood-stabilized BD patients vs. HC. This heterogeneity in findings could have several explanations, such as differences in mood states or the presence of an effective pharmacological treatment.

It has to be noted that ethnic differences in Val66Met polymorphism [88] and in mature/pro BDNF levels [89] have been reported. However, possible explanations underlying these differences are currently unknown and none of the studies included in this review have addressed this issue. Therefore, further investigations are still needed in order to provide a reasonable explanation of these differences and to assess whether they have an impact on clinical practice.

Taken together, the results of our work show BDNF to be a promising biomarker, with possible future applications in clinical practice. In particular, in the near future, BDNF levels could be used to support the diagnosis of BD, to improve precision in the detection of early stages of BD, and to differentiate between BD and other affective disorders, such as major depressive disorders. In fact, although BD and MDD are distinct clinical entities, they share clinical features, resulting in high rates of misdiagnosis in some cases [90]. As an example, the frequent occurrence of depressive episodes and the later onset of mania in BD subjects may delay a proper diagnosis for years, resulting in greater severity of symptoms, impaired psychosocial functioning, treatment resistance, and higher suicidality [91]. Such a delay is also associated with a higher number of lifetime relapses and hospitalizations, with increased direct and indirect costs associated with the treatment and management of both MDD and BD [92]. Despite increasing knowledge of the pathophysiology of affective disorders, clear clinical indicators and biomarkers for a reliable differential diagnosis between MDD and BD are still missing, which calls for an investigation of novel indices and biomarkers. Future studies are needed in order to identify the predictive role of BDNF in differentiating between MDD and BD. These studies should include the inclusion of patients with affective disorders (MDD and BD) both during acute phases and in euthymic states and should compare their BDNF levels with healthy controls. However, in line with a precision medicine approach, BDNF might be useful in order to predict response to pharmacological treatments in BD patients, since the link between response to treatments and BDNF expression has been reported in some studies included in this review. However, data in this regard are too scarce, and large multicentric studies are needed to support this early evidence.

Our findings should be interpreted in light of some limitations. First, this is not a systematic review; however, we used the most frequently searched scientific databases using generic keywords in order to include as many articles as possible. Furthermore, we did not identify any RCT potentially eligible for inclusion in the review. Additionally, high heterogeneity has been observed regarding sample size, clinical differences among included patients, and data analysis approaches, reducing comparisons among studies. Moreover, we included only papers enrolling patients with BD. It is still unknown if BDNF

should be considered as a trans-nosographic marker for more psychiatric disorders, or if it is pathognomonic of a specific condition, such as BD [93,94].

5. Conclusions

Taken together, the results of our review show a correlation between the downregulation of BDNF and BD, suggesting a potential role as a biomarker of this neurotrophic factor. In fact, BDNF could be used as a marker for acute BD states and as a marker of clinical response to pharmacological treatments since the normalization of BDNF circulating levels has been found after effective pharmacological treatment. However, this interpretation remains speculative and further studies with larger and less heterogeneous samples are required. Another area open to research is the potential pathogenetic role of BDNF, since its modifications can be a cause or a consequence of BD. Future studies on BDNF and neuroinflammation will clarify the exact mechanism underlying the changes in BDNF serum levels.

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brain sciences

MDPI

Systematic Review

Comparison between Single-Dose and Two-Dose Psilocybin Administration in the Treatment of Major Depression: A Systematic Review and Meta-Analysis of Current Clinical Trials

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Abstract: Current pharmacological treatments for major depressive disorder (MDD) are often only partially effective, with many patients experiencing no significant benefit, leading to treatment-resistant depression (TRD). Psilocybin, a classical serotonergic psychedelic, has emerged as a notable emerging treatment for such disorders. The aim of this systematic review and meta-analysis is to summarize and discuss the most recent evidence about the therapeutic effects of single-dose and two-dose psilocybin administration on the severity of depressive symptoms, as well as compare the efficacy of these interventions among patients with a primary diagnosis of MDD or TRD. Articles were collected from EBSCOhost and PubMed following the PRISMA guidelines, yielding 425 articles with 138 duplicates. After screening 287 records, 12 studies met the eligibility criteria and were included in the review. A quantitative analysis of the studies indicates that psilocybin is highly effective in reducing depressive symptoms severity among patients with primary MDD or TRD. Both single-dose and two-dose psilocybin treatments significantly reduced depressive symptoms severity, with two-dose administration sometimes yielding more pronounced and lasting effects. However, it is unclear if this was solely due to dosage or other factors. Future research should include standardized trials comparing these dosing strategies to better inform clinical practice.

Keywords: major depressive disorder; MDD; treatment-resistant depression; TRD; psilocybin; psychedelics

1. Introduction

Major depressive disorder (MDD) is one of the most diagnosed psychiatric disorders worldwide, and it afflicts between 4% and 5% of the global population each year [1,2]. In addition to being extremely disabling in most cases, with symptoms such as significant mood swings, anhedonia, and recurrent thoughts about death, it also affects the individual's vital spheres of appetite, sleep, psychomotor activity, and attention [3]. MDD comes with a heavy financial burden as well [4]. During the eight-year period 2010–2018, the economic burden associated with adults with MDD in the United States grew from $236.6 billion to $326.2 billion, an increase of 37.9% [5]. Currently, the management of MDD involves the use of various psychotherapeutic approaches, such as cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT), as well as assorted pharmacological interventions, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), as well as serotonin and norepinephrine reuptake inhibitors (SNRIs) [6]. However, despite

the availability of such treatments, a significant percentage of patients, around 30%, do not respond positively to two or more of the psychotherapeutic or pharmacological strategies available on the market [7]. In these cases, the label of treatment-resistant depression (TRD) is given [8]. The drugs currently used for the treatment of MDD, other than being often ineffective [9], also present numerous side effects. The most frequently discussed aftereffects in the literature are: sexual problems and dysfunctions (that may persist even after stopping the treatment) [10,11], nausea [12], weight gain [13,14], and alterations to sleep structure (e.g., a prolongation of the REM phase and an increase in the number of awakenings) [12]. Furthermore, discontinuing SSRIs after prolonged use can result in withdrawal symptoms such as headaches, anxiety, agitation, and lethargy, although these tend to resolve within three weeks [15]. The latency period of these drugs is quite long, ranging from 2 to 12 weeks [16]. This latency could lead to adverse consequences, such as non-adherence to therapy and an increased risk of suicide [17]. Six meta-analyses on the suicide rate [18–23] discovered that individuals with MDD did not see a decrease in suicide ideation after SSRI therapy. Notably, a meta-analysis found that it was even higher [18].

Every important aspect that has been brought up emphasizes how crucial it is to look for novel, potentially effective, pharmaceutical treatments. Currently, among the new drugs explored for the treatment of MDD is psilocybin, i.e., a compound found within more than a hundred species of fungi, mostly belonging to the family *Psilocybe*. Psilocybin can be considered a psychotropic substance due to the hallucinogenic properties of its active metabolite, i.e., psilocin. In particular, psilocybin belongs to the category of classical serotoninergic psychedelics, and it is characterized by inducing altered states of consciousness through heterogeneous molecular mechanisms [24]. Indeed, psilocybin was originally thought to act as a serotonergic (5-HT) receptor agonist [25], specifically the 5HT-2A receptor, believed to be responsible for the substance's potent hallucinogenic effects [26]. However, more recent investigations indicated that psilocin binds with high affinity to tropomyosin receptor kinase B (TrkB) receptors for brain-derived neurotrophic factor (BDNF), and its effects on synaptic plasticity as well as antidepressant-like behavior in mice depended on TrkB-BDNF signaling but were independent of 5-HT2A receptor activation [27].

In contrast to conventional antidepressant drugs, psilocybin, like other psychoactive substances (e.g., ketamine; [28,29]), showed a rapid onset of action, with significant improvements in depressive symptoms severity observed as early as the first few days after treatment [30]. Although ketamine has already shown strong response rates among MDD patients [31], its therapeutic effects are closely associated with the development of tolerance, dependence, and the potential risk of abuse, as well as the sporadic occurrence of severe adverse events (e.g., dissociation and sedation) and withdrawal-related symptoms [32,33]. Conversely, psylocibin shows a significantly lower physical dependence potential, and its side effects, including headache, nausea, and dizziness, appear milder and rarer [34–36]; yet, it can still cause tolerance, and psychological dependence might occasionally develop [37,38]. Psilocybin tends to be administered orally, and its effects last from two to six hours [39]. Importantly, drug delivery is accompanied by preparatory and integrative psychological sessions, forming an indispensable part of the broad treatment protocols [40,41]. Psychological guarantees not only support during the psychedelic experience to guarantee a reduction of adverse effects [42], but also a reflection and elaboration of the experiences lived during such a timeframe, thus allowing the remission of symptoms to be maintained even in the long term [43,44].

An issue that can be found upon careful analysis of clinical trials conducted with psilocybin for the treatment of MDD is that there is currently no unified treatment. This might be linked to the relative novelty of the research field, and conducting trials with different designs potentially allows to infer which modalities of drug use are most effective. The data currently available on psilocybin are increasing drastically, and between clinical trials, numerous differences can be observed in terms of psychological support (e.g., duration of sessions, support offered, psychotherapeutic orientation), dosage (e.g., varies in a range

from 10 mg to 30 mg), and number of administrations (e.g., one, two, or more than two). Although one systematic review measuring the efficacy of the different numbers of dosing sessions already exists [45], there is no recent systematic review and/or meta-analysis in the literature comparing the efficacy of different numbers of psilocybin administrations in a sample of patients with a primary diagnosis of MDD or TRD, also discussing the evidence brought to light by the latest clinical trials.

The aim of this systematic review is to (1) summarize and discuss the current evidence on the therapeutic effects of single-dose and two-dose psilocybin administration on MDD and TRD core symptoms, and to (2) compare the efficacy of these two approaches in reducing depressive symptoms severity among patients with a primary diagnosis of MDD or TRD.

2. Materials and Methods

The present systematic review and meta-analysis was carried out referring to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [46], and it was successfully registered on the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42024543828).

2.1. Information Sources and Research Strategies

A literature search was conducted to identify studies using one or two doses of psilocybin for the treatment of MDD. The search was carried out within two electronic databases: PubMed and EBSCOhost, which comprise records retrieved from PsycINFO, PsycARTICLES, PSYNDEX: Literature and Tests, MEDLINE, and ERIC. The search string used was as follows: "("psilocybin" OR "psilocybin-assisted") AND ("major depressive disorder" OR MDD OR "treatment-resistant depression" OR TRD OR "secondary depression" OR "depression") AND ((clinical trial) OR ((randomized controlled trial) OR (RCT)) OR ((open trial) OR (open-label)))". The two databases were last searched on 27 February 2024.

2.2. Eligibility Criteria

Below are the eligibility criteria drawn up on the basis of the PICOs model [47], which allowed the selection of the studies in this systematic review. To be included in this systematic review, studies needed to meet the following inclusion criteria:

- Language: only articles in English were selected. This is for uniformity with other systematic reviews in the literature.
- Population: as it was the aim of this systematic review to investigate the efficacy of psilocybin with a focus on MDD, it was considered necessary to select only the population with a primary diagnosis of MDD, including subjects with TRD, a label of MDD itself.
- Types of studies: only data from clinical trials conducted on humans were taken into account.
- Intervention: only those studies involving the administration of a single dose or two doses of psilocybin were included, regardless of the specific dosage and mode of administration.
- Outcome: only studies that assessed a possible decrease in the severity of depressive symptoms among participants using standardized instruments were included.
- Comparison: the presence of one or more control groups that were treated with active (e.g., niacin) or standard placebo (e.g., saline) was not mandatory for inclusion.

Studies were excluded from the systematic review in the following cases:

- Population: trials with participants who did not report a diagnosis of MDD or reported it as a secondary diagnosis to other psychiatric disorders or other conditions of organic nature (e.g., cancer) were excluded.
- Types of studies: clinical trials performed on animal models, case studies, and systematic reviews were excluded.

- Intervention: studies in which other psychedelics than psilocybin, e.g., mescaline or bufotenine, were administered to patients were excluded, as well as studies involving no or more than two doses of psilocybin.
- Outcome: trial studies that did not include scales measuring depressive symptoms or in which timepoints were missing were excluded.

2.3. Study Screening and Selection Process

Using Zotero (Version 6.0.31, https://www.zotero.org accessed on 1 March 2024), the first author eliminated duplicates after conducting searches in the electronic databases and finding pertinent studies. Both the primary and secondary authors conducted independent screenings of all the data based on the inclusion and exclusion criteria. Two steps made up the screening process: (1) authors checked to see if preprints, conference presentations, research protocols, or non-clinical trial articles were retrieved; and (2) specific inclusion criteria related to participants, intervention, outcome measure, and study design were applied for the assessment of the remaining manuscripts. The situations that were determined to be ambiguous were further examined with the help of other authors.

2.4. Data Extraction Process

Data were extracted from the full text of the articles. The data extracted for this review were as follows: research design, sample details (number of participants, % women, mean age, and standard deviation), measurements conducted (rating scales used to measure depressive symptoms), participants' diagnoses (with assessment of severity), dosages used (number of doses and quantity in mg), treatment structure (including information on psychological support and group treatment conditions), and the results that emerged regarding depressive symptoms. The extraction work was carried out by the first author with the help of the others in cases of ambiguity.

2.5. Risk of Bias in Individual Studies

The risk of bias was assessed using the updated Cochrane Risk-of-Bias tool for randomized controlled trials (RoB 2; [48]) for articles that had a randomized design, whereas using the Risk of Bias in Non-randomized Studies—of Intervention (ROBINS-I; [49]) for the studies lacking a control group. Employing the RoB2, five domains were assessed: (1) bias arising from the randomization process; (2) risk of bias due to deviations from the intended interventions; (3) risk of bias due to missing outcome data; (4) risk of bias in measurement of the outcome; and (5) risk of bias in selection of the reported result. On the other hand, using the ROBINS-I, seven domains were assessed: (1) bias due to confounding; (2) bias in selection of participants into the study; (3) bias in classification of interventions; (4) bias due to deviations from intended interventions; (5) bias due to missing data; (6) bias in measurement of outcomes; and (7) bias in selection of the reported results.

2.6. Statistical Analysis

Two separate meta-analyses were conducted to evaluate the treatment effect on patients' depressive symptoms severity. First, we examined the effect size linked to the active intervention alone, considering the standardized mean difference (SMD), i.e., Cohen's d, between post-treatment and baseline scores within the active treatment groups. Second, we tested whether there was a significant treatment effect compared to control, thus considering the SMD between post-treatment scores obtained by active and control groups, where applicable. The formula SD = SEM $\times \sqrt{n}$ (n = sample size) was used for the conversion of standard errors of the mean (SEM) into standard deviations (SD). Both meta-analyses were carried out using random effects models due to the large heterogeneity in the estimates. Funnel plots were employed in order to visually assess heterogeneity and potential outliers. Cochran's Q was used to assess heterogenicity in the effect size distribution, while the I^2 index (95% confidence interval) was employed to evaluate heterogeneity resulting from effect size variability and sampling error. Heterogeneity levels (I^2) were

categorized as low at 25%, moderate at 50%, and high at 75% [50]. To examine publication bias, Egger's [51] test was computed. The analyses were performed using R (Version 4.4.1, https://www.r-project.org accessed on 15 June 2024).

3. Results

The search results and the study selection process are depicted in the flowchart below (Figure 1). The search string, once entered into the two databases, produced a total of 425 results (of which 170 on PubMed and 255 on EBSCOhost). Following removal of duplicates (N = 138), 287 articles were screened. Following reading of the title and abstract 268 were excluded, leading to 20 studies. All studies were found; therefore, 20 trials were subjected to the final screening step by full text reading. A further 8 studies were excluded as they did not meet the eligibility criteria outlined above. Three studies were excluded because participants' primary diagnosis was not MDD [52–54], one because it was not a clinical trial but a research protocol [40], and four because they reported other variables of no interest for the present review on the population affected [55–58]. Overall, the studies included in this review were 12 [30,59–69].

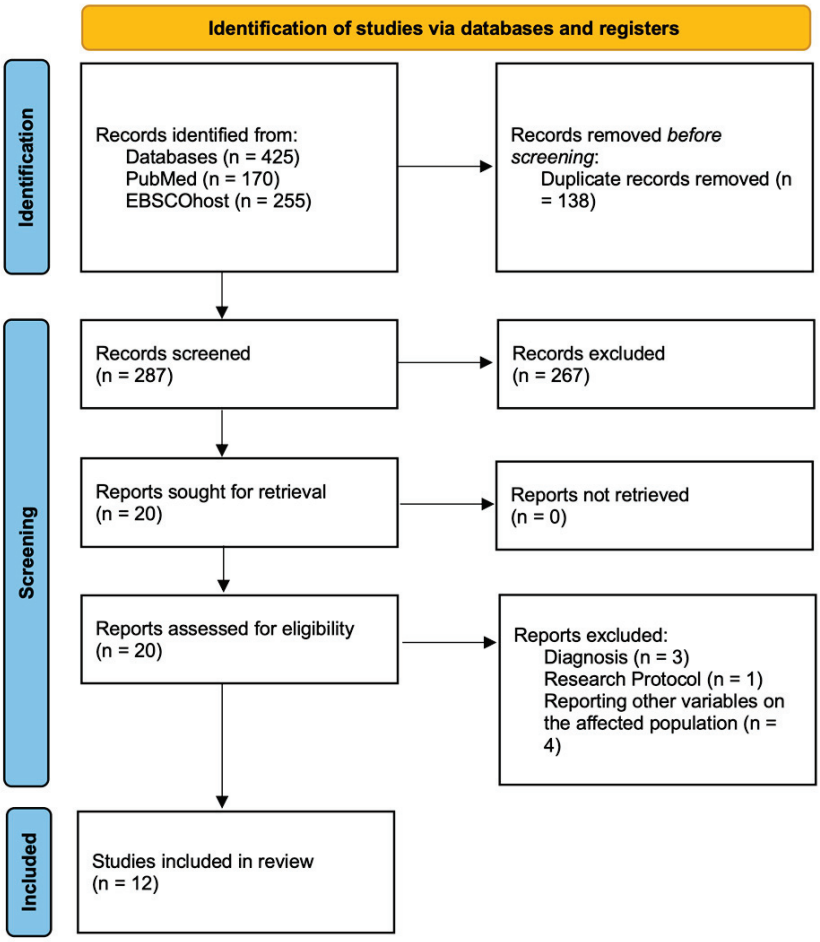

Figure 1. PRISMA Flow Chart. Adapted from Page et al. [46]. For more information, please visit: https://www.prisma-statement.org accessed on 1 April 2024.

3.1. Risk of Bias Assessment

Using the RoB2 tool, all six randomized controlled studies were judged to have a low risk of bias in all five domains, resulting in an overall low risk of bias (Figure 2).

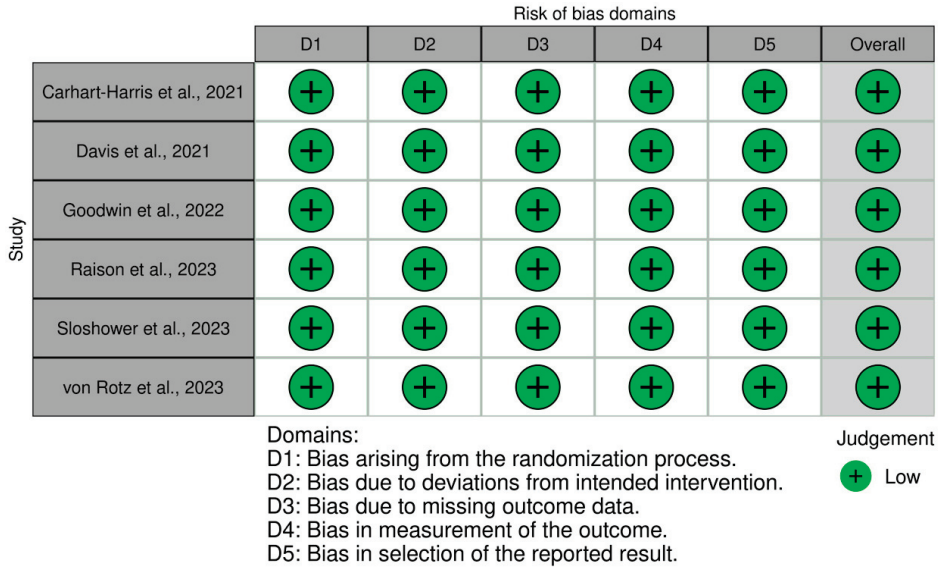

Figure 2. Traffic light plot showing risk of bias assessment of the included studies using the RoB2 tool [30,62,64,67–69].

On the other hand, the six non-randomized or non-controlled trials, assessed using the ROBINS-I tool, emerged with a global moderate-level risk of bias (Figure 3). The first and sixth domains (bias due to confounding, bias in measurement of outcomes) resulted moderately in all five studies included. Moreover, two studies showed a moderate level of bias in the seventh domain (bias in selection of the reported result), and one study was evaluated with a moderate level of risk of bias in the fifth domain (bias due to missing data).

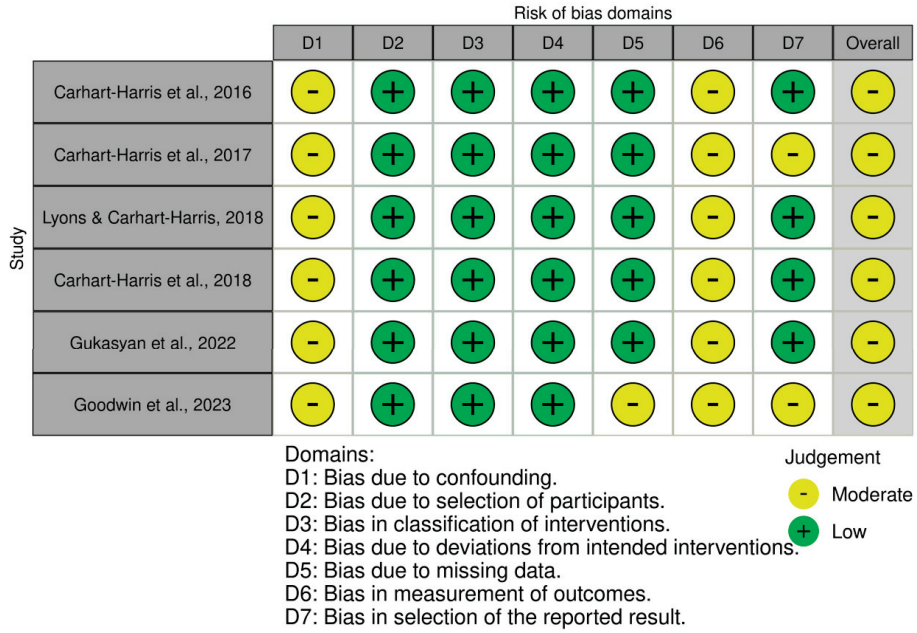

Figure 3. Traffic light plot showing the risk of bias assessment of the included studies using the ROBINS−I tool [59–61,63,65,66].

3.2. Sample Demographics

A total of 600 subjects were included from all the studies discussed. The mean age of the sample was 41.61 (2.13) years. A total of 51.1% of the sample was male, whereas 48.9% of subjects were female. Of the total subjects, 515 (85.8%) had a diagnosis of MDD,

while 85 (14.2%) were affected by TRD. In most cases, moderate-to-severe depression was diagnosed. See Table 1 for more detailed information concerning each study.

Table 1. Summary of the demographic characteristics of the samples from all the included studies.

ID	Sample Size (*n*)	% Female	Age, Mean (DS)	Diagnosis with Severity
Carhart-Harris et al., 2016 [59]	12	50%	42.6 (10.2)	TRD: moderate-severe, HAMD = 19.2
Carhart-Harris et al., 2017 [60]	19	21%	42.8 (10.1)	TRD: severe, QIDS = 18.9
Carhart-Harris et al., 2018 [61]	20	30%	44.1 (11)	TRD: severe, BDI = 34.5
Lyons and Carhart-Harris, 2018 [66]	15	27%	45.4 (2.9)	TRD: moderate-severe, BDI = 34.3
Carhart-Harris et al., 2021 [30]	59	34%.	41.2	MDD: moderate-severe, BDI = 29.1
Davis et al., 2021 [62]	24	67%	39.8 (12.2)	MDD: moderate-severe, HAMD = 22.8
Goodwin et al., 2022 [64]	233	52%	39.8 (12.2)	MDD: moderate (30%), Severe (68%)
Gukasyan et al., 2022 [65]	24	67%	39.8 (12.2)	MDD: moderate-severe, HAMD = 22.8
Goodwin et al., 2023 [63]	19	58%	42.2 (10.8)	TRD: moderate; MADRS = 31.7
Raison et al., 2023 [67]	104	50%	41.1 (11.3)	MDD: moderate-severe, MADRS = 35.25
Sloshower et al., 2023 [68]	19	68%	42.8 (13.8)	MDD: moderate-severe, HAMD = 22.57
von Rotz et al., 2023 [69]	52	63%.	36.75	MDD: moderate, BDI = 27.35

Notes: MDD = Major Depressive Disorder, TRD = Treatment-resistant Depression, BDI = Beck Depression Inventory, HAMD = Hamilton Rating Scale for Depression, MADRS = Montgomery-Åsberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptomatology, DS = standard deviation.

3.3. Effects of a Single Dose of Psilocybin on Depressive Symptoms

Goodwin et al. [64] conducted a double-blind dose-finding parallel-group randomized trial, consisting of three groups of subjects with MDD: the first group (n = 79, 56% female, mean age: 40.2 ± 12.2) received a 25 mg dose of psilocybin, the second group (n = 75, 55% female, mean age: 40.6 ± 12.8) received a 10 mg dose of psilocybin, and the third group (n = 79, 46% female, mean age: 38.7 ± 11.7), considered a placebo, was given a 1 mg dose of psilocybin. Three weeks after the intervention, a decrease from baseline on the MADRS scale of 12 points was observed in the first group (i.e., 25 mg), of 7.9 points in the second group (i.e., 10 mg), and of 5.4 points in the third group (i.e., 1 mg). Following treatment, the mean difference between the first and third groups was statistically significant (mean difference: −6.6, 95% CI [−10.2; −2.9], $p < 0.001$), whereas the mean difference between the second and third groups was not (mean difference: −2.5; 95% CI [−6.2; 1.2], $p = 0.18$) [64]. The same research group conducted a subsequent open-label fixed-dose exploratory trial on 19 patients with TRD currently using SSRIs augmented with a single 25 mg dose of psilocybin [63]. At 3 weeks after treatment, a decrease of 14.9 points (95% CI [−20.7; −9.2]) was detected on the MADRS. Furthermore, such improvement in patients' depressive symptoms severity was apparent at 2 days after treatment and maintained throughout the 3-week follow-up [63]. Based on these findings, Raison et al. [67] applied a randomized placebo-controlled trial on 104 patients with MDD, in which the treatment group (n = 51, 47% female, mean age: 40.4 ± 11.7) received a single dose of 25 mg psilocybin followed by niacin, whereas the control group (n = 53, 53% female, mean age: 41.8 ± 11.7) received two subsequent 100 mg doses of niacin. Forty-three days after treatment, the mean difference between the two groups was 12.3 ($p < 0.001$) in favor of the psilocybin-treated group [67]. Conversely, Sloshower et al. [68] conducted a placebo-controlled within-subject fixed-order trial on 19 patients with a diagnosis of MDD undergoing an initial administration of a placebo dose (i.e., microcrystalline cellulose) followed by the dispensation of a 0.3 mg/kg dose of psilocybin, 4 weeks apart. In partial contrast to the previously discussed studies, here depressive symptoms severity significantly decreased following both placebo and

psilocybin intervention, with no significant difference in the degree of change between the two conditions. However, antidepressant effect sizes were larger after psilocybin (d = 1.02–2.27) than after placebo (d = 0.65–0.99) [68]. Lastly, von Rotz et al. [69] employed a double-blind randomized trial comprising 52 participants with MDD subdivided into two independent groups: the experimental group (n = 26, 65% female, mean age: 37.6 ± 10.9) was treated with a 0.215 mg/kg dose of psilocybin, whereas the control group (n = 26, 62% female, mean age: 37.6 ± 10.9) was given a placebo dose. Fourteen days after the intervention, the psilocybin administration resulted in an absolute decrease in depressive symptom severity of 13 points from baseline (95% CI [−15.0; −1.3], $p < 0.01$, d = 0.97) in the MADRS scores and reached an absolute decrement of 13.2 points (95% CI [−13.4; −1.3], $p < 0.05$, d = 0.67) in the BDI scores. Also, the depression-related subscale of SCL-90-R showed a statistically significant mean difference between the active and control groups following the treatment (mean difference: −0.83, 95% CI [0.18; 1.01], $p < 0.01$, d = 0.83) [69]. Table 2 shows more detailed specifics of each above-mentioned clinical trial in which a single dose of psilocybin was administered.

Table 2. Summary of the characteristics of the studies in which a single-dose psilocybin was used.

ID	Study Design	Treatments	Psilocybin Dosage	Control (Dosage)	Clinical Measures	Effects
Goodwin et al. (2022) [64]	RCT	Three preparatory meetings, one dose of psilocybin with music, and two psychological integration sessions	10 mg or 25 mg	Psilocybin (1 mg)	MADRS	Mean MADRS scores decreased by 12 points in the first group (25 mg), by 7.9 points in the second group (10 mg), and by 5.4 in the third group (1 mg) at 3 weeks after treatment
Goodwin et al. (2023) [63]	Open-label	Three preparatory meetings, one dose of psilocybin with music, and two integration sessions	25 mg	-	MADRS, QIDS	Mean MADRS scores decreased by 14.9 points at week 3 weeks after treatment
Raison et al. (2023) [67]	RCT	Preparatory sessions totaling 6–8 h, one dose of psilocybin or niacin with music, followed by 4 h integration sessions	25 mg	Niacin (100 mg)	MADRS	Significant reduction in mean MADRS scores in the treatment group (−19.1) compared to controls (−6.8) from baseline to 43 days after treatment
Sloshower et al. (2023) [68]	Placebo-controlledwithin-subjects	2 h preparatory sessions, a single dose of psilocybin or placebo, and two sessions of psychotherapy	0.3 mg/kg	Placebo	HAMD, QIDS	Greater reduction in mean QIDS scores following psilocybin administration (Δ = 6.3–8.7) than placebo (Δ = 4.4–5.8) at 2 weeks after treatment
von Rotz et al. (2023) [69]	RCT	Two preparatory sessions, one dose of psilocybin or placebo, and three integration sessions	0.215 mg/kg	Placebo	MADRS, BDI	Reduction in mean MADRS scores in the treatment group (−13.2) compared to baseline, with an effect size significantly larger than placebo at 2 weeks after treatment

Notes: RCT: Randomized Controlled Trial, BDI = Beck Depression Inventory, HAMD = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptomatology.

3.4. Effects of a Two-Dose Psilocybin Administration on Depressive Symptoms

Carhart-Harris et al. [59] conducted an open-label feasibility trial on 12 subjects with moderate-to-severe TRD in which two oral doses of psilocybin (10 mg and 25 mg) were administered 7 days apart. At 1-week after treatment, psilocybin markedly reduced depressive symptoms severity compared to baseline (mean difference: −11.8, 95% CI [−14.35; −9.15], $g = 3.1$, $p < 0.01$). Such an improvement in patients' clinical conditions remained significant even at 3-month follow-up (mean difference: −9.2, 95% CI [−12.71; −5.69], $g = 2$, $p < 0.01$) [59]. The same research group carried out an additional pre-post neuroimaging study on 19 subjects with a diagnosis of TRD, applying the same intervention modalities as outlined above and also collecting self-reported clinical outcomes [60]. They highlighted that the delivery of two doses of psilocybin successfully reduced patients' depressive symptoms severity at 5 weeks after treatment compared to baseline (mean difference: −8, $t = -6.3$, $p < 0.001$) [60]. Carhart-Harris et al. [61] conducted a third open-label single-arm trial, recruiting 20 subjects with TRD who received two doses of psilocybin (10 mg and 25 mg), spaced 7 days apart. Here, measurements of depressive symptoms severity were taken at baseline, 1-week, 2 weeks, 3 weeks, and 5 weeks after treatment, as well as at 3-month and 6-month follow-up. QIDS scores showed a significant decrease in all timepoints compared to baseline with the maximum effect size at 5 weeks ($t = -7.2$, $p < 0.001$, d =2.3). Moreover, of the 19 patients who completed the follow-up, all showed a reduction in depression intensity already at 1-week, and for most of them this clinical improvement persisted until 3–5 weeks [61]. Lyons and Carhart-Harris [66] carried out a further open-label pilot study on 15 individuals with a diagnosis of TRD, undergoing two dosing sessions: an initial safety dose (i.e., 10 mg) and a subsequent treatment dose (i.e., 25 mg) 1 week later. Clinical patients showed a significant decrease in BDI scores at 1-week after the psilocybin treatment compared to baseline ($t = 7.9$, 95% CI [16.17; 28.23], $p < 0.001$, $g = 1.9$) [66]. Unlike the above-mentioned investigations, Carhart-Harris et al. [30] recruited 59 patients with moderate-to-severe MDD in a double-blind randomized controlled trial. Participants were assigned to two independent groups: the treatment group ($n = 30$, 30% female, mean age: 43.3 ± 9.7) was given two 25 mg doses of psilocybin 3 weeks apart, along with a daily placebo for 6 weeks, whereas the active control group ($n = 29$, 31% female, mean age: 41.2 ± 11.7) received two placebo doses, also 3 weeks apart, but with daily escitalopram. Six weeks following the intervention, the mean QIDS scores dropped from baseline by 8 points in the treatment group and by 6 points in the active control one, leading to a non-statistically significant between-group difference equal to 2 points (95% CI [−5.0; 0.9]) [30]. Another randomized controlled trial was carried out by Davis et al. [62], who collected data from 24 subjects with MDD. Here, participants were split into two groups: the treatment group ($n = 13$, 69% female, mean age: 43.6 ± 13.0) received immediate medication consisting of two psilocybin administrations of 20 mg and 30 mg, respectively, whereas the control group ($n = 11$, 64% female, mean age: 35.2 ± 9.9) remained on the waiting list. Psilocybin successfully ameliorated patients' depressive symptoms severity with larger effect sizes at 5 weeks ($d = 2.5$, 95% CI [1.4; 3.5], $p < 0.001$) and 8 weeks ($d = 2.6$, 95% CI [1.5; 3.7], $p < 0.001$) after treatment. Conversely, the control group remained stable at both timepoints compared to baseline [62]. Lastly, Gukasyan et al. [65] conducted a follow-up study by adding to the original sample of Davis et al. [62] those clinical patients who were previously included in the waiting list (and who had now received the same treatment as the experimental group). Compared to baseline, subjects' depressive symptoms severity was markedly decreased across the following timepoints: 1-week, 1-month, 3-months, 6-months, and 12-months after treatment, with larger effect sizes at 6-months ($d = 2.6$) and 12-months ($d = 2.4$). The mean difference between the baseline scores and the various timepoints was statistically significant ($F = 34.9$, $p < 0.001$, $\eta^2_p = 0.61$), but no significant effect of condition (i.e., immediate versus delayed treatment) or a time-by-condition interaction was detected [65]. Table 3 shows more detailed specifics of each above-mentioned clinical trial in which two doses of psilocybin were administered.

Table 3. Summary of the characteristics of the studies in which two doses of psilocybin were used.

ID	Study Design	Treatments	First Psilocybin Dosage	Second Psilocybin Dosage	Control (Dosage)	Clinical Measures	Effects
Carhart-Harris et al. (2016) [59]	Open-label	Preparatory sessions totaling 4 h, two doses of psilocybin with music, 1-week apart, and two integration sessions	10 mg	25 mg	-	QIDS, BDI, HAMD, MADRS	Decrease in QIDS scores compared to baseline (−11.8) at 1-week after treatment. A further decrement in mean QIDS scores (−9.2) was observed at 3-month follow-up
Carhart-Harris et al. (2017) [60]	Open-label	Preparatory sessions totaling 4 h, two doses of psilocybin with music, 1-week apart, and two integration sessions	10 mg	25 mg	-	QIDS	Reduced QIDS scores compared to baseline (−8.0) at 5 weeks after treatment
Carhart-Harris et al. (2018) [61]	Open-label	Preparatory sessions totaling 4 h, two doses of psilocybin with music, 1-week apart. After each dose, an integrative session was conducted	10 mg	25 mg	-	QIDS, BDI, HAMD	Reduction in mean QIDS scores compared to baseline at 1-week, 2 weeks, 3 weeks, 5 weeks, and 3 months after treatment. BDI scores were significantly lower compared to baseline at 1-week, 3-months, and 6-months after treatment
Lyons and Carhart-Harris (2018) [66]	Open-label	Preparatory sessions totaling 4 h, two doses of psilocybin with music, 1-week apart, and two integration sessions	10 mg	25 mg	-	BDI, HAMD	Decrease in BDI scores (−22.2) compared to baseline at 1-week after treatment
Carhart-Harris et al. (2021) [30]	RCT	Preparatory sessions totaling 3 h, two doses of psilocybin or escitalopram, 3 weeks apart, and an integrative session	25 mg	25 mg	Psilocybin (1 mg)	QIDS, BDI, HAMD, MADRS	At 6 weeks, the mean QIDS change score compared to baseline was −6.0 in the escitalopram group and −8.0 in the psilocybin group
Davis et al. (2021) [62]	Randomized waiting-list	Preparatory sessions totaling 8 h, two doses of psilocybin with music, spaced ~2 weeks apart, and two integration sessions	20 mg	30 mg	Waiting list	HAMD, QIDS	Mean HAMD scores decreased in the immediate treatment group compared to baseline at 1-week (−8.0) and 1-month (8.5) after treatment. Mean HAMD scores remained stable in subjects belonging to the waiting list

Table 3. *Cont.*

ID	Study Design	Treatments	First Psilocybin Dosage	Second Psilocybin Dosage	Control (Dosage)	Clinical Measures	Effects
Gukasyan et al. (2022) [65]	Follow-up	Preparatory sessions totaling 8 h, two doses of psilocybin with music, spaced ~2 weeks apart, and two integration sessions	20 mg	30 mg	-	HAMD, QIDS	Mean HAMD scores decreased in both immediate and delayed treatment groups compared to baseline at 1-week, 1-month, 3-months, 6-months, and 12-months after treatment

Notes: RCT: Randomized Controlled Trial, BDI = Beck Depression Inventory, HAMD = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, QIDS = Quick Inventory of Depressive Symptomatology.

3.5. Single-Dose versus Two-Dose Psilocybin Administration on Depressive Symptoms

Random-effect meta-analysis showed that psilocybin significantly reduces patients' depressive symptoms severity compared to baseline ($z = -12.11$, $p < 0.001$, $d = -2.14$, 95% CI [−2.48; −1.78]; Figure 4). Such an effect was observed not only when single-dose psilocybin was administered (k = 6), but also when two-dose psilocybin was delivered (k = 7). Although two-dose psilocybin treatment displayed a more pronounced effect size compared to single-dose intervention ($d = -2.42$, 95% CI [−2.74; −2.11] versus $d = -1.87$, 95% CI [−2.43; −1.30]), the test for subgroups difference was not statistically significant ($\chi^2_{(1)} = 2.86$, $p = 0.09$). Overall heterogeneity resulting from effect size variability and sampling error was high ($I^2 = 73.1\%$, 95% CI [53.2%; 84.5%]; H = 1.93, 95% CI [1.46; 2.54], $\tau^2 = 0.27$, 95% CI [0.07; 0.86]), as well as the heterogeneity in the effect size distribution ($Q_{(12)} = 44.62$, $p < 0.001$). The funnel plot displayed minor signs of asymmetry and a few outliers (Figure 5). Nonetheless, such asymmetry was not statistically significant ($t_{(10)} = -0.85$, $p = 0.39$).

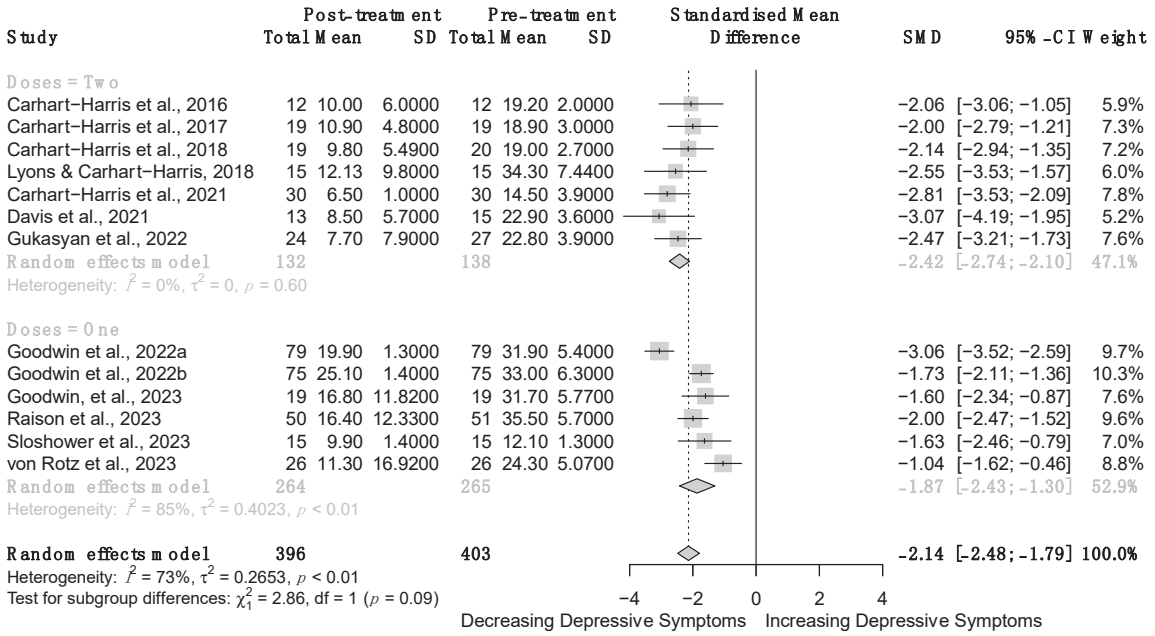

Figure 4. Forest plot of the meta-analysis conducted on pre- and post-treatment outcomes. SD = Standard Deviation, SMD = Standardized Mean Difference, 95% CI = 95% Confidence Interval [30,59–69].

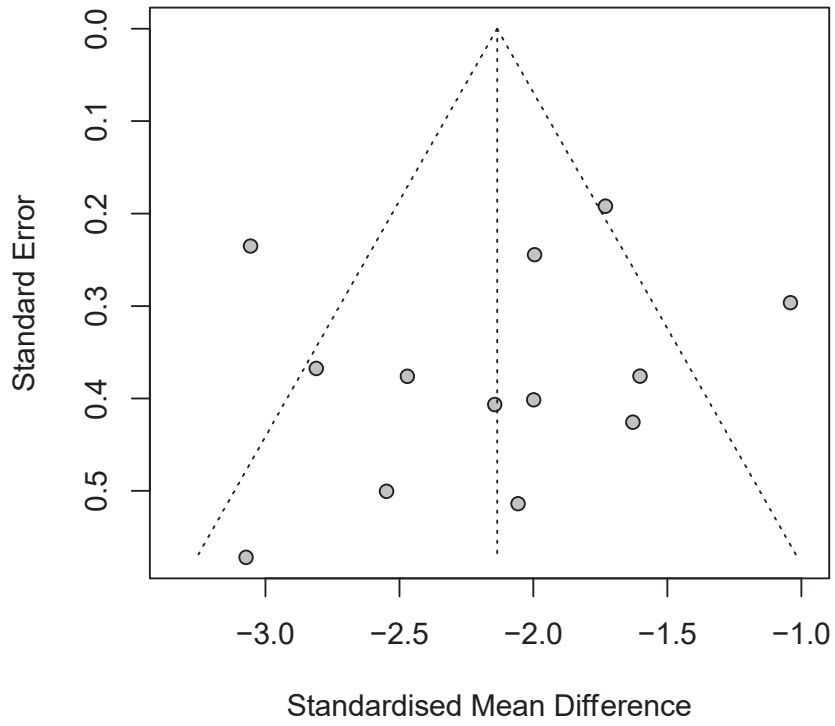

Figure 5. Funnel plot of the studies included in the meta-analysis on pre- and post-treatment outcomes.

The psilocybin effect on patients' depressive symptoms severity was also compared to the consequences sorted by 'inactive' interventions (e.g., placebo, niacin), where control groups were included in the research designs. Random-effect meta-analysis showed that psilocybin significantly reduces subjects' depressive symptoms severity compared to control ($z = -3.60$, $p < 0.001$, $d = -2.37$, 95% CI [−3.66; −1.08]; Figure 6). Subgroup analyses were not conducted in this case due to the low number of studies employing a control group/condition (k = 7). Overall heterogeneity resulting from effect size variability and sampling error was high ($I^2 = 96.3\%$, 95% CI [94.3%; 97.6%]; H = 5.23, 95% CI [4.20; 6.52], $\tau^2 = 2.89$, 95% CI [1.13; 14.39]), as well as the heterogeneity in the effect size distribution ($Q_{(6)} = 164.37$, $p < 0.001$).

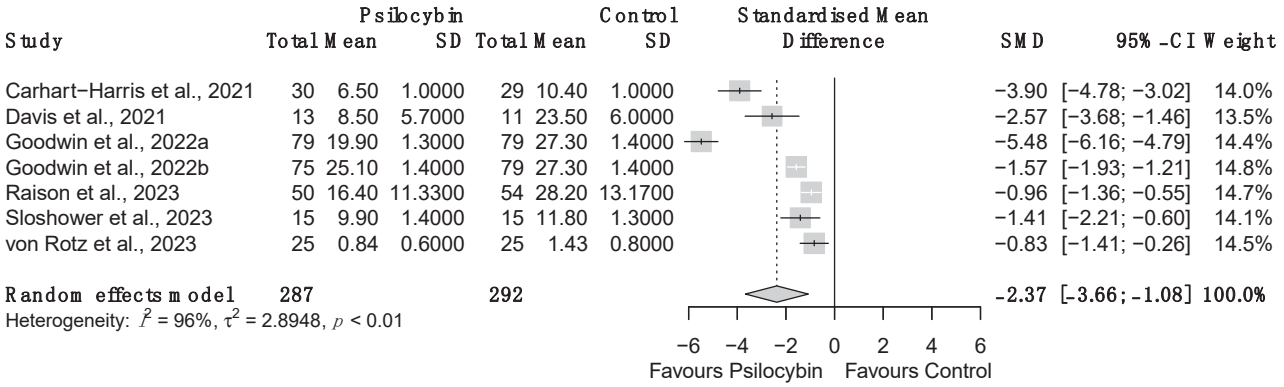

Figure 6. Forest plot of the meta-analysis conducted comparing the post-treatment outcomes among active psilocybin and control groups. SD = Standard Deviation, SMD = Standardized Mean Difference, 95% CI = 95% Confidence Interval [30,62,64,67–69].

4. Discussion

The aim of the present systematic review was firstly to summarize and analyze the current evidence concerning the therapeutic effects of a single- and a two-dose psilocybin administration with a specific focus on the treatment of TRD and MDD, including the latest trials, and then to compare the efficacy of these two different dosages on the severity of depressive symptoms reported by patients with a primary diagnosis of MDD or TRD. The twelve studies taken into consideration highlighted a pronounced efficacy of psilocybin for the treatment of MDD/TRD. Indeed, both single- and two-dose administration solutions proved their effectiveness in reducing depressive symptoms severity compared to baseline [30,61–65,67–69]. Moreover, studies involving a control group showed greater efficacy of psilocybin treatment compared to active or standard placebo [64,67,69], as well as compared to other pharmacological interventions, e.g., SSRIs (escitalopram; [30]). In both single- and double-dose approaches, therapeutic effects of psilocybin treatment were maintained over the long term, with decreases in standardized self-report measurements lasting up to 12 months after treatment in some cases [65]. Overall, these results are in line with the findings of previous systematic reviews and meta-analyses demonstrating the efficacy of psilocybin in ameliorating MDD/TRD symptoms severity [70–72]. However, in contrast to prior investigations highlighting that higher doses and two sessions of psilocybin treatment were associated with superior antidepressant effects [45,73,74], we did not observe a statistically significant difference in post-treatment depressive symptoms severity between single- and two-dose psilocybin administration. Indeed, such a presumed enhanced effect of multiple treatment sessions might stem from methodological factors other than the two-dose regimen itself, e.g., the variety of preparatory and integrative psychological sessions provided to patients before/after treatment and the dosage administered per session. Nevertheless, psilocybin shows a large effect size comparable to that of other cutting-edge approaches currently used for the treatment of MDD/TRD, including transcranial magnetic stimulation and ketamine [70,75–78]. Yet, the number of studies and the sample size available to date on the topic of the present work are still too small to allow a reliable comparison between these interventions [79]. Therefore, additional primary research on psilocybin efficacy on depressive disorders is needed to fill this gap.

Another relevant issue that still has to be addressed regards the risk-benefit profile associated with both single- and two-dose administration [80]. Among the included studies, psilocybin was well tolerated by the vast majority of the patients undergoing both single- and two-dose regimens, and rare serious or unexpected adverse events occurred. Drug-related side effects were especially reported by participants within the first day after treatment, encompassing headache, nausea, dizziness, fatigue, palpitations, confusion, and a transient increase in their blood pressure [30,59,62–65,67,69]. Severe adverse events were only observed in a small portion of patients who reported suicidal ideation, intentional self-injury (i.e., nonsuicidal self-injurious behavior), and suicidal behavior [64], symptoms that might also be linked to MDD/TRD. Considering the similarity between the effect sizes of the two treatment approaches, a feasible strategy to maintain the therapeutic effect and minimize the risk of incurring these unwanted drug-related consequences might be to opt for the single-dose regimen. Nonetheless, forthcoming investigations could focus on comparing the safety profiles associated with single- and two-dose psilocybin administration in order to clarify the potential risks and benefits of different dosing regimens. A related key point to be further explored could be whether the enhanced outcomes associated with the two-dose intervention detected by previous studies sufficiently justify the inherent risks of a dual psilocybin administration [45]. Beyond the risk itself, the requirement for doubled psychological support and a double pharmacological dose could make the psilocybin-assisted treatment less affordable to those in need. A better understanding of these matters would significantly enhance the generalizability and appeal of psilocybin usage within clinical settings.

The present systematic review and meta-analysis suffers, however, from major limitations. First, most of the clinical trials included in the review had a small sample size

(i.e., under 25 participants), which inevitably affects the external validity of this work. Moreover, the percentage of women included in the original studies was unexpectedly low. Although such a population appears to be two to three times more likely to receive a formal diagnosis of MDD [81,82], in half of the selected papers (i.e., 6 out of 12), the percentage of female participants was 50% or less. Second, almost half of the studies were open-label and were assessed by the authors with a moderate risk of bias, highlighting the lack of randomized controlled trials concerning the research topic within the current literature. Third, treatment protocols appeared markedly heterogeneous across the studies, complicating a direct comparison between the trials. Fourth, several impacting factors were left out of the meta-analysis, e.g., illness duration, eventual comorbidities, and number of previous treatments, therefore making our results limitedly reliable and in need of corroboration by future studies.

Further investigations and reviews are necessary to address not only the efficacy of psilocybin on depressive symptoms severity but also the effects of such a treatment on higher-order cognitive functions. A possible candidate to be tested could be delay discounting, i.e., the depreciation of the value of a reward related to the delay to its receipt [83–85], as it has been shown to be steeper among patients with MDD [86], and amenable to modulation by non-invasive treatment approaches [87]. Furthermore, subjects with MDD show lower confidence in their judgements and dysfunctional (meta-)cognitive abilities, such as decentering, metacognitive beliefs, and aspects of self-conscious attention [88]. These metacognitive domains, which can also be modulated by non-invasive brain stimulation [89], might be affected by psilocybin as well through the induction of synaptic plasticity mechanisms [90,91].

5. Conclusions

The results from the clinical trials analyzed in this systematic review and meta-analysis underline the efficacy of psilocybin in the treatment of MDD patients, identifying this psychedelic tryptamine as a possible tool for the treatment of such disorders. Indeed, comparing the effects of a single and two-dose psilocybin administration, both treatment strategies were associated with a significant decrease in depressive symptoms severity compared to baseline assessment. Nonetheless, subsequent clinical trials, systematic reviews, and meta-analyses aimed at furthering this research topic are essential. With the results provided by future investigations, it could be possible to elaborate a more in-depth analysis of the available efficacy data, thus favoring the construction of evidence-based guidelines for intervention that would make the use of psilocybin within clinical settings more feasible and reliable.

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brain sciences

MDPI

Study Protocol

The Efficacy of Psychoeducational Family Intervention for Major Depression: Study Protocol of a Randomized Controlled Trial

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Abstract: This study aims to assess the efficacy of a psychoeducational family intervention (PFI) to reduce the severity of depressive symptoms and to improve psychosocial functioning and to increase social contacts in a sample of patients with major depressive disorder (MDD). The degree to which PFI will reduce patients' relapses, hospitalizations, and self-stigmatization and will improve their quality of life will also be assessed. Other secondary outcomes include the improvement of relatives' coping strategies, family burden, expressed emotions and quality of life. This non-profit, unfunded, national, multicentric randomized controlled trial with blinded outcome assessments will be carried out in 24 Italian university outpatient units. Families will be assessed at baseline and at 6, 12, and 24 months post-randomization. Our working hypothesis is that the PFIs will reduce the patients' severity of depressive symptoms, their relapses, and their hospitalizations, and that they will improve their psychosocial functioning and quality of life. We expect these results to be maintained after 12 and 24 months, albeit with a reduction in magnitude. The sample will consist of 384 patients randomized at a 1:1 ratio and stratified according to center, age, gender, and educational level.

Keywords: family psychoeducation; major depression; caregiver; family burden; relapse rates; depressive symptoms; social contacts

1. Introduction

Major depressive disorder (MDD) is the most common mental disorder, with prevalence rates ranging from 7.2% to 10.8% in the general population [1]. It is a highly recurrent disorder [2], with approximately 50% of patients experiencing a relapse after a first episode, 70% after a second episode, and 90% after a third one [3].

According to the World Health Organization, MDD is among the top 10 causes of disability worldwide, and it is associated with high personal and societal costs and a significant reduction in the quality of life of both patients and their relatives [4,5].

Caring for a patient with MDD can be highly demanding and cause significant distress in family members, as is evidenced by the high rates of divorce and the frequent financial difficulties found among patients with MDD and their family members [6]. Balkaran et al. report that the levels of subjective and objective burden experienced by relatives of patients with depression are significantly higher than those reported by the families of patients with other mental disorders, including schizophrenia and bipolar disorder [7]. Relatives of patients with MDD often report financial difficulties, reduced social activity, concerns about stigma and prejudice toward people with depression and their families, and feelings of loneliness [8–12].

Between 40 and 70% of relatives of patients with major depression develop clinically significant anxiety and/or depressive symptoms [13,14], though these tend to recede as the severity of the depressive symptoms in their ill relatives reduce [14]. Additionally, family members often report a lack of adequate information on how to interact with their loved one [15], along with high levels of expressed emotions, in particular emotional overinvolvement and criticism [16].

The few available data about the impact of dysfunctional family environments and the long-term outcomes of MDD indicate that high levels of family burden, expressed emotions, and dysfunctional coping strategies by family members have a significant impact on the long-term outcomes of patients with major depression [17]. Heru et al. [13] and Keitner et al. [18] found that patients with MDD living in families with high levels of expressed emotion and burden achieve a full functional recovery after an acute episode less frequently than those living in less problematic families.

The available evidence shows that patients with MDD and their relatives should receive effective psychosocial interventions [19,20]. However, research on the best treatment options for MDD is scarce, and data are mainly derived from research on schizophrenia and bipolar disorder. For both of these disorders, psychoeducational family interventions (PFIs) have been shown to be particularly effective [21–23]. In fact, when provided to patients with schizophrenia and their family members, PFIs reduce relapses [24] and hospitalizations [25–28], and when provided to patients with bipolar disorder and their relatives, both during the acute phase [29] and in the long term [30,31], PFIs prevent relapses, reduce the number of acute episodes [32], improve patients' adherence to pharmacological treatments [33,34], and foster psychosocial functioning [35] as well as coping strategies in their family members [36–40]. Based on this evidence, several international guidelines [41–44] recommend the use of PFIs in the clinical management of severe mental disorders, as well as the adoption of new delivery approaches which include modern technologies [38–40].

Despite the relevance of the family context to the recovery of patients with major depression [45,46], studies on the efficacy of PFIs in patients with major depression are limited. The efficacy of PFIs in patients with MDD and their relatives has been explored in only a few randomized controlled trials [47–50]. A recent metanalysis which included five RCTs found that the intervention had a small but significant effect in improving depressive symptoms [49], though the included studies had serious limitations. Thus, firm conclusions about the effectiveness of PFIs in the treatment of MDD cannot yet be drawn.

2. Aims

The primary aim of this study is to assess the efficacy of PFIs in a group of patients with a diagnosis of MDD in terms of: (1) reduction of depressive symptoms; (2) improvement of psychosocial functioning; and (3) increase of social contact. The efficacy of PFIs will also be evaluated in terms of: (1) reduction of relapses and hospitalizations at 18 months post-randomization; (2) improvement of adherence to pharmacological treatments and of patients' quality of life; (3) reduction of self-stigmatization; (4) improvement of coping strategies and expressed emotion in family members, and reduction of family burden; (5) improvement of quality of life of family members. Finally, we will investigate whether the efficacy of the psychoeducational intervention is mediated by the presence of specific temperamental profiles and childhood traumas.

3. Methods

This will be a multicentric randomized controlled trial with blinded outcome assessments coordinated by the Department of Mental and Physical Health and Preventive Medicine at the University of Campania Luigi Vanvitelli, and it will be conducted in 24 Italian outpatient clinics.

Eligible patients and their families will be identified by their treating clinicians and referred to the specialized staff to be included in the study. After acceptance, an informed consent form will be signed and an appointment for baseline assessments will be made. Consent can be withdrawn at any time by both patients and their relatives. Patients will be randomly assigned in a 1:1 ratio to the experimental group or the control group. The randomization will be stratified according to the recruiting center and each patient's age, sex, and educational level. The procedure will be implemented in the coordinating center using specific statistical software. The researchers and statisticians involved in the patients' assessments will be blinded each patient's allocation. The mental health professionals providing the interventions will not be blinded to the patients' allocations.

Patients referred to the outpatient units of participating mental health centers will be invited to participate in the study if they meet the following inclusion criteria: (1) diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5); (2) between 18 and 65 years of age; (3) admitted to the local mental health center for at least 6 months, with at least one access per month; (4) ability to provide written informed consent; (5) cohabitation with at least one family member.

Patients with intellectual disabilities will not be eligible, and neither will patients who experience a clinically relevant worsening of psychiatric symptoms (i.e., requiring a substantial change in the therapeutic dosage of psychiatric medications or access to emergency care or hospitalization) during the two months before recruitment. Patients with comorbid physical illnesses will not be excluded from the study unless the physical condition is so severe and disabling as to require intensive medical care. All recruited patients will continue to receive the treatments usually provided in their centers, which include regular outpatient psychiatric assessments, pharmacological treatments, and management of the side effects of medications. All patients will receive an adequate pharmacological treatment according to the NICE [51] guidelines for the whole duration of the study.

4. Interventions

The experimental intervention will consist of the Falloon psychoeducational family intervention, which was developed for the treatment of schizophrenia [52], but which we have adapted for the treatment of major depression. The experimental intervention will be administered individually to each recruited family and consist of the following six phases: (1) engagement of the family unit; (2) individual assessment; (3) family assessment; (4) informative sessions; (5) communication skills sessions; and (6) problem-solving skills sessions.

The informative sessions will deal with the following issues: (1) clinical characteristics of MDD, symptoms, prognosis, risk and protective factors; (2) available pharmacological and non-pharmacological treatments for MDD, indications, side effects and strategies to cope with them, treatment duration, risk factors for relapse, and effects related to abrupt cessation of the therapy; and (3) early warning signs. A specific informative session on suicide risk has been developed, and this will be administered only to patients who report suicidal ideation during the intervention or who have a history of suicide attempts or ideation.

The sessions will take place three times a month for a period ranging from 4 to 6 months (about 18 sessions in total). The number of sessions, as well as their frequency, may vary depending on each patient's clinical situation. Sessions will have an average duration of 60–90 min and will require the active participation of all family members, including the patient. Between sessions, participants will be invited to organize "family meetings" to discuss the topics covered during the previous meeting, progress made, and problems encountered in implementing changes. Each meeting will ideally be divided into three phases: a first phase dedicated to clarifications and questions regarding the topics previously discussed, a second phase focused on the main topic of the meeting (the so-called "teaching phase"), and a final phase in which the key points addressed during the session are summarized and in which "homework" is assigned.

The control group will receive an educational five-session intervention, administered every 7–10 days, on the following topics: healthy lifestyle (diet and nutrition), stress management, regulation of circadian rhythms, and the management of medication side effects. The control group sessions will last 60–90 min and will be as interactive as possible. At the end of each session, participants will receive leaflets and cards summarizing the key-points addressed during the session.

Treatment fidelity among the different centers will be secured by the development of manuals for both interventions and by continuous supervision, either on site or via phone calls.

The interventions will be discontinued under the following circumstances: (1) if patients or their relatives are unable to attend more than five consecutive psychoeducational sessions; (2) if patients are hospitalized or experience any affective relapse during the intervention; or (3) if patients or relatives withdraw their consent.

5. Training of Mental Health Professionals

Two mental health professionals per center (at least one being a psychiatrist) will participate in a four-day training course on the use of the interventions. During the training, a manual explaining how to conduct the experimental intervention will be provided to participants, and several role-play sessions will be organized. An additional training course on the use of assessment instruments will be organized, and this will include the following phases: (a) presentation of the assessment instruments; (b) group reading; (c) role-play; and (d) video-recorded interviews. In each center, at least one researcher who is not involved in the administration of the interventions will be trained in the use of assessment tools and inter-rater reliability.

6. Ethical Issues

This study will be carried out in accordance with globally accepted standards of good practice and in agreement with the Declaration of Helsinki and with local regulations. The study investigators will ensure that all mental health professionals involved in the study are qualified and informed about the protocol, interventions, and trial-related duties.

A formal ethical approval has been obtained by the Coordinating Center's Ethics Committee (approval number: prot. 0032758/i). Each participating center will submit the approval to their local ethics committees.

7. Assessment Time and Instruments

The following activities are planned for the first three months of the study: (1) the obtaining of approval from local ethics committees; (2) the training of mental health professionals in the interventions and in the use of evaluation tools; and (3) the implementation of the interventions. The recruitment of the patients and their relatives will take place between month 4 and month 12. The patients will be randomly assigned by the coordinating center only after the receipt of written informed consent. The implementation of the intervention will take place between month 3 and month 18. Assessments will be performed between month 3 and month 36. The timeline of the study is shown in Table 1.

The socio-demographic and clinical characteristics of the patients and their relatives will be collected at baseline through validated assessment instruments (Table 2). Researchers participating in the study will be blinded to patient allocation. All patients will be assessed at the following time points: baseline (T0); 6 months post-randomization (T1); 12 months post-randomization (T2); and 24 months post-randomization (T3). All data will be collected during paper and pencil interviews. Each assessment is expected to take about 90/120 min per patient and 60/90 min per relative. During the evaluation, if the participant feel distressed or exhausted, the assessment can be stopped and another appointment can be scheduled for the following 2/3 days.

Table 1. Timeline of the project.

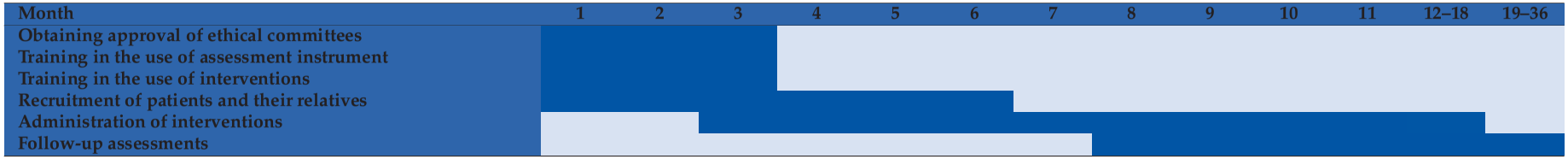

Table 2. Assessments instruments.

Assessment Tool	Assessed Domains	Description	Study Population	Assessment Time-Points
Patients' socio-demographic schedule	**Patients' socio-demographic and clinical characteristics**	**Recorded information will include illness duration, age at onset, number of affective episodes and previous hospitalizations, age at first hospitalization, number of suicide attempts, age, gender, educational level, occupational status, and pharmacological and psychosocial interventions. The information will be compiled by the researcher in collaboration with the patient. If the information is inadequate, or if the researcher is not sure about the patient's reliability, other sources (e.g., treating physician, relatives) can be consulted.**	**Patients**	**T0, T1, T2, and T3**
Relatives' socio-demographic schedule	**Relatives' sociodemographic characteristics**	**Recorded information will include age, gender, educational level, occupational status, nature of relationship with the patient, number of years cohabiting with the patient, and mean number of daily hours spent with the patient.**	**Relatives**	**T0**
Hamilton Depression Rating Scale (HAM-D) [53]	Severity of depressive symptoms	The HAM-D includes 17 items. Of these, eight items are scored from 0 (absent) to 4 (severe), while nine are scored from 0 to 2. The total score is the sum of the item scores, and ranges from 0 to 52 points.	Patients	T0, T1, T2, and T3

Table 2. *Cont.*

Assessment Tool	Assessed Domains	Description	Study Population	Assessment Time-Points
Personal and Social Performance Scale (PSP) [54]	Psychosocial functioning	The total score (which can range from 0 to 100) can be used to assess the patient's overall functioning (higher scores indicate higher functioning). Ratings are based mainly on assessments of a patient's functioning in four main areas: (1) socially useful activities; (2) personal and social relationships; (3) self-care; and (4) disturbing and aggressive behaviors.	Patients	T0, T1, T2, and T3
Family Problems Questionnaire—Patients' and relatives' versions (FPQ) [55]	Practical and psychological burden	The FPQ is a self-administered questionnaire containing 34 items. These items are rated on a 4-point scale, from 1 (never) to 4 (always).	Patients and relatives	T0, T1, T2, and T3
Social Network Questionnaire (SNQ) [56]	**Social contacts**	**The SNQ is a self-administered questionnaire which includes 15 items grouped into 4 subscales (practical support, affective support, social and professional help, and help in an emergency). Items range from 1 (never) to 4 (always).**	**Patients and relatives**	**T0, T1, T2, and T3**
Hamilton Anxiety Rating Scale (HAM-A) [57]	Severity of anxiety symptoms	The HAM-A is a 14-item questionnaire developed to measure the severity of anxiety symptoms, both psychic (mental agitation and psychological distress) and somatic (physical complaints related to anxiety). The score for each item ranges from 0 (not present) to 4 (extreme severity).	Patients	T0, T1, T2, and T3
Morisky Medication Adherence Scale [58]	Adherence to pharmacological treatments	This is a 4-item questionnaire. The response options are yes/no for each item, and a five-point Likert scale is used for the last item.	Patients	T0, T1, T2, and T3
Brief Temperament Evaluation of Memphis, Pisa, Paris, and San Diego (B-TEMPS-M) [59]	Affective temperaments	The B-TEMPS-M includes 35 items and uses a five-point Likert scale.	Patients	T0

Table 2. *Cont.*

Assessment Tool	Assessed Domains	Description	Study Population	Assessment Time-Points
Childhood Trauma Questionnaire (CTQ) [60]	Childhood trauma and abuse	The CTQ is a 70-item questionnaire which uses a five-point Likert scale. Ratings are grouped into five subscales: emotional abuse, physical abuse, sexual abuse, physical neglect, and emotional neglect.	Patients	T0
Clinical Global Impression Scale (CGI) [61]	Illness severity (CGI-S), global changes in the severity of symptoms (CGI-C), and therapeutic response.	The CGI-S employs a seven-point scale, from 1 (normal) to 7 (the most severely ill patients). CGI-C scores range from 1 (very much improved) to 7 (very much worse). Treatment response ratings should take into account both the therapeutic efficacy and the treatment-related adverse events, and they range from 0 (marked improvement and no side effects) to 4 (unchanged or worse, and the side effects outweigh the therapeutic effects).	Patients	T0, T1, T2, and T3
Columbia Suicide Severity Rating Scale (C-SSRS) [62]	Suicidality	The clinician-administered version of the C-SSRS (screening version) will be administered. An individual's suicidal ideation is rated on a scale from 1 (wish to be dead) to 5 (active suicidal ideation with a specific plan and intent). An individual's previous suicide attempts are rated on a scale from 1 (actual attempt, defined as "a potentially self-injurious act committed with at least some wish to die, as a result of act") to 4 (preparatory acts or behavior, defined as "Acts or preparation towards imminently making a suicide attempt"). All patients are rated as positive for suicide attempts if they respond positively to one of the four items assessing suicidal behaviors.	Patients	T0, T1, T2, and T3
Level of Expressed Emotion Scale (LEE) [63]	Expressed emotions	The LEE is a 60-item self-administered assessment instrument. The items are rated as true or false and are grouped into four subscales: (1) intrusiveness; (2) emotional response; (3) attitude toward illness; and (4) tolerance/expectations.	Patients and relatives	T0, T1, T2, and T3

Table 2. *Cont.*

Assessment Tool	Assessed Domains	Description	Study Population	Assessment Time-Points
Insomnia Severity Index (ISI) [64]	Insomnia	The ISI is a seven-item questionnaire. Each item is rated on using a five-point Likert scale. It is a brief test that assesses the different components of insomnia.	Patients	T0, T1, T2, and T3
Manchester Short Assessment of Quality of Life for the evaluation of quality of life (MANSA) [65]	Quality of life	The MANSA is a 17-item questionnaire, 12 of which are rated using a 7-point Likert scale, ranging from 1 ("could not be worse") to 7 ("could not be better"), and 5 of which are rated as either yes or no.	Patients and relatives	T0, T1, T2, and T3
Internalized Stigma of Mental Illness Inventory (ISMI) [66]	Stigma	The ISMI is a 29-items questionnaire for evaluating the subjective experience of stigma.	Patients	T0, T1, T2, and T3
Family Coping Questionnaire (FCQ) [56]	**Coping strategies**	**The FCQ is a self-administered questionnaire consisting of 34 items rated using a 4-point scale, from 1 (never) to 4 (always). The items can be grouped into the following 11 subscales: seeking information on a patient's illness, positive communication toward the patient, relatives' maintenance of social interests, patient's involvement in social activities, talking with friends about the patient's condition, coercion, avoidance, resignation, use of alcohol and drugs, collusion, and searching for spiritual help. A higher score is indicative of a stronger endorsement of each coping strategy.**	**Relatives**	**T0, T1, T2, and T3**

8. Anticipated Results

8.1. Primary Outcomes

We expect that, at the end of the intervention, the MDD patients in the experimental group will show a significant reduction in the severity of their depressive symptoms compared with those in the control group. Moreover, we also expect the treated patients to report an improvement in their functioning and an increase in their social network at six months (i.e., improvements in the number of weekly social contacts, practical and emotional support from their social network, and an improvement in the quality of their intimate supportive relationships). We expect that these results will be maintained after 12 and 24 months, albeit with a reduction in magnitude.

8.2. Secondary Outcomes

We expect that, compared with those in the control group, the patients receiving the PFI will report a significantly lower number of relapses and hospitalizations after 12 and 24 months as well as improvements in their adherence to pharmacological treatments, quality of life (evaluated using the Manchester Short Assessment of Quality of Life), and coping strategies, and a reduction in their internalized stigma. With respect to coping strategies, we expect an increase in the relatives' problem-oriented coping strategies (i.e., maintenance of social interests, involving the patient in social activities, positive communication with the patient, seeking information, talking with friends and/or relatives about the patient's situation) and a reduction in emotion-focused coping strategies (i.e., collusion, avoidance, resignation, coercion, use of alcohol and/or drugs). Moreover, we expect reductions in objective and subjective family burden and improvements in expressed emotions and quality of life, both at the end of the intervention and at follow-ups.

8.3. Exploratory Outcomes

The presence of childhood traumas and certain affective temperaments (i.e., cyclothymic, irritable, and hyperthymic temperaments) can be considered possible predictors and/or mediators of response to psychosocial treatments. Thus, these risk factors will be included as possible moderators in order to assess the influence of these variables on the efficacy of the experimental intervention. Additionally, a series of clinical indicators of illness severity will be collected (including age at onset of the first episode, previous psychiatric hospitalizations, number and type of suicide attempts, alcohol and drug use, presence of psychotic symptoms during acute phases, severity of symptoms at baseline, and adherence to pharmacological treatments), and these will be used as explanative variables. Multivariable models will be corrected for these variables in order to identify patients who are more likely to be responsive to the effects of PFIs.

9. Statistical Analyses

9.1. Power Analysis

The sample size was estimated with respect to the measurement of the main outcomes of the study, and the measure that required the largest sample size (HAM-D) was taken as the reference. Specifically, a sample size sufficient to reduce the total HAM-D score by 10%, with a two-tailed probability of 0.05% and a power of 90%, was estimated. The multicenter design of the study required an adjustment of the sample size estimate in accordance with the value of the intracluster correlation coefficient, set at 0.030, and the coefficient of variation of cluster sizes, set at 0.400. The estimated sample size is 176 patients, 88 for each arm. Based on previous studies conducted with similar patient populations, a dropout rate of 15% is expected. Therefore, it will be necessary to recruit 384 families, 192 for each arm. Each participating center is expected to recruit 16 families (8 for each arm).

9.2. Statistical Analyses

The statistical analyses will be conducted in accordance with the intention-to-treat analysis. Missing data will be handled using a last observation carried forward (LOCF) analysis. Descriptive statistics will be calculated for the dependent and confounding variables for both groups. Confidence intervals will be calculated at 95%.

The analytical plan will include the following: (1) the use of generalized estimating equations (GEEs), which will provide an estimation of the impact of the intervention on the primary and secondary outcomes while controlling for multiple confounders (i.e., age, gender, illness duration, number of previous relapses, severity of symptoms at baseline, previous psychiatric admissions, physical and mental comorbidities, presence of psychotic symptoms during acute phases, suicidality, pharmacological treatments); (2) the application of a structural equation model to identify possible mediators and moderators of intervention efficacy (i.e., specific temperamental profiles, the presence of childhood trauma and/or abuse, severity of symptoms at baseline, the patient's psychosocial functioning at baseline, number of family members, the relatives' coping strategies and levels of expressed emotions at baseline); and (3) the use of a multivariate logistic regression model to identify predictors of a poor response to the experimental intervention.

10. Discussion

Although most of the relevant studies have been carried out with the families of patients with schizophrenia and bipolar disorder, evidence has shown that family functioning also has a significant impact on the course of MDD [67,68]. Relatives of patients with MDD report high levels of burden, including financial difficulties (which are mainly due to loss of productivity in both patients and caregivers), reduced social contact, problems with marital relationships, emotional exhaustion, and worries about the future. Family members also report high levels of anxiety and depressive symptoms, feelings of loneliness and hopelessness, and insomnia [47]. A direct correlation between family burden and patients' adherence to treatments has been found, and this further emphasizes the importance of family members as allies in the treatment of patients with MDD.

The coping strategies of relatives are also significantly correlated with patient outcomes and with the mental health and wellbeing of relatives. In fact, the adoption of positive thinking and problem-oriented coping strategies by relatives is associated with a decrease in their levels of anxiety; in contrast, the adoption of avoidant coping strategies increases depressive and anxiety symptoms in caregivers, as well as anxiety in patients [15]. Surprisingly, few reports about family burden in MDD and its consequences for the medium- and long-term outcomes of patients are available. This can be explained by the fact that, in the past, major depression was thought to be a less burdensome mental disorder compared with schizophrenia, bipolar disorder, and substance abuse disorders [69].

It may seem obvious to suggest that interventions aimed at enhancing caregiver well-being and reducing caregiver distress may have a positive impact on patient outcomes [49]. In particular, among family interventions, psychoeducational family interventions are recognized as one of the most effective add-on treatments that can be used in conjunction with pharmacological therapy for people with bipolar disorder and schizophrenia [70–73], while there is little evidence concerning the efficacy of PFIs in the treatment of MDD. The few available studies report that PFIs contribute to shortened hospital admissions, reduced symptom severity, improved social functioning, and increased subjective well-being [74]. In addition, other studies suggest that psychoeducational family interventions may play a role in the prevention of suicidality and disease recurrence [51,74]. It has to be noted that the most recent meta-analysis of the efficacy of PFIs in patients with MDD [49] included only 301 patients with MDD from five randomized controlled trials. The authors reported that the studies had several limitations, including methodological weaknesses such as a lack of detail concerning the randomization process, a lack of blinding assessments, and low certainty concerning each outcome considered in the studies. Therefore, replications of these RCT results are desperately needed.

Our study will aim to overcome these limitations. In fact, one of the main novelties of the present study is the fact that the efficacy of PFIs will be tested on different clinical outcomes and will not be limited to depressive symptoms, i.e., rather than adhering to a recovery-oriented approach to mental disorders [75], the study will be more in line with the needs and values of patients [76–78]. It will also evaluate the efficacy of the experimental intervention on several psychosocial and psychological domains, both in patients and in their relatives. The majority of existing studies have assessed the efficacy of the intervention over the short and middle term, while data concerning its efficacy over a longer term are lacking. For this reason, we included a two-year follow-up assessment in order to verify whether the effects of the intervention, usually seen after 6 and 12 months, are maintained over a longer period. Moreover, a major strength of our trial is its adoption of a well-known and validated family psychoeducational model, which has been adapted for the treatment of patients with MDD. Specifically, the Falloon psychoeducational intervention was initially developed for the community management of schizophrenia [19], and then adapted for patients with bipolar disorder [79]. In these disorders, the efficacy of this model has been well documented in RCTs and in real-world trials. To our knowledge, its efficacy has never been tested in patients with MDD. Major depression may represent an ideal target for this approach since it is highly dependent on stressful life events and on family context [42].

Moreover, to our knowledge, no study has assessed the possible mediators and moderators of the efficacy of PFIs, and this is undoubtedly a novel aspect of the present study. Specifically, in our study, we tested the hypothesis that affective temperaments and childhood traumas can impact the responsiveness of patients to family treatments. It has been reported that affective temperaments play a significant role in influencing the long-term outcomes of affective disorders, and that cyclothymic and irritable affective dispositions are associated with a reduced response to pharmacological and/or psychosocial interventions [80]. Regarding childhood traumas, several studies have reported that the presence of physical and psychological abuse, as well as the presence of traumas during childhood, are associated with worse outcomes in MDD patients, reduced problem-solving and social skills, increased disease burden, and increased risk of suicidality [81]. Patients with childhood traumas may present more severe symptoms, be more reluctant to implement changes proposed during an intervention, and show resistance to pharmacological and psychosocial treatments.

Another novelty of the present study is its multicentric nature. In fact, the 24 centers involved in the study are highly representative of the whole Italian nation. The sample size is very large (a total of 384 families enrolled). To our knowledge, no study so far carried out on the efficacy of PFIs in MDD patients and their relatives has been as representative of an entire European country.

Additionally, in the present trial, assessments will be blinded, meaning that the researchers and statisticians will be unaware of the allocations of the patients and their relatives. We decided to collect a variety of "hard clinical indicators", including age at onset of mental illness, previous hospitalizations for mental illness, suicide attempts, and alcohol and drug use, all of which will be used as explanative variables. These variables will be used to assess potential moderators of the efficacy of PFIs and will inform us about factors that can potentially mitigate the efficacy of such interventions [82,83].

The clinical breakthrough power of this study consists of several aspects. First, the emphasis is not only on reducing symptom severity, but also on restoring a meaningful life so that patients feel satisfied with their personal and social lives [84]. Subjective feelings of being supported by relatives and friends strongly influence the recovery of patients. In fact, the available data show that 51.2% of patients with major depression consider lack of social support an important complication hindering their recovery [85].

Another innovative aspect of our proposed study is the total duration of the intervention (from 4 to 6 months), which includes an average of 18 planned sessions. In addition, the experimental intervention will be flexible, meaning that the number of sessions and their durations can be modulated according to the specific needs of each family. This is intended to increase the scalability of the intervention under routine conditions.

However, the proposed study has some unavoidable limitations. First, some psychopathological dimensions will be assessed using self-assessment instruments. This is necessary if we want to apply the intervention in real-world settings, where the resources are limited, and long evaluations are very difficult. Second, the total number of delivered sessions will not be standardized. Although this might seem a limitation, according to the original PFI Falloon model, psychoeducation should be adapted to the needs of families and, thus, it cannot be too structured. However, a minimum number of 12 sessions will be delivered in order to overcome this limitation. Moreover, we will not include an assessment of the barriers hindering the implementation of PFIs in the participating centers. This is because the main focus of our study is to explore the efficacy of PFIs for patients with MDD and their family members; the scalability of the intervention can be assessed in a forthcoming study, after its efficacy has been documented. Lastly, another possible limitation is the shorter duration of the intervention provided to the control group. However, most RCTs involving psychosocial interventions explore the efficacy of an experimental intervention against treatment as usual, or against a waiting list (meaning no active comparator), or against no intervention. Thus, we believe that the comparison between two active interventions adds value to our protocol.

11. Conclusions

In conclusion, from a clinical perspective, the proposed study has the potential to provide valuable insight into the efficacy and effectiveness of family psychoeducation interventions for patients with MDD and their families. If the intervention proves to be effective in reducing depressive symptoms, improving psychosocial functioning, and reducing relapse rates, it will have to be added to the clinical management of MDD, according to the personalized treatment approach.

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