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Reviews in psychiatry personality disorders 2023

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Reviews in psychiatry 2023: personality disorders

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Editorial: Reviews in psychiatry 2023: personality disorders

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Editorial on the Research Topic
Reviews in psychiatry 2023: personality disorders

Introduction

In this Research Topic, we provide an overview and discussion of key points from the nine articles published in this 2022 Research Topic entitled "*Reviews in psychiatry 2023: personality disorders*." The overview has been thematically organized by topic.

The dimensions of personality

The dimensional view of personality disorders (PDs) represents these conditions as extreme variants of normal personality continua. Hualparuca-Oliveira et al. examined whether there is a sufficient correlation between PDs measures of the ICD-11 (1) and DSM 5 (2) alternative models of personality disorder (AMPD) in the general population. The quality of the sixteen included studies was moderate. The authors found a strong and significant degree of heterogeneity and moderate association both for the overall model (r=0.62) and for the subgroup of associations (0.57 for the severity model and 0.63 for the association between the ICD-11 and DSM 5 AMPD trait models). When considering specific trait domains the correlation was high (0.71) for negative affectivity and moderate for Detachment (0.59), Dissociality/Antagonism (0.55), and Disinhibition (0,68). The results indicate satisfactory empirical evidence for the interchangeable usefulness of these measures between the two models.

Szucs et al. carried out a meta-analysis of 48 studies on the association between personality and help-seeking (HS). Schizotypal and borderline PDs and neuroticism traits are likely to engage in mental healthcare despite negative general attitudes toward care seeking, while paranoid, schizoid and obsessive-compulsive PDs are related to both negative HS attitudes and behavior, despite the unfavorable long-term prognosis. Limited evidence has linked extraversion to social support seeking and conscientiousness to care-seeking behavior.

Meta-analyses on the Five Factor model confirmed modest associations between neuroticism and more negative attitudes toward seeking professional psychological help and between agreeableness and more positive attitudes toward seeking professional psychological help, but the latter is lost in a sensitivity analysis. HS behavior is

negatively associated with reality weakness and cynicism, and positively associated with abasement and rigidity.

The neurobiology of personality disorders

Zhou et al. used two sample Mendelian randomization (TSMR) (3) to evaluate the causal relationship between BPD and atrial fibrillation (AF), and found that genetically predicted BPD was associated with an increased risk of AF in both the fixed effects inverse variance weighted model (p=0.0031) and the random effects inverse variance weighted model (p=0.0394). The authors pointed to genetic evidence of a causal relationship between BPD and increased risk of AF through TSMR, with no causal relationship of AF to BPD risk, concluding that inflammation may be a mediating factor between BPD and AF.

di Giacomo et al., systematically reviewed the existing literature on the complex interplay between BPD and oxytocin, following the hypothesis that dysregulation of the oxytocin system may contribute to the emotional instability and interpersonal difficulties observed in individuals with BPD (4). In the 70 studies included in their qualitative analysis, the authors found that Oxytocin may influence attachment styles, parenting behaviors, and stress responses, particularly in individuals with a history of childhood trauma. The interaction between oxytocin, genetics, early life experiences, and environmental factors contributes to the complexity of BPD, while genetic variations in the oxytocin receptor gene may influence social and emotional abilities and contribute to the development of psychopathology. Moreover, early adverse experiences, such as childhood maltreatment, could alter oxytocin functioning and impact social cognition and emotional regulation. They concluded that there is evidence for both potential benefits for specific symptoms, such as social threat avoidance, and adverse effects on nonverbal behavior and mentalizing.

Personality disorders and musculoskeletal disorders

Quirk et al. carried out a systematic review to evaluate the quality and extent of evidence for associations of PD with chronic back/neck/spine conditions, arthritis, fibromyalgia, and reduced bone mineral density in eleven population based studies. The association was strongest for cluster B PDs. In younger groups, any PD, schizoid PD, and obsessive compulsive PD were each associated with increased odds of arthritis. Similarly, people with arthritis had increased odds of several specific PDs (paranoid, schizoid, histrionic, antisocial, avoidant and obsessive compulsive). Spinal pain was associated with BP, while muscular pain but not fibromyalgia was associated with PD and women with cluster A, but not cluster B and C PDs had poorer bone health. The authors concluded the need for new evidence from case control and cohort studies.

Personality disorders and seizures

People with temporal lobe epilepsy (TLE) have frequently been described as having specific personality features (hyper-religiosity, hypergraphia, hyposexuality, and irritability) called Geschwind syndrome (5). Viola et al., in a mini-review of 23 studies, tried to collect and synthesize the existing evidence on PDs in subjects with epilepsy. They found higher prevalence rates (18-42%) of PDs in focal epilepsies (not specifically TLE) that are candidates for surgery, with cluster C personality being the most common. In juvenile myoclonic epilepsy prevalence rates were 8-23% with no strong correlation with any subtype. In functional seizures (FS), the prevalence ranged between 30% and 60% with a higher correlation with cluster B PDs. Comorbidity with PDs complicated treatment. The authors pointed out that studies have usually focused on traits rather than specific PDs and that often a substantial gap in knowledge exists about the common etiology, and effects of AEDs and epilepsy surgery in PDs.

The role of personality in the development of FS has been studied in recent literature (6, 7). Sammarra et al. systematically reviewed 14 studies on the FS population (prevalence of PDs, frequency of clusters A, B and C and comparison with patients with epilepsy). The rate of PDs as comorbidity in FS ranged from 18% to 87%, with a mean of 53.7% (41.7%-84.6% cluster B, 0%-48.3% for cluster A and 7.7%-75.9% for cluster C) Individuals with FS have nearly three times the odds of having PDs than patients with epilepsy ($p<0.00001$), a fourfold increased OR of having cluster B, ($p<0.00001$), an OR<1 of having cluster A ($p=0.024$), or cluster C ($p=0.014$) PD. The authors concluded that future research should assess the advantages of a systematic evaluation of personality disorders in FS, to address specific treatment planning and evaluate its effectiveness on seizure recurrence, psychological comorbidities and quality of life.

Personality traits and axis I spectrums

More than 25% of patients diagnosed with obsessive-compulsive disorder (OCD) do not respond adequately to treatment (8) and the complex examination of risk factors can be conducted by using a new approach in the study of OCD, namely the empirical and theoretical framework of maladaptive schemas. Csigò and colleagues tried to identify the early maladaptive schemas characteristic of 112 (58 men and 54 women) Hungarian patients diagnosed with OCD, and to examine the presence and severity of comorbid anxiety and depressive symptoms in light of early maladaptive schemas (Mistrust-Abuse, Inferiority/Shame, Dependence/Incompetence, Insufficient Self-Control/Self-Discipline and Entitlement/Grandiosity (reverse effect)). Not the severity, but the *number* of the early maladaptive schemas showed a stronger correlation with the OCD symptom variables. The authors concluded that the relationship between OCD symptom severity and personality impairment does not appear to be directly proportional. Moreover, they emphasized that OCD is only one and not the most serious consequence of personality damage, indicated by early maladaptive schemas.

A more comprehensive understanding of the co-occurrence of alcohol abuse and PDs appears to be necessary for several reasons. For instance, treatments for each of these conditions are more likely to fail in the presence of the other (9). Jarcuskova et al. examined in their cross sectional study the clinical characteristics of 80 adults with alcohol dependence syndrome, 35% of whom had comorbidity with antisocial personality disorder (APD). The authors found that patients with a comorbid APD were younger, had lower education levels, were more likely to be unemployed and unmarried, and started drinking earlier ($p<0.05$). They usually have traumatic experiences, and were more likely to report comorbid anxiety, depression stress, ($p<0.05$), sleep problems ($P = 0.058$), and linguistic and attention deficits ($P = 0.046$). The authors concluded that understanding the comorbidities could lead to targeted interventions.

Conclusions

This Research Topic underscores the multifaceted nature of personality disorders (PDs) and their extensive implications for clinical practice and research. The studies reviewed reveal the intricate interplay between dimensional models of personality and categorical approaches, emphasizing the potential for harmonization between frameworks such as the ICD-11 and DSM-5. Furthermore, neurobiological insights, such as the role of genetic factors, inflammation, and neuropeptides such as oxytocin, illuminate the biological underpinnings of PDs, offering promising avenues for biomarker development and targeted interventions. The associations between PDs and physical health conditions, such as musculoskeletal disorders and epilepsy, highlight the bidirectional relationships between mental and physical health, necessitating integrated approaches to treatment. Similarly, the exploration of comorbidities, such as obsessive-compulsive disorder and alcohol dependence, illustrates how maladaptive schemas and personality traits add to the complexity of treatment, often requiring personalized and multidisciplinary strategies to address overlapping symptoms and improve outcomes. These studies also draw attention to the societal and behavioral dimensions of PDs, particularly about help-seeking behavior and the stigma surrounding mental health.

Future studies should aim to address existing gaps, particularly through longitudinal and cohort designs, to build a more comprehensive understanding of the mechanisms and impact of personality disorders across different populations. Emphasizing both biological and psychosocial determinants, future efforts should focus on early detection, comprehensive assessment, and tailored therapeutic approaches to address the complex needs of individuals with PDs. By bridging the gaps between research and practice, we can contribute to more holistic and effective care for this vulnerable population.

Author contributions

MB: Conceptualization, Writing – original draft, Writing – review & editing. MS: Conceptualization, Writing – original draft, Writing – review & editing.

Conflict of interest

MB has collaborated on a Lundbeck and an Angelini project.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Convergence between the dimensional PD models of ICD-11 and DSM-5: a meta-analytic approach

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In the current diagnostic systems, the International Classification of Diseases-11th rev. (ICD-11) and the Diagnostic and Statistical Manual of Mental Disorders-5th ed. (DSM-5), the evaluation and diagnosis of personality disorder (PD) aim at dimensional examination of the severity of its dysfunction and the stylistic features that accompany it. Since their implementation, or even before, several measures have been developed to assess PD severity and traits in both models. Thus, convergent validity metrics have been reported with various PD measures; however, the convergence of the same constructs included in the measures of these two models remains undefined. The objective of the present review was to examine whether there is a sufficient relationship between PD measures of the ICD-11 and DSM-5 AMPD in the general population. For this meta-analytic review, systematic searches were conducted in Web of Science, PubMed, Scopus, and Google Scholar. We included studies that reported Pearson's *r* correlations without restrictions on language, age, sex, setting, type of sample, or informant of the measures. We excluded associations with anankastia, psychoticism or the borderline pattern because they were not comparable between one dimensional model and the other. We examined the quality of the evidence with the JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies, and performed the random effects meta-analysis with the 'meta' package of the RStudio software. Of the 5,629 results returned by the search, 16 studies were eligible; and showed moderate quality. The risk of bias was manifested by not specifying the details of the sample, the recruitment environment, and the identification and control of confounding factors. Thirteen studies provided two or more correlations resulting in a total of 54 studies for meta-analysis. The overall effect size estimate (correlation) was moderate for the overall model ($r = 0.62$, 95% CI [0.57, 0.67], $p < 0.0001$, $I^2 = 97.6\%$). For the subgroup of associations, ICD-11 severity model and DSM-5 AMPD severity model, the correlation was also moderate ($k = 10$, $r = 0.57$, 95% CI [0.48; 0.66]; $I^2 = 92.9\%$); as for the subgroup of associations, ICD-11 traits model and DSM-5 AMPD traits model ($k = 44$, $r = 0.63$, 95% CI [0.57; 0.69], $I^2 = 97.9\%$). The convergent validity between measures of PD severity and traits between one diagnostic system and another has been demonstrated in this review and they can probably be used interchangeably because they also measure the same constructs. Future research can address the limitations of this study and review the evidence for the discriminant validity of these measures.

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KEYWORDS

ICD-11, DSM-5, personality disorder, dimensional models, severity, traits, convergent validity, meta-analysis

1 Introduction

Personality involves the way a person behaves, interprets themselves, perceives life, other people and situations; while PD is a marked alteration in personal and social functioning (1). The construct of personality and its pathology has always attracted the interest of mental health professionals because it is linked to other conditions or clinically relevant results. In the last 10 years, or even more, personality disorder has been conceived in a dimensional way in the most used diagnostic systems to improve their validity and clinical usefulness (2). In both diagnostic systems for the dimensional diagnosis of PD, two similar steps are followed: identification of the level of severity of PD dysfunction and assignment of the accompanying stylistic features (1, 3). Both steps reflect the most influential paradigms in personality psychopathology. Thus severity reflects the current state of basic internal capabilities; and trait domains, the stylistic dispositions with which severity probably interacts bidirectionally (4, 5). Supplementary Table S1 shows the conceptually equivalent constructs between the ICD-11 and DSM-5 models for personality disorder.

In the DSM-5 AMPD, the PD severity model is criterion A and is defined as a unidimensional spectrum of problems in the components of identity and self-direction for the self-dysfunction domain, and of problems in empathy and intimacy for the interpersonal dysfunction domain. In the ICD-11, the first diagnostic step is the severity of intra- and interpersonal functioning, similar to that of the other model; however, guidelines for manifestations (cognitive, emotional and behavioral) and deterioration (personal and social) are added (6). Small differences are also observed at the subcomponent level.[1] For example, in the self-direction component of the DSM-5 AMPD, two additional subcomponents are evident compared to those already described in the ICD-11 severity model: (i) the use of constructive and prosocial internal norms of behavior and (ii) the capacity for productive self-reflection. Likewise, in the empathy component of the DSM-5 AMPD, two additional subcomponents to what is mentioned in the ICD-11 are also noted: (a) tolerance of different perspectives and (b) understanding of the effects of one's own behavior on others. Finally, regarding intimacy, the ICD-11 severity model emphasizes the ability to manage conflicts in relationships; while in the DSM-5 AMPD there is no explicit description for it (7). On the other hand, there are differences in the terms of thresholds between the two severity models. In the ICD-11, severity ranges from: none (implicit), personality difficulty, mild PD, moderate PD, and severe PD; while PD severity in DSM-5 AMPD expands from: no impairment, some impairment, moderate impairment, severe impairment, and extreme impairment; respectively.

In the DSM-5 AMPD trait model (Criterion B) there are five trait domains: negative affectivity, detachment, disinhibition, antagonism, and psychoticism. The latter does not correspond to any trait in the ICD-11 PD trait model. The ICD-11 PD traits model includes negative affectivity, detachment, disinhibition, dissociality, and anankastia.[2] The antagonism of the DSM-5 AMPD traits model is similar to the dissociality of the ICD-11 PD traits model; and the anankastia of this last model does not have an explicit domain in the DSM-5 AMPD traits model. Although several authors have suggested that the anankastia is the inverse of the disinhibition domain, certainly other studies have found it to be an independent domain (7, 8). Furthermore, in bipolarity it is difficult, if not impossible, to qualify the absence or very low levels of the trait. At the facet level, greater differences are evident between the two models.[3] This may be because, for example, in the DSM-5 AMPD traits model, several facets are interstitial and/or are located in the incorrect domain (9). We mention only the facets belonging to four of the five domains because they are comparable between the models as stated above.

The negative affectivity of the DSM-5 AMPD traits model mainly includes: emotional lability, anxiety, insecurity due to separation; on the other hand, its counterpart in the ICD-11 PD traits model includes: anxiety, worry, depression, vulnerability, fear, anger, hostility, guilt, shame, intra and interpersonal pessimism, emotional lability and dysregulation, low self-esteem and self-distrust (including avoidance, dependence, envy, and worthlessness), and interpersonal mistrust. Likewise, the detachment of the DSM-5 AMPD traits model mainly includes withdrawal, avoidance of intimacy, and anhedonia; while its counterpart in the ICD-11 PD traits model includes only social detachment and emotional detachment. Similarly, the DSM-5 AMPD antagonism traits model mainly includes manipulation, deception, and grandiosity; while dissociality in the ICD-11 PD traits model includes egocentrism and lack of empathy. Finally, the disinhibition of the DSM-5 AMPD traits model mainly includes irresponsibility, impulsivity and distractibility; while its counterpart in the ICD-11 PD traits model includes impulsivity, distractibility, irresponsibility, recklessness and lack of planning.

Previous studies have described instruments to evaluate both severity and traits in both models (2, 4, 8, 10–12). These measures include the Personality Inventory for DSM-5-Brief Form-Plus (PID-5-BF+) and the Personality Inventory for DSM-5-Brief

1 In the ICD-11 PD severity model there are no components or subcomponents as such, thus the comparisons with the other model described in this article are based on the guidelines provided for the identification of PD severity.

2 An additional qualifier is also included, the borderline pattern, which is not a dimensional trait, but rather a specifier associated with a diagnostic category from the previous edition of this diagnostic system.

3 There are no facets in the ICD-11 PD traits model, and comparisons with the other model described in this work are based on the guidelines provided for each trait domain.

Form-Plus Modified (PID-5-BF + M), which are compatible with both trait models by integrating the psychoticism and anankastia domains. We consider these instruments only within the DSM-5 AMPD traits model because they are based on items from the Personality Inventory for DSM-5 (PID-5). Demonstrations of convergent validity — significant and substantial associations between various measures developed to measure a common construct— are a basic and minimum requirement for the validity of any psychological test (13). Several authors agree that PD severity and the trait domains of negative affectivity, detachment, dissociality/antagonism, and disinhibition in both models are conceptually equivalent (14–17); this, despite the subtle differences described in this article. As a result, measures from one model were used to report results from the other model (18–20). This is further evidence that in psychological measurement this metric is often assumed rather than directly demonstrated (13). To overcome this knowledge-practice gap, it is necessary to empirically and deeply explore the significance and the strength of association between the constructs of one model and the other.

2 The present review

The aim of this systematic review was to explore the convergence between measured constructs of AMPD and ICD-11 personality disorders severity and trait domains —except for the associations with anankastia, psychoticism or the borderline pattern because they are not comparable between one dimensional model and the other—. We excluded studies of convergent validity between severity and trait measures between both models because this does not have major implications in clinical practice. We also excluded associations with sub-constructs (domains/components/sub-components of severity or trait facets) because the internal structure at these sub-dimensional levels is still debated (9, 21–24). Thus, we systematically searched the literature (in any language) using four databases: Web of Science, PubMed, Scopus, and Google Scholar. Similar to a previous paper (2), we used the following keywords: ((personality) AND ((disorder*) OR (pathолog*))) AND (dimension*) AND ((function*) OR (severi*)) AND ((trait*) OR (domai*)) AND ((validity) OR (assessment)) AND ((ICD) OR (International Classification of Diseases)) AND ((DSM-5) OR (Diagnostic and Statistical Manual of Mental Disorders)). For this review, the Preferred Reporting Items for Systematic reviews and Meta-Analyses [PRISMA; (25, 26)] guidelines were followed.

The search returned 5,629 results (44 from Web of Science, 30 from PubMed, 5,518 from Scopus, and 37 from Google Scholar). There were no restrictions regarding the sex, age of the participants, the type of sample used or type of informant of the measures; since we assumed that the literature collected could be austere. Only studies that presented Pearson's correlation coefficients for the severity and trait scales of both models were included. We contacted the authors of the studies to obtain the full text of the articles when they had restricted access. The quality of evidence of the included studies was assessed using the JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies (27, 28); and synthesis, with the 'Meta' package v. RStudio software 6.5-0-2023.09.0–463. We used only six of the eight questions in the risk of bias tool because the questions 'Was the exposure measured in a valid and reliable manner?' and 'Were objective, standard criteria used to measure the condition?' explicitly qualified etiological and risk studies.

3 Results

3.1 Description of the chosen studies

Table 1 shows the 19 studies included and covers the results on this issue in the last 6 years. In these investigations, the measures that evaluate severity from the ICD-11 PD model included: the ICD-11 Personality Disorder Severity Scale (PDS-ICD-11), its version clinician rating form (PDS-ICD-11-CRF), and the ICD-11 PD Severity Clinician Rating Form. Likewise, the instruments that measure severity from the DSM-5 AMPD model include: the Level of Personality Functioning Scale–Brief Form (LPFS-BF), its second version (LPFS-BF 2.0), its informant version (LPFS-BF 2.0-I), and the Semi-Structured Interview for Personality Functioning DSM-5 (STiP 5.1). On the other hand, the measures that examine the trait domains from the ICD-11 PD model include: four scales from the PiCD, the ICD-11 PD Traits Clinician Rating Form and the PAQ-11. Similarly, the instruments that measure the trait domains from the DSM-5 AMPD model involved: four scales of the PID-5, its short form (PID-5-SF), its brief form plus (PID- 5-BF+), its informant brief form plus (I-PID-5-BF+), and the LPFS-SR-FFM Trait Coded (LPFS-SR-FFM-TC). Supplementary Table S2 describes the scales measuring personality disorder severity and trait domains from the studies analyzed.

The included studies used samples from seven countries (one non-Western society) with instruments developed/adapted in six languages: Danish, English, German, Korean, Polish, and Spanish. These instruments consisted of clinician-administered interviews, and self-report and informant-report questionnaires. Four studies used clinical samples of adults (30–32, 38), eight studies used community samples of adults (29, 36, 37, 39–41, 43, 44), and four studies used mixed samples (clinical and community-based) of adults (33–35, 42). The recruitment settings were: community mental health treatment units, psychiatric hospitals, a psychiatric outpatient clinic, and a women's college. The total sample of 16 studies involved 11,085 participants; with an average of 62.5% women, and an average age of 35.8 years. The range of the correlation coefficients r was from 0.31 to 0.74 between the severity measures of both models; and r from 0.26 to 0.89, between the trait scales of both models.

3.2 Quality and synthesis of studies

Overall, the quality of the included studies was considered moderate. No studies have reported the risk of bias in more than three domains of the JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies (see Supplementary Figure S1). Indeed, bias was found in 81.3% of the studies in the domains of 'Confounding Identification' and 'Confounding Management'. Likewise, 25% of studies presented a risk of bias in the 'Sample and Setting' domain. There was no risk of bias (0%) in the domains 'Eligibility Criteria', 'Measurement', or 'Statistics'. Four studies presented bias in 'Sample and Setting' (39, 40, 43, 44), as they did not adequately report demographic data, location or time period. Thirteen studies presented

TABLE 1 Description of included studies.

Study	Year	Associated models of PD	ICD-11 PD measure	AMPD measure	r coefficient	Sample size	Sample type	Setting	Country	Language	Gender, % female	Age, M	Technique / informant	Quality assessment
1. Bach et al. (29)	2023	ICD-11 Severity-DSM-5 Severity	PDS-ICD-11	LPFS-BF 2.0	0.67	3,044	Community adults	Digital post	Denmark	Danish	55.8%	NR	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: Yes Confounding Management: Yes Measurement: Yes Statistics: Yes
2. Brown and Sellbom (30)	2023	ICD-11 Severity-DSM-5 Severity	PDS-ICD-11 PDS-ICD-11 PDS-ICD-11	STiP 5.1 LPFS-BF 2.0-I LPFS-BF 2.0	0.63 0.35 0.66	234	Clinical adults	Community mental health treatment	New Zealand	English	59%	NR	Interview / Clinician Questionnaire / Other Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes
3. Sellbom et al. (31)	2023	ICD-11 Severity-DSM-5 Severity	PDS-ICD-11 CRF PDS-ICD-11 CRF	LPFS-BF 2.0-I LPFS-BF 2.0	0.46 0.57	46 86	Clinical adults	Community mental health treatment	New Zealand	English	71%	36.7	Questionnaire / Clinician Questionnaire / Other Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes

(Continued)

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TABLE 1 (Continued)

Study	Year	Associated models of PD	ICD-11 PD measure	AMPD measure	r coefficient	Sample size	Sample type	Setting	Country	Language	Gender, % female	Age, M	Technique / informant	Quality assessment
4. Brown and Sellbom (32)	2022	ICD-11 Severity-DSM-5 Severity	ICD-11 PD severity ICD-11 PD severity	LPFS-BF 2.0-I LPFS-BF 2.0	0.31 0.54	311	Clinical adults	Community mental health treatment	New Zealand	English	64.30%	NR	Interview / Clinician Questionnaire / Other Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes
5. Bach et al. (33)	2021	ICD-11 Severity-DSM-5 Severity	PDS-ICD-11	LPFS-BF 2.0	0.68	515	Mixed (clinical and community) adults	Digital post	USA and New Zealand	English	50,9% community (USA) 61,5% clinical (New Zealand)	NR	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes
6. Oltmanns and Widiger (34)	2019	ICD-11 Traits-DSM-5 Traits	PiCD_NA PiCD_DT PiCD_DL PiCD_DN	LPFS-SR-FFM-TC_NA LPFS-SR-FFM-TC_DT LPFS-SR-FFM-TC_ANT LPFS-SR-FFM-TC_DN	0.73 0.46 0.53 0.56	269	Mixed (clinical and community) adults	Digital post	USA	English	68%	31.8	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes

(Continued)

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TABLE 1 (Continued)

Study	Year	Associated models of PD	ICD-11 PD measure	AMPD measure	r coefficient	Sample size	Sample type	Setting	Country	Language	Gender, % female	Age, M	Technique / informant	Quality assessment
7. Damovsky et al. (35)	2022	ICD-11 Traits-DSM-5 Traits	PiCD_NA PiCD_DT PiCD_DL PiCD_DN	PID-5-BF+_NA PID-5-BF+_DT PID-5-BF+_ANT PID-5-BF+_DN	0.80 0.70 0.74 0.77	939	Mixed (clinical and community) adults	Psychiatric hospital and Digital post	Germany	German	69%	32.17	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes
8. Zimmermann et al. (36)	2022	ICD-11 Severity-DSM-5 Severity	PDS-ICD-11	LPFS-BF	0.74	1,228	Community adults	Digital post	Germany	German	50.4%	49.1	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: Yes Confounding Management: Yes Measurement: Yes Statistics: Yes
9. McCabe and Widiger (37)	2019	ICD-11 Traits-DSM-5 Traits	PiCD_NA PiCD_DT PiCD_DL PiCD_DN	PID-5_NA PID-5_DT PID-5_ANT PID-5_DN	0.86 0.78 0.81 0.89	300	Community adults	NR	USA	English	54%	36.51	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: No Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes

(Continued)

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TABLE 1 (Continued)

Study	Year	Associated models of PD	ICD-11 PD measure	AMPD measure	r coefficient	Sample size	Sample type	Setting	Country	Language	Gender, % female	Age, M	Technique / informant	Quality assessment
10. Brown and Sellbom (38)	2023	ICD-11 Traits-DSM-5 Traits	ICD-11 PD Traits_ NA ICD-11 PD Traits_ DT ICD-11 PD Traits_ DL ICD-11 PD Traits_ DN ICD-11 PD Traits_ NA ICD-11 PD Traits_ DT ICD-11 PD Traits_ DL ICD-11 PD Traits_ DN	PID-5-BF+_NA PID-5-BF+_DT PID-5-BF+_ANT PID-5-BF+_DN I-PID-5-BF+_NA I-PID-5-BF+_DT I-PID-5-BF+_ANT I-PID-5-BF+_DN	0.48 0.63 0.43 0.52 0.26 0.38 0.27 0.40	336	Clinical adults	Community mental health treatment	New Zealand	English	65.1	NR	Interview / Clinician Questionnaire / Other Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes
11. Cieciuch et al. (39)	2022	ICD-11 Traits-DSM-5 Traits	PiCD_NA PiCD_DT PiCD_DL PiCD_DN	PID-5_NA PID-5_DT PID-5_ANT PID-5_DN	0.77 0.68 0.73 0.70	597	Community adults	NR	Poland	Polish	51.4%	30.24	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: No Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes

(Continued)

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TABLE 1 (Continued)

Study	Year	Associated models of PD	ICD-11 PD measure	AMPD measure	r coefficient	Sample size	Sample type	Setting	Country	Language	Gender, % female	Age, M	Technique / informant	Quality assessment
12. García et al. (40)	2022	ICD-11 Traits-DSM-5 Traits	PiCD_NA PiCD_DT PiCD_DL PiCD_DN	PID-5-SF_NA PID-5-SF_DT PID-5-SF_ANT PID-5-SF_DN	0.77 0.61 0.71 0.81	1,565	Community adults	NR	Spain	Spanish	53.8%	36.5	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: No Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes
13. Sellbom et al. (41)	2022	ICD-11 Traits-DSM-5 Traits	PAQ-11_NA PAQ-11_DT PAQ-11_DL PAQ-11_DN	PID-5-BF+_NA PID-5-BF+_DT PID-5-BF+_ANT PID-5-BF+_DN	0.72 0.58 0.48 0.57	428	Community adults	Digital post	USA	English	50.9%	45.7	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: Yes Confounding Management: Yes Measurement: Yes Statistics: Yes
14. Kim et al. (42)	2021	ICD-11 Traits-DSM-5 Traits	PAQ-11_NA PAQ-11_DT PAQ-11_DL PAQ-11_DN	PID-5-SF_NA PID-5-SF_DT PID-5-SF_ANT PID-5-SF_DN	0.74 0.67 0.70 0.57	409	Mixed (clinical and community) adults	Women's university and Psychiatric outpatient clinic	South Korea	Korean	93.64%	23.7	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: Yes Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes

(Continued)

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TABLE 1 (Continued)

Study	Year	Associated models of PD	ICD-11 PD measure	AMPD measure	r coefficient	Sample size	Sample type	Setting	Country	Language	Gender, % female	Age, M	Technique / informant	Quality assessment
15. Kerber et al. (43)	2020	ICD-11 Traits-DSM-5 Traits	PiCD_NA PiCD_DT PiCD_DL PiCD_DN	PID-5-BF+_NA PID-5-BF+_DT PID-5-BF+_ANT PID-5-BF+_DN	0.81 0.76 0.65 0.75	493	Community adults	NR	Germany	German	70.8%	35.7	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: No Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes
16. Oltmanns and Widiger (44)	2017	ICD-11 Traits-DSM-5 Traits	PiCD_NA PiCD_DT PiCD_DL PiCD_DN	PID-5_NA PID-5_DT PID-5_ ANT PID-5_DN	0.81 0.80 0.77 0.85	285	Community adults	NR	USA	English	66%	35.1	Questionnaire / Self	Eligibility Criteria: Yes Sample and Setting: No Confounding Identification: No Confounding Management: No Measurement: Yes Statistics: Yes

NR, not reported; _NA, _Negative Afectivity; _DT, _Detachment; _DL, _Dissociality; _ANT, _Antagonism; _DN, _Disinhibition; PDS-ICD-11, ICD-11 Personality Disorder Severity Scale; PDS-ICD-11-CRF, ICD-11 Personality Disorder Severity Scale Clinician Rating Form; ICD-11 PD severity, ICD-11 Personality Disorder Severity Clinician Rating Form; LPFS-BF, Level of Personality Functioning Scale– Brief Form; LPFS-BF 2.0, Level of Personality Functioning Scale– Brief Form Version 2; LPFS-BF 2.0-I, Informant's Level of Personality Functioning Scale – Brief Form Version 2; STiP 5.1, Semi-Structured Interview for Personality Functioning DSM-5; PiCD, Personality Inventory for ICD-11; ICD-11 PD Traits, ICD-11 Personality Disorder Traits; PAQ-11, Personality Assessment Questionnaire for ICD-11; LPFS-SR-FFM-TC, LPFS-FFM Trait Coded; PID-5, Personality Inventory for DSM-5; PID-5-BF, Personality Inventory for DSM-5-Brief Form; PID-5-SF, PID-5-BF, Personality Inventory for DSM-5-Short Form; PID-5-BF+, Personality Inventory for DSM-5-Brief Form Plus; I-PID-5-BF+, Informant's Personality Inventory for DSM-5-Brief Form Plus.

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risk of bias in the 'Confounding Identification' and 'Confounding Management' domains (30–35, 37–40, 42–44), as baseline characteristics or prognostic factors of the results were not identified; nor were strategies such as matching or stratification used to address these confounders. Although three studies provided only one metric of interest for this study (29, 33, 36), the remainder provided two or more association coefficients that were useful for this investigation. Consequently, 54 studies in total were included in this meta-analysis. Figure 1 shows the forest plot of the studies that were meta-analyzed using the random effects method. Two subgroups are shown: the associations between the ICD-11 severity model and the DSM-5 AMPD severity model, and the associations between the ICD-11 traits model and the DSM-5 AMPD traits model.

A strong and significant degree of heterogeneity was observed in the general model ($k = 54$). That is, $\tau^2 = 0.04$, 95% CI [0.02; 0.05], which denotes a significant variance in true effects between studies (45, 46). The I^2 statistic, which describes the proportion of the true variance found (46), also showed a considerable level of heterogeneity ($I^2 = 97.6$, 95% CI [97.3%; 97.9%]). Cochrane's Q also showed a significant level of heterogeneity ($\chi^2 = 2226.80$ (53), $p = 0$). The group estimator of the effect size—i.e., the summary coefficient of association—of the general model was significantly moderate ($r = 0.62$, 95% CI [0.57, 0.67], $p < 0.0001$). A significant degree of publication bias was also found using Egger's regression test ($t = -6.27$ (52), $p < 0.0001$; see the funnel plot in Supplementary Figure S2). For the subgroup of associations between the ICD-11 severity model and DSM-5 AMPD severity model ($k = 10$), significant levels of heterogeneity were also found $\tau^2 = 0.02$, $I^2 = 92.9\%$, $\chi^2 = 126.15$. The estimated coefficient of this subgroup was significantly moderate ($r = 0.57$, 95% CI [0.48, 0.66]). In the subgroup of associations between the ICD-11 traits model and the DSM-5 AMPD traits model ($k = 44$), significant levels of heterogeneity were found $\tau^2 = 0.04$, $I^2 = 97.9\%$, $\chi^2 = 2019.80$. The estimated coefficient for this subgroup was also significantly moderate ($r = 0.63$, 95% CI [0.57, 0.69]). Finally, there was no significant difference between the associations found in these two subgroups ($\chi^2 = 1.25$ (1), $p = 0.26$). However, there is evidence that sample type and language moderated the overall effect size ($\chi^2 = 50.7$ (2), $p < 0.0001$ and $\chi^2 = 14.27$ (5), $p = 0.01$; respectively).

We also performed further analyzes of each of the trait domains as subgroups (see Supplementary Figure S3). For the subgroup of

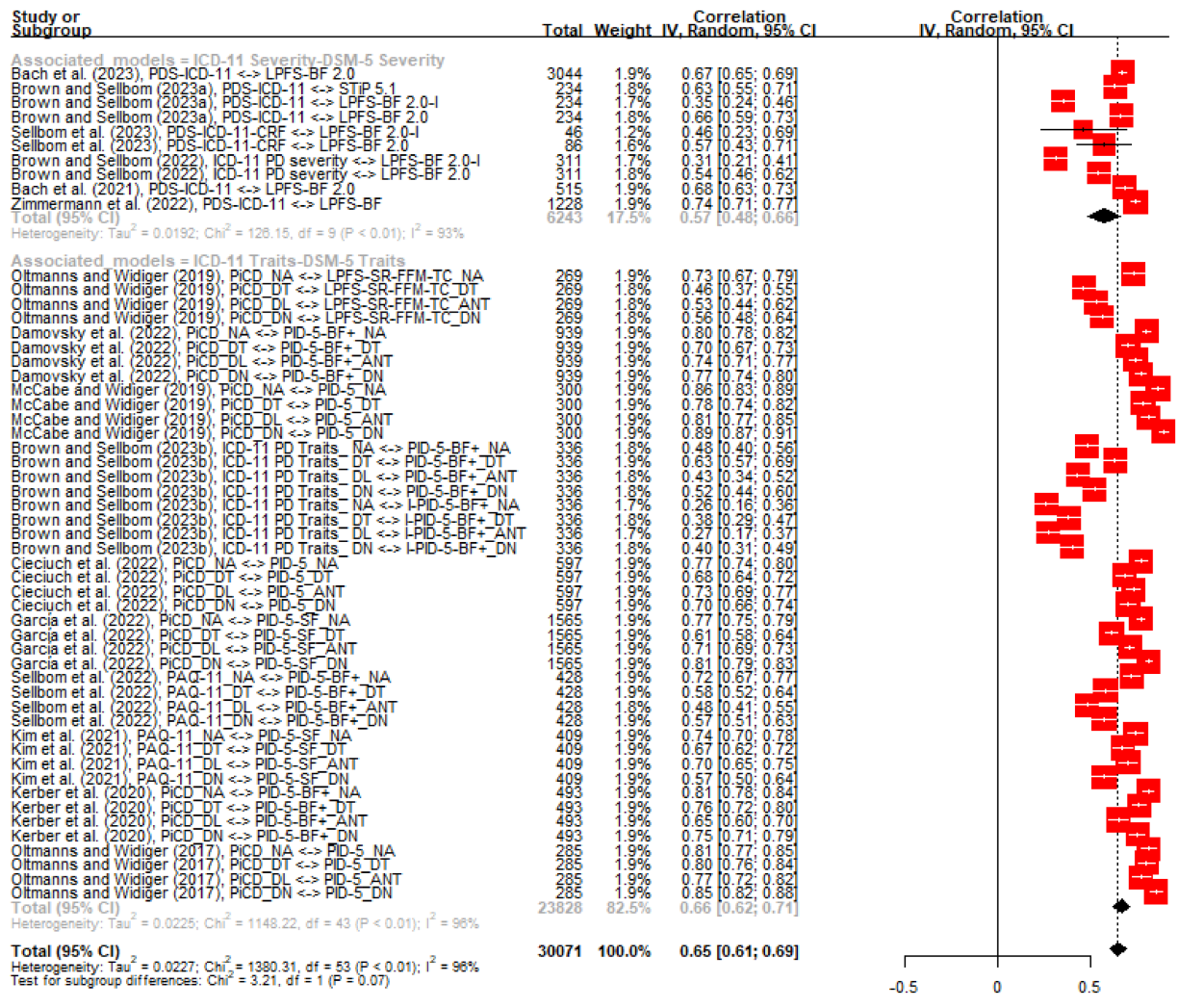

FIGURE 1
Forest plot of the reviewed studies.

Negative Affectivity associations between the ICD-11 model and the DSM −5, a significant level of heterogeneity was found $\tau^2 = 0.03$, $I^2 = 95.2\%$, $\chi^2 = 206.22$. The coefficient estimate for this subgroup was significantly high ($r = 0.71$, 95% CI [0.61, 0.81]). Likewise, for the subgroup of Detachment associations between the ICD-11 model and the DSM −5, a significant level of heterogeneity was found $\tau^2 = 0.04$, $I^2 = 97.7\%$, $\chi^2 = 432.20$. The coefficient estimate for this subgroup was significantly moderate ($r = 0.59$, 95% CI [0.48, 0.71]). Similarly, for the subgroup of Dissociality/Antagonism associations between the ICD-11 model and the DSM-5, a significant level of heterogeneity was found $\tau^2 = 0.06$, $I^2 = 98.4\%$, $\chi^2 = 636.14$. The coefficient estimate for this subgroup was significantly moderate ($r = 0.55$, 95% CI [0.41, 0.70]). Also, for the subgroup of Disinhibition associations between the ICD-11 model and the DSM-5, a significant level of heterogeneity was found $\tau^2 = 0.02$, $I^2 = 97.1\%$, $\chi^2 = 349.06$. The coefficient estimate for this subgroup was significantly moderate ($r = 0.68$, 95% CI [0.58, 0.77]). Finally, there was no significant difference in these four subgroups ($\chi^2 = 4.23$ (3), $p = 0.24$).

4 Discussion

To our knowledge, this review is the first study to meta-analytically examine the convergence between the measures that evaluate PD from the new dimensional models of the two most used diagnostic standards in the world, the ICD-11 and the DSM-5 AMPD. In general, our findings indicate moderate convergence between these instruments, both for the severity and trait models. Although a high summary association would be more satisfactory —given that these instruments conceptually measure the same constructs— the results may already indicate empirical evidence for the interchangeable usefulness of these measures between one model and another. Publication bias can occur for various reasons, including heterogeneity in the methodology of studies in the meta-analysis (45), as presented here. Our results align with those described in more extensive non-meta-analytic reviews that included the convergent validity of the LPFS, and its derivatives, with other self-reported measures of PD severity (4, 24, 47). Likewise, our findings are similar to those of reviews that reported adequate levels of convergent validity between PID-5, and its derivatives, with other measures of maladaptive traits (8, 47, 48). The literature described in these reviews of the DSM-5 AMPD model instruments in relation to the ICD-11 PD model measures was extremely scarce and an update of the evidence was necessary.

The main strength of this research was the inclusion of gray literature [e.g., (31, 38)], and texts of articles in languages other than English [e.g., (35)]. However, this study has several limitations to declare. Regarding the evidence included in this review, most studies used small samples and the methodology was predominantly based on self-report questionnaires instead of using multimethod designs. Previous studies have already warned about these practices that limit the adequate interpretation of evidence (23, 49). Our study quality assessment tool is the most used by researchers because it is brief (50); however, for the same reason it may not adequately address all the shortcomings of the studies. Another limitation of the included studies was the majority use of community samples, in which the few vulnerabilities associated with PD may not reflect the exact relationship metrics that interest us. Regarding the limitations of the review processes used, we were unable to access relevant data from two studies (51, 52) because of the lack of response from the authors or the failure to understand our requirement. Likewise, we could not perform moderator analyses because the number of studies with the same measure or another possible moderator was insufficient. However, we assert that none of these methodological limitations would change the general inferences of this review. Future research could address these limitations or conduct discriminant validity analyses to complete evidence of the construct validity of the measures of one or another dimensional model of PD.

Author contributions

LH-O: Conceptualization, Writing – original draft. TC-R: Methodology, Supervision, Writing – review & editing. JT: Conceptualization, Supervision, Validation, Writing – review & editing. DR-C: Conceptualization, Formal analysis, Methodology, Writing – original draft.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1325583/full#supplementary-material

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Corrigendum: Convergence between the dimensional PD models of ICD-11 and DSM-5: a meta-analytic approach

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KEYWORDS

ICD-11, DSM-5, personality disorder, dimensional models, severity, traits, convergent validity, meta-analysis

A Corrigendum on

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In the published article, there was an error in Table 1, *7. Damovsky et al. (35)*, Column 6. Two incorrect r coefficients were mentioned. Instead of "0.14" and "0.00", they should be "0.70" and "0.74", respectively.

In the published article, there was an error in Figure 1. The figure showed incorrect correlation indices for 'Damovsky et al. (2022), PiCD_DT <-> PID-5-BF+_DT' and for 'Damovsky et al. (2022), PiCD_DL <-> PID-5-BF+_ANT'. Instead of "0.14" and "0.00", it should be "0.70" and "0.74", respectively.

The correct Figure 1 appears below.

In the published article, there was an error in Supplementary Figure S3. The figure showed incorrect correlation indices for 'Damovsky et al. (2022), PiCD_DT <-> PID-5-BF+_DT' and for 'Damovsky et al. (2022), PiCD_DL <-> PID-5-BF+_ANT'. Instead of "0.14" and "0.00", it should be "0.70" and "0.74", respectively.

In the published article, there was an error in **3 Results**, *3.1 Description of the chosen studies*, Paragraph 2. This sentence previously stated:

"The range of the correlation coefficients r was from 0.31 to 0.74 between the severity measures of both models; and r from 0 to 0.89, between the trait scales of both models."

The corrected sentence appears below:

"The range of the correlation coefficients r was from 0.31 to 0.74 between the severity measures of both models; and r from 0.26 to 0.89, between the trait scales of both models."

The authors apologize for these errors and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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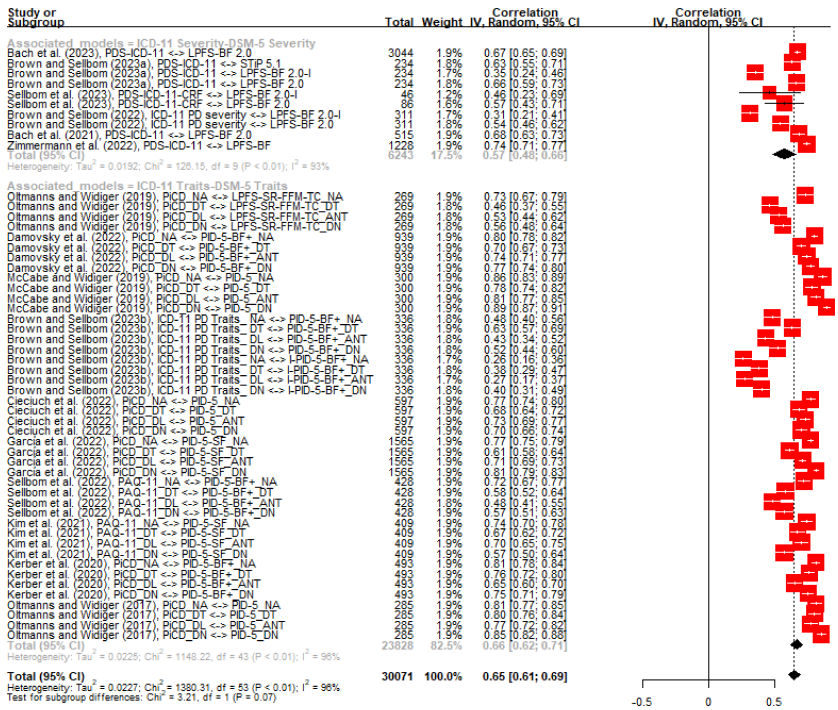

FIGURE 1

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Personality disorders in people with epilepsy: a review

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Epileptologists and psychiatrists have long observed a correlation between epilepsy and personality disorders (PDs) in their clinical practice. We conducted a comprehensive PubMed search looking for evidence on PDs in people with epilepsy (PwE). Out of over 600 results obtained without applying any time restriction, we selected only relevant studies (both analytical and descriptive) limited to English, Italian, French and Spanish languages, with a specific focus on PDs, rather than traits or symptoms, thus narrowing our search down to 23 eligible studies. PDs have been investigated in focal epilepsy (predominantly temporal lobe epilepsy - TLE), juvenile myoclonic epilepsy (JME) and psychogenic non-epileptic seizures (PNES), with heterogeneous methodology. Prevalence rates of PDs in focal epilepsy ranged from 18 to 42% in surgical candidates or post-surgical individuals, with Cluster C personality disorders or related traits and symptoms being most common. In JME, prevalence rates ranged from 8 to 23%, with no strong correlation with any specific PDs subtype. In PNES, prevalence rates ranged from 30 to 60%, with a notable association with Cluster B personality disorders, particularly borderline personality disorder. The presence of a PD in PwE, irrespective of subtype, complicates treatment management. However, substantial gaps of knowledge exist concerning the neurobiological substrate, effects of antiseizure medications and epilepsy surgery on concomitant PDs, all of which are indeed potential paths for future research.

KEYWORDS

epilepsy, personality disorders (PDs), PNES, juvenile myoclonic epilepsy (JME), temporal lobe epilepsy, epilepsy surgery

Introduction

Epilepsy is a chronic disease of the brain defined as "an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition" (1). It is a common neurological disease, with a calculated incidence rate of 61.4 per 100,000 person-years and a prevalence of 7.60 per 1,000 population

(2), it affects approximately 46 million people, therefore representing a significant fraction of the worldwide disease burden (3). Remarkably, nearly half of people with epilepsy (PwE) experience comorbidities, with certain conditions exhibiting a higher prevalence among PwE compared to the general population, often impacting on epilepsy prognosis itself (4). Psychiatric disorders have garnered particular attention, due to their association with poor seizure outcome, drug-resistance, heightened suicide risk (5–7). While extensive research has been devoted to psychotic, anxiety and mood disorders, limited attention has been directed to the relationship between epilepsy and personality disorders (PDs). This neglect is somewhat surprising given historical observations dating back to the last century, originating from studies involving institutionalized PwE. Several clinical conditions have been described, such as Geschwind syndrome (8), gliscroid personality or Blumer syndrome (9). These data were not universally supported or agreed upon (10) and were related, in particular, to the presence of temporal lobe epilepsies (TLE) with drug-resistant seizures, social isolation, and the use of certain medications, such as phenobarbital or bromine. Subsequent studies showed that other types of epilepsy, such as the Idiopathic Generalized Epilepsies (IGE), showed very different personological characteristics from those described for TLE (11). Features such as superficiality, tendency to elation, poor compliance and critical traits were noted, often attributed to frontal lobe involvement (11). However the debate about the existence of personological alterations during epilepsy has waned in subsequent years, partly in connection with the use of medications with less impact on cognitive function and with the improved social integration of PwE, so much so that the Commission on Epilepsy, Risks and Insurance of the International Bureau for Epilepsy regarded the risk for psychological disorders in epilepsy to be negligible, at least when considered as such (12). Furthermore, the emergence of a revised classification system both for epilepsies and for personality disorders (DSM-5) has provided more rigorous and precise definitions, warranting a reevaluation of the association between epilepsy and PDs. In light of these developments, it is imperative to revisit the nexus between epilepsy and PDs, incorporating contemporary scientific evidence and examining diverse populations.

Our review focuses specifically on PDs in PwE, with the aim to collect and synthesize existing evidence, identify gaps of knowledge and propose potential avenues for future research.

Material and methods

In November 2023 we performed a search on PubMed database using the following terms: "Epilepsy"[Mesh] AND ["personality disorder"(All Fields) OR "paranoid personality disorder" (MeSH) OR "schizoid personality disorder" (Mesh) OR "schizotypal personality disorder" (MeSH) OR "antisocial personality disorder" [MeSH] OR "borderline personality disorder "(MeSH) OR "histrionic personality disorder" (MeSH) OR "narcissistic personality disorder" (All Fields) OR "avoidant personality disorder" (All Fields) OR "dependent personality disorder" (Mesh) OR "obsessive compulsive disorder" (MeSH)].

We selected studies (both descriptive and analytical) written in English, Italian, French and Spanish investigating the prevalence of personality disorders in PwE. Exclusion criteria were reviews, case reports, case series with small populations (i.e. less than 10 patients) and editorial comments. Additionally, studies emphasizing personality traits or symptoms without a formal diagnosis of personality disorder were excluded. Studies focusing on personality traits or symptoms without a diagnosis of personality disorder were excluded. No time restrictions were applied, and the entire selection process was carried out manually without the use of any automated tool.

The identified references were screened and provisionally selected for inclusion on the basis of title and abstract, when available. The full texts of articles meeting the inclusion criteria were then assessed.

Results

The initial PubMed search yielded a total of 638 articles. Following a multi-step selection process, 23 studies met the inclusion criteria and were considered eligible for analysis (see Figure 1 for further details). The findings of these studies are presented in distinct subchapters, according to the main themes investigated (see Table 1).

Personality disorders and focal epilepsy

Among the included studies, eleven investigated the relationship between PDs and focal epilepsy. These studies showed a significant prevalence of PDs within the studied population, with the strongest association observed between TLE and Cluster C PDs (13–15) and, to a lesser extent, between TLE and schizotypal personality (21).

Several studies investigated PDs in people with focal epilepsy who underwent epilepsy surgery, investigating its impact on both medical conditions. Notably, one study reported a statistically significant improvement in pre-surgical PD symptoms, although details on seizure outcomes were not provided (15). In another work, surgical resection of the epileptogenic zone led to remarkable improvements in all five patients diagnosed with concomitant PD, with two even being able to discontinue antipsychotic medications. Post-surgical seizure outcomes, assessed using the Engel Surgical Outcome Scale, were also highly favorable, with patients either becoming completely seizure-free or experiencing only rare seizures (12). Interestingly, a large population- based study in people with TLE revealed that PDs were predictive of surgery failure, defined as significantly lower rates of Engel class I and IA (16). The authors speculated that complex brain microstructural abnormalities in people with TLE and psychiatric comorbidities might underlie this association, emphasizing the need for further research.

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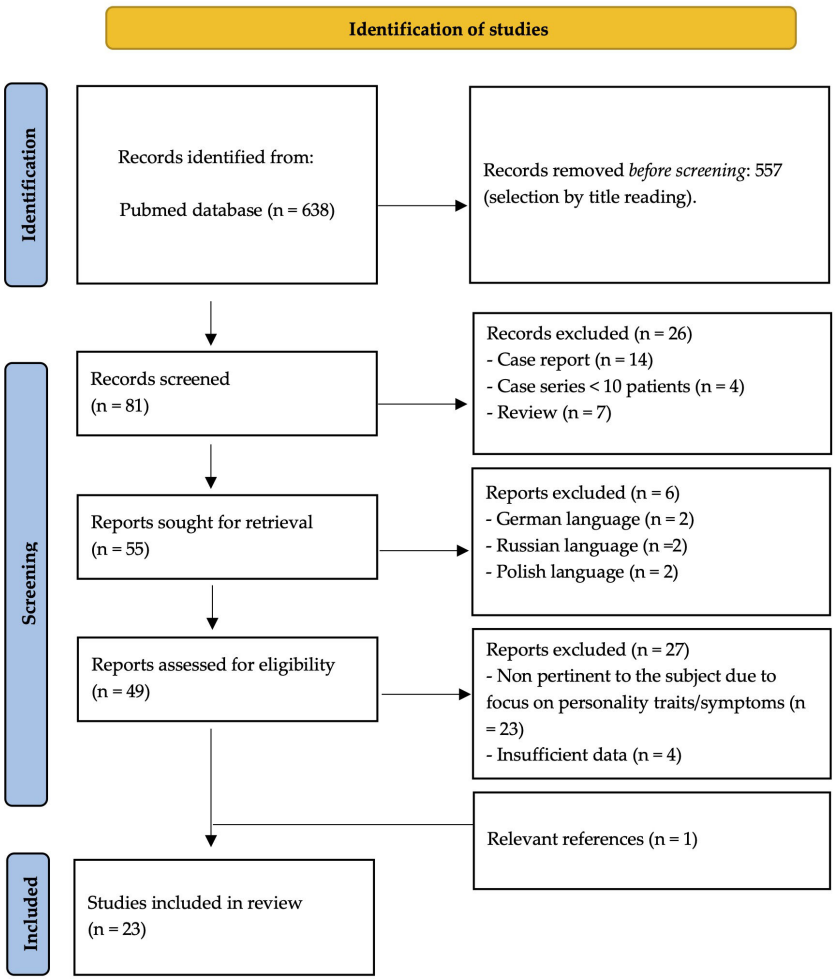

FIGURE 1
Detailed multi-step process for source identification.

TABLE 1 Results.

Authors & Bibliography reference	Year of publication	Type of study	N. of patients	Population	PDs assessment	Findings
Sair A. et al. (13)	2021	Comparative study	60	TLE vs Healthy controls	SCID-II for DSM III-R	PDs higher in TLE 76.7% (23/30) Cluster C higher in TLE 53.5% (16/30) ($p = 0.035$) Individually taken, only dependent PD was statistically significantly higher ($p = 0.010$)
Baishya J. et al. (14)	2019	Comparative study	120	TLE with MTS vs Healthy controls	IPDE-ICD10	PDs higher prevalence in TLE 71.7% ($p < 0.001$) with schizoid ($p = 0.002$) and cluster C traits prevalent ($p < 0.003$) Correlation with longer history of disease ($p = 0.026$) and drug-resistance ($p = 0.033$)

(Continued)

TABLE 1 Continued

Authors & Bibliography reference	Year of publication	Type of study	N. of patients	Population	PDs assessment	Findings
Novais F. et al. (15)	2019	Observational cohort study	199	DRE treated with surgery (TLE vs ExTLE)	ICD-10 and MCMI-II	Surgery improved dysfunctional personality pattern ($p = 0.0013$). TLE significant predictor of Cluster C: - Avoidant ($p = 0.0051$) - Compulsive ($p = 0.008$)
Kock-Stoecker S. C. et al. (16)	2017	Observational study	434	TLE treated with TL lobectomy	SCID-II for DSM III-R and SCID-II for DSM IV	PDs predictors of failure of Engel class I and Engel class IA ($p < 0.001$): Cluster A ($p = 0.027$) Cluster C ($p = 0.006$) Organic PD ($p < 0.001$)
Landais A. et al. (17)	2016	Observational study	10	TLE due to DNET in patients treated with surgery	DSM IV-TR ICD-10	PDs 50% with general improvement after surgery
Thorbecke et al. (18)	2014	Retrospective study	351	TLE	DSM III-R or DSM IV	PDs associated with poorer employment outcome ($p < 0.001$)
Dalmagro C.L. et al. (19)	2012	Observational retrospective study	490	Drug-resistant epilepsy (MTLE, NeoTLE, ExTLE)	DSM IV e DSM IV-TR	No significant relationship between PDs and type of epilepsy
Sperli F. et al. (20)	2009	Observational study	217	Drug-resistant epilepsy (TLE vs ExTLE)	SCID-II for DSM IV	PDs associated with ExTLE ($p = 0.001$) and less likely to be operated ($p = 0.002$)
Mula M. et al. (21)	2008	Cross-sectional study	89	Epilepsy (mixed diagnoses)	SPQ	TLE correlates with SPQ total ($p = 0.009$)
Manchanda R. et al. (22)	1996	Observational study	300	Drug-resistant epilepsy (TLE, ExTLE, generalized and multifocal seizure onset)	DSM III-R and PSE	PDs in 18%, but no diagnosis of specific subtype
Deb S. & Hunter D (23).	1991	Comparative study	150	PwE vs Healthy controls	SAP and T-L PBI	No statistically significant difference in the prevalence of SAP/T-L personality
Kumar Panda P. et al. (24)	2023	Cross-sectional comparative study	200	JME vs Healthy controls	SCID for DSM V and FFM-APQ	PDs higher in JME ($p < 0.001$)
Taura M. et al. (25)	2020	Comparative study	104	JME vs Healthy controls	PBQ	PDs higher in JME: - Narcissistic ($p < 0.001$) - Borderline ($p = 0.002$) - Paranoid ($p = 0.017$) - Histrionic ($p = 0.041$)
Trinka et al. (26)	2006	Observational study	43	JME	SCID-II for DSM IV	23% PDs
Sobregau et al. (27)	2023	Cross-sectional and comparative study	125	Drug-resistance epilepsy vs PNES	PDQ-4+	No significant differences

(Continued)

TABLE 1 Continued

Authors & Bibliography reference	Year of publication	Type of study	N. of patients	Population	PDs assessment	Findings
Sullivan-Baca et al. (28)	2022	Retrospective comparative study	233	PNES vs Epileptic seizures (defined as ictal and/or interictal EEG anomalies and concordant semiology)	Clinical diagnosis through medical records non further specified	BPD higher in females with PNES ($p < 0.001$)
Rady A. et al. (29)	2021	Comparative study	66	PNES vs Epilepsy (generalized onset motor epilepsy and focal motor seizures with impaired awareness)	SCID-II for DSM IV	Cluster B PDs higher in PNES ($p < 0.05$) and BPD higher in PNES ($p < 0.001$)
Direk N. et al. (30)	2012	Comparative study	107	PNES vs Epileptic seizures (complex partial) vs Healthy controls	SCID-II for DSM-III-R	PDs higher prevalence in PNES Cluster B higher prevalence in PNES ($p < 0.001$) Cluster C higher prevalence in ES (statistically not significant)
Harden C. L. et al. (31)	2009	Comparative study	32	PNES vs Epileptic seizures (not specified)	SCID-II for DSM IV-TR	Cluster A-B higher in PNES and Cluster C higher in ES ($p = 0.007$)
Baillés E. et al. (32)	2004	Observational study	30	PNES	SCID-II for DSM III-R	PDs 60% (18/30) with Cluster B prevalent (12/18)
Kalogjera-Sackellares D. & Sackellares J. C (33).	1997	Comparative study	55	PNES vs PNES + ES	MMPI	No significant difference
Drake Jr Miles E. et al. (34)	1992	Observational study	20	PNES	Psychiatric diagnosis non otherwise specified	Cluster B PDs 30% (6/20): - 3/20 BP - 3/20 Mixed BP-Histrionic
Vanderzant C. W. et al. (35)	1986	Comparative study	39	PNES vs Generalised Seizures	MMPI	No statistically significant difference

SCID-II for DSM III-R, Structured Clinical Interview for DSM-III Axis II Disorders, Revised edition; IPDE-ICD10, The International Personality Disorder Examination in the International Classification of Disease 10th Edition; ICD-10, The International Classification of Disease 10th Edition; MCMI-II, The Million Clinical Multiaxial Inventory – II; DSM IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision; SCID-II for DSM-IV, Structured Clinical Interview for DSM IV; SPQ, Schizotypal Personality Questionnaire; PSE, Present State Examination; SAP, Standardised Assessment of Personality; T-L PBI The T-L, Personality Behaviour Inventory; SCID for DSM V, Structured Clinical Interview for DSM IV; FFM-APQ, Five-Factor Model Adolescent Personality Questionnaire; PBQ, Personality Belief Questionnaire; PDQ4+, Personality Diagnostic Questionnaire 4+; SCID-II for DSM IV-TR, Structured Clinical Interview for DSM IV, Text Revised; MMPI, Minnesota Multiphasic Personality Inventory.

In a separate comparative study, PDs were more commonly associated with extratemporal lobe epilepsy (ExTLE) rather than TLE, leading to lower rates of surgical intervention for individuals with this comorbidity. Nevertheless, those who did undergo surgery exhibited similarly successful outcomes (20). Moreover, people with epilepsy and PDs seem to suffer from an even bleaker stigma, as shown by lower employment rates two years after surgery (18).

Conversely, three studies did not detect significant differences in PD prevalence among PwE. One uncontrolled study focused only on people with intellectual disability and epilepsy, thus this finding could be attributed to a population selection bias (23). In the other two studies, discrepancies in results might be attributed to the specific assessment scales utilized – as questioned by the Authors themselves (17) - or the comparison of PD prevalence across different subtypes of focal epilepsy (19) that did not yield statistically significant differences.

Personality disorders and juvenile myoclonic epilepsy

Three studies on PDs and juvenile myoclonic epilepsy (JME) were identified. Two recent comparative studies showed that PDs were significantly more prevalent in JME compared to healthy controls. While one study did not identify specific correlation between PD subtypes and JME (24), the other reported strong associations between narcissistic, borderline, paranoid and histrionic PDs and JME (25). These discrepancies may stem from variations in assessment scales used, as the populations examined exhibited otherwise similar characteristics. A third older and purely descriptive study focused on assessing the prevalence of PDs in a medium-size sample of patients with JME, without providing statistical analyses (23).

Personality disorders and psychogenic non-epileptic seizures

Among the 9 studies investing the association between PDs and psychogenic non-epileptic seizures (PNES), seven were comparative studies comparing people with PNES to various control groups, including those with epilepsy/epileptic seizures alone (27–31, 35), PwE and PNES (33), or healthy controls (30). The remaining two studies were observational uncontrolled studies that gathered data on people with PNES through medical history and hospital charts (32, 34). While the evidence from these latter two studies was undoubtedly of lower quality due to the lack of proper statistical analysis and, in one case, insufficient details on the methods used to diagnose PD (34), we deemed it important to include them as seminal works that highlighted a higher prevalence of Cluster B PDs in people with PNES, a finding largely confirmed by subsequent literature and deemed statistically significant in the majority of our results (28–31). However, three studies presented discordant findings in this regard, potentially influenced by factors such as the assessments tools used. For instance, one study (27) reported statistically significant high scores in the "extraversion" section of the NEO-Personality Inventory-Revised among patients with PNES. The other two studies assessed PDs by the Minnesota Multiphasic Personality Inventory (MMPI), despite criticisms regarding its limitations and inconsistency of results obtained using this tool (36, 37).

Regarding gender differences, two studies show a statistically significant higher prevalence of PDs in women with PNES (28, 29).

Discussion

Despite the known higher prevalence of psychiatric comorbidities in PwE, the relationship between epilepsy and PDs has been inadequately investigated in the most recent scientific literature (38).

Our review demonstrates that the literature available on this topic is extremely heterogeneous in terms of methodology, population size, type of epilepsy investigated and assessment tools used for evaluating the disorder, with many works even failing to differentiate between psychiatric disorders in general and PDs (38–43). This last issue seems particularly relevant as the vast majority of the examined studies tend to combine and investigate various psychiatric conditions together (44). Conversely, when studies do focus on personality comorbidities, they often center on traits or symptoms rather than formally diagnosed PDs (39–41). Such methodological inconsistencies present a significant barrier to the comprehensive inclusion of pertinent evidence in our analysis, consequently constraining our capacity to derive meaningful insights regarding the relationship between PDs and epilepsy.

Another issue encountered in reviewing the existing literature on this subject is the lack of strong evidence due to the limited scope of studies carried out thus far, as, in spite of the higher prevalence of psychiatric comorbidities in PwE and the impact they seem to have on epilepsy prognosis itself, the number of well-designed case-control studies investigating their correlation remains insufficient (24). Ideally, to ensure statistical validity and clinical relevance, systematic comparisons should be made among different types of epilepsy and between PWE and healthy controls. Moreover, it seems very interesting to observe that there is relatively little standardized work on the issue of diagnostic tools used to identify PDs in epilepsy. Many studies relied on the MMPI, despite concerns raised by some researchers (36, 37). The consequence of it, however, is the vast array of diagnostic tools used subsequently, such as the Bear-Fedio Inventory (BFI), the DSM-IV axis I and axis II, the Structured Clinical Interview for DSM-III-R PDs (SCID-II), the Clinical Interview Schedule (CIS) and many others, making the different results obtained arduous to analyse in a comprehensive fashion (38). Moreover, as reiterated by Trimble (36), the diagnosis made by scales cannot be considered valid tout court for a clinical diagnosis.

On the other hand, the change in the classification of the same disorders in relation to different editions of the DSM, the same different classification of epilepsies, the change in the treatment of them in recent years and, in particular, the increased social integration of individuals with epilepsy do not allow the historically acquired data to be considered valid.

Furthermore, the literature revision is complicated by its heterogeneity, as specific different types of epilepsy were investigated in individual studies, while, on the contrary, some neglected to differentiate between epilepsy and isolated seizures. There is a long-standing and established interest in exploring the relationship between PDs and PNES (35) and, more recently, a rapidly growing body of evidence on PDs in people with focal epilepsy has emerged (19–21), even applying the recently proposed dimensional approach to personality profile (45). However, there are only scattered studies on other subtypes of epilepsy, such as JME (24), and, to our best knowledge, very few works on the correlation between PDs and epilepsy as a whole, most of which also happen to be quite dated (36, 46–48).

Given these limitations, our study aimed to aggregate and summarize available findings to offer a current perspective on the state of research in this area. By highlighting these constraints, we hope to identify potential research directions for future exploration. The relationship between PDs and focal epilepsy, particularly TLE, is well-established, with prevalence rates ranging from 18 to 42% in surgical candidates or post-surgical individuals (49). While there is no clear agreement as to what type of PD is the most prevalent, cluster C personality disorders or related traits and symptoms seem to be the most frequent (13–15, 31, 40, 50). However, the correlation between TLE, PDs and surgical treatment remains inconclusive, highlighting the need for future works to delve in this complex relationship, due to its profound impact on patients' outcome.

In the context of JME, the prevalence and specific types of PDs remain contentious among the limited available studies (51). Nevertheless, the significance of exploring this relationship is undeniable, given the prevalence of JME. Analysing the correlation between JME and PDs within the broader framework of the idiopathic generalized epilepsies, ideally comparing JME with the other subtypes, could yield robust evidence on their psychiatric and personality profiles.

Our research underscores a strong connection PDs and PNES, particularly in females, with a strong association with cluster B personality disorders, notably borderline personality disorder (52). Delayed diagnosis of PNES, averaging 7-9 years from the initial clinical episode, leads to unnecessary hospitalizations and inappropriate treatment with antiseizure medications (ASMs) (53). Regarding the association with PNES, it must, in any case, be considered, that since PNES is a psychiatric disorder, many authors wonder whether we are really facing an association of different pathologies or a single one (11).

Regarding ASMs in general, our review highlights that the presence of a PD in PwE, regardless of the subtype, complicates treatment management. Clinicians face challenges in maintaining a delicate balance due to the potential for ASMs to worsen or exacerbate underlying PDs, as observed with drugs like perampanel and levetiracetam (7, 54–57).

This review has methodological limitations. We conducted our research through only one database, potentially excluding relevant evidence available from other online sources. Moreover, few studies were not included for language reasons (58–61). Lastly, we did not offer an analysis of the evidence strength provided by each work as the grand variety of statistical methodology used, population size, type of epilepsy and parameters considered made us opt for a purely descriptive presentation of our findings. However, we do not think that these limits significantly reduce the strength of our results, which allowed us to identify research paths worthy of further investigation.

Conclusions and directions for future research

While the relationship between psychiatric comorbidities and epilepsy has been discussed since time immemorial (47), our study reveals a notable lack of definitive data on various aspects concerning PDs in PwE. The literature in this domain is limited and methodologically diverse, yet our findings suggest that PDs are a prevalent comorbidity in PwE.

Future research should prioritize the identification of significant correlations between PDs and specific types of epilepsy, as well as elucidate how their co-occurrence influence patients' prognosis. Additionally, it is crucial to investigate the effects of current ASMs on concomitant PDs.

Given the increasing number of patients being considered for epilepsy surgery, it is of the utmost importance to deepen our understanding of the neurological basis and pathological mechanisms that intertwine PDs and epilepsy, given the current scarcity of evidence that may inadvertently hinder optimal treatment decisions for some patients.

Based on our findings and with the aim of enhancing patient care and wellbeing, we advocate for a collaborative, multidisciplinary approach involving neurologists and psychiatrists, which should begin from the early stages of diagnosis and extend to the selection of personalized therapeutic strategies for each patient.

Author contributions

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Conflict of interest

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A systematic review of personality and musculoskeletal disorders: evidence from general population studies

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Introduction: We conducted a systematic review to evaluate the quality and extent of evidence on associations between personality disorders (PDs) and musculoskeletal disorders (MSDs) in population-based studies, since these disorders are leading causes of disease burden worldwide.

Methods: A search strategy of published, peer-reviewed and gray literature was developed in consultation with a liaison librarian and implemented for Embase, CINAHL Complete, Medline Complete, and PsycINFO via the EBSCOhost platform from 1990 to the present and CORDIS and ProQuest Dissertations & Theses Global, respectively. The inclusion criteria were as follows: I) general population participants aged ≥15 years; II) self-report, probable PD based on positive screen, or threshold PD according to the DSM-IV/5 (groupings: any, Clusters A/B/C, specific PD) or ICD-10/11; III) MSDs identified by self-report or ICD criteria (arthritis, back/neck conditions, fibromyalgia, osteopenia/osteoporosis) and III) cohort, case-control, and cross-sectional study designs. Two reviewers independently screened articles and extracted the data. Critical appraisal was undertaken using the Joanna Briggs Institute checklists for systematic reviews of etiology and risk. A descriptive synthesis presents the characteristics of included studies, critical appraisal results, and descriptions of the main findings. This review adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results: There were 11 peer-reviewed, published articles included in this review (n = 9 cross-sectional and n = 2 case-control studies); participants were ≥18 years in these studies. No published gray literature was identified. Semi-structured interviews were the most common method to ascertain PDs; all studies utilized self-reported measures to identify MSDs. Overall, we detected limited and conflicting evidence for associations between PDs and MSDs.

Discussion: The main result may be explained by lack of population-based longitudinal evidence, heterogenous groupings of PD, and few comparable cross-sectional and case-control studies. Strengths of the review include a

comprehensive search strategy and a discussion of mechanisms underlying possible associations between PDs and MSDs.

Conclusions: The quality of most studies included in this review that examined associations between PD and MSDs in general population adults was high. However, the results demonstrated limited and conflicting evidence for these associations, in part, due to lack of comparable evidence, which should be addressed in future research.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier CRD42021243094.

KEYWORDS

personality disorder, PD, musculoskeletal disorders, musculoskeletal diseases, review, systematic review, comorbidity

1 Introduction

Mental disorders and musculoskeletal disorders (MSDs) are each leading contributors to years lived with disability (YLD) (1). Personality disorders (PDs) are a common form of mental disorders, with a worldwide prevalence estimate of approximately 8% (2). PDs manifest as difficulties with emotion regulation, interpersonal relating, and adaptive functioning such as coping with daily life stressors and demands (3, 4). Existing classifications characterize PD as 10 distinct categorical disorders that are organized into Clusters A ("odd-eccentric" features), B ("dramatic/emotional/erratic" features), and C ("anxious/fearful" features) (5). Contemporary approaches to the classification of PD have resulted in the International Classification of Diseases (ICD-11) adopting a dimensional approach to classification focusing on patterns of traits that contribute to impairment in global personality functioning (6). Separately, MSDs are a group of conditions or consequences from injury that affect bones (i.e., osteoporosis, osteopenia), joints (i.e., types of arthritis such as osteoarthritis, rheumatoid arthritis, and psoriatic arthritis), muscles, and other soft tissues, as well as those that implicate multiple body areas or systems (i.e., chronic back/neck pain and fibromyalgia) (7). These MSDs can result in courses of acute or chronic painful symptoms, significantly restricting mobility and functioning, and leading to increased morbidity and mortality [see literature review by Briggs et al. (8)]. There is growing evidence of high occurrences of comorbid PD with common types of MSDs in clinical populations (9). However, awareness of these associations in the general population is still limited.

Among patients with chronic back/neck pain, the proportion of PD is reported to range between 43.6% and 69.6% (clinically based studies) (10–12). Longitudinally, the occurrence of chronic back pain in patients with remitted and non-remitted borderline PD is 47.8% and 57.7%, respectively (at 16 years of follow-up) (13). In addition, PD is common among patients with fibromyalgia with frequencies ranging from 8.7% to 65.0% in clinical studies (14–18). Moreover, in a retrospective cohort study using hospitalization/physician claim data, patients with rheumatoid arthritis had increased incidence of PD (incident rate ratio = 1.61; 95% CI: 1.29–1.99) compared to controls (matched 5:1 on sex, age, and region of residence in Manitoba, Canada) as well as other types of immune-mediated inflammatory diseases (19). Moreover, there is longitudinal evidence that remission status among patients with borderline PD is associated with osteoarthritis over the long term with 4.0% (remitted) and 15.5% (non-remitted) having osteoarthritis at the study baseline and 11.9% (remitted) and 26.8% (non-remitted) after 16 years (13, 20). However there was no population-based control group. There is also clinical cross-sectional evidence to suggest patients (women only) with borderline PD may have reduced bone mineral density (BMD) and be at risk of osteoporosis (21, 22).

Improved recognition of these associations in a population-based setting is warranted; evidence from a large epidemiological study showed that as separate categories of disorders, PDs and MSDs, such as arthritis, are associated with significant population-level quality-adjusted life year (QALY) losses, which suggests a high overall burden to individuals and society (23).

Recently, we undertook a scoping review of the comorbidity of PD and MSDs, which included existing reviews (9). It revealed that there were no existing systematic reviews that incorporated critical appraisal of the evidence, or meta-analyses, and none that focused on population-based associations between PD and MSDs. Therefore, we developed and published a protocol, which outlines the methodological approach to conduct a systematic review, and address this gap in the literature (24). Prior to commencing the conduct, we confirmed no existing systematic review on this topic via a search of PROSPERO, Open Registries, and Medline Complete, CINAHL Complete, and PsycInfo databases

(EbscoHost platform). The systematic review is needed to assess the quality of existing evidence and quantify associations to provide directions for future research and practice. In addition, evaluating the evidence will enable inferences to be made about these associations in the population, along with potential associated needs (23).

Therefore, a systematic review was undertaken, with the objective of evaluating population-based epidemiological associations between PD and burdensome MSDs including arthritis, back/neck pain, fibromyalgia/muscular pain, and osteopenia/osteoporosis. These MSDs were selected as outcomes for this review, as we recently scoped the evidence on this topic (9) and identified these MSDs as possibly highly comorbid with PD in clinical and/or general population settings. In addition, we identified emerging evidence of associations with poorer bone health (25). In accordance, the research questions were as follows:

1. Is there an association between PDs and arthritis, back/neck pain, fibromyalgia/muscular pain, and osteopenia/osteoporosis and/or "any" of these conditions?

1.1. What methodological characteristics explain the heterogeneity in results?

2. For the question above, what is the quality and levels of evidence for these associations?

2 Methods

The protocol for this review is published (24), registered with PROPSERO (CRD42021243094), and was conducted in accordance with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) (26). It was also guided by the Joanna Briggs Institute resources for conducting systematic reviews of etiology and risk (27).

2.1 Inclusion criteria

The Population, Exposure, Outcome (PEO) framework (27) was used to characterize the inclusion and exclusion criteria for this review and is presented in Table 1. Eligible study designs were population based, observational cross-sectional (analytical), case-control, or cohort studies. Therefore, intervention, qualitative, and descriptive study designs were not considered eligible. No restrictions on participant characteristics or language of publications were applied.

2.2 Evidence sources

Peer-reviewed and published gray literature evidence sources were restricted to those published in or after 1990. For this review, published gray literature included dissertations published in ProQuest Dissertations & Theses Global or reports/publications deriving from relevant projects/programs housed in the European Commission's Community Research and Development Information Service (CORDIS). These evidence sources were considered due to the potential to extract relevant epidemiological data. Additional information sources were identified by screening and reviewing the reference lists of eligible studies. Further details are presented below (see section on search strategy).

TABLE 1 Inclusion and exclusion criteria according to the Population, Exposure, Outcome (PEO) framework.

PEO framework	Inclusion(s)	Exclusion(s)
Population	General population participants aged 15 years and over • No restrictions on characteristics • No restrictions on language	• Participants under the age of 15 years • Studies conducted in clinical settings
Exposure(s)	PDs according to existing classifications: • DSM-IV/5 • ICD-10 or ICD-11 criteria Assessed/identified by: • Structured/semi-structured interview administered by a trained interviewer (i.e., graduate with a relevant qualification or lay interviewer) or expert (i.e., relevant health professional) • Screening/self-reported instruments	• Does not examine PDs according to the inclusion criteria
Outcome(s)	Presence of (yes/no) • Arthritis • Back/neck pain • Fibromyalgia/muscular pain • Osteopenia/osteoporosis • Any of these conditions Assessed/identified by: • ICD criteria, diagnosed by a relevant health professional, or other relevant clinical criteria reported in linked medical records (i.e., "expert diagnosis") • Self-reported from questionnaire responses or semi-structured interviews (i.e., "self-report")	• Does not examine MSDs according to the inclusion criteria • MSDs that are grouped with other conditions • Non-MSD-related pain conditions/types of chronic pain such as cancer-related pain, chronic fatigue syndrome, headache, inflammatory bowel disease, migraine, temporomandibular joint dysfunction •Does not examine MSDs according to the inclusion criteria

2.3 Study identification and selection

2.3.1 Search strategy

A comprehensive search strategy was developed to identify eligible evidence sources. First, in consultation with a liaison librarian (LG), a pilot search was developed and implemented in Medline Complete using the EBSCOhost platform on 26 August 2021 as part of the protocol development (24). Text words contained in the titles and abstracts of relevant articles were identified, and the search was developed using index terms (MeSH) and keywords, Boolean operators, truncations, and explode functions. A "gold set" list (25, 28–34) of relevant articles were identified from a recent scoping review (9) and used to test the preliminary search. All gold set articles were returned in the pilot search yield. Next, the search for Medline Complete was translated for CINAHL Complete and APA PsycINFO (via EBSCOhost), and Embase. Gray literature was searched using an adapted search for ProQuest Dissertations & Theses Global databases and CORDIS. The complete search was implemented on 16 September 2021 and updated on 20 February 2024 (see Supplementary Tables 1-6). Finally, the reference lists of included studies were exported using SCOPUS.

Assisted by the liaison librarian (LG), one reviewer (SEQ) implemented the search strategy and managed the records. The records from the combined searches were exported to Mendeley reference management software and Covidence (35) with duplicates removed. The flow of citations and reasons for exclusion at the full-text review are presented in Figure 1 and in the results (see Section 3).

2.3.2 Search strategy

Two reviewers (LJW and SEQ) conducted pilot testing of the inclusion and exclusion on a sample of 25 randomly selected articles from the search yield prior to screening. Next, the same two reviewers independently undertook screening of titles/abstracts and review full-text review of articles in Covidence. Discrepancies at the screening and full-text review phase were resolved in one consensus meeting each. One reviewer (SEQ) screened the records identified from the other methods. The final list of published peer-reviewed and gray literature was confirmed by the supervising author (LJW).

2.4 Data collection, extraction, and reporting

2.4.1 Critical appraisal of individual studies

Two reviewers (ALS and SEQ) independently assessed for risk of bias of the included studies using an adapted version of the critical appraisals tools by the Joanna Briggs Institute (36). Disagreements were resolved between the reviewers in one consensus meeting.

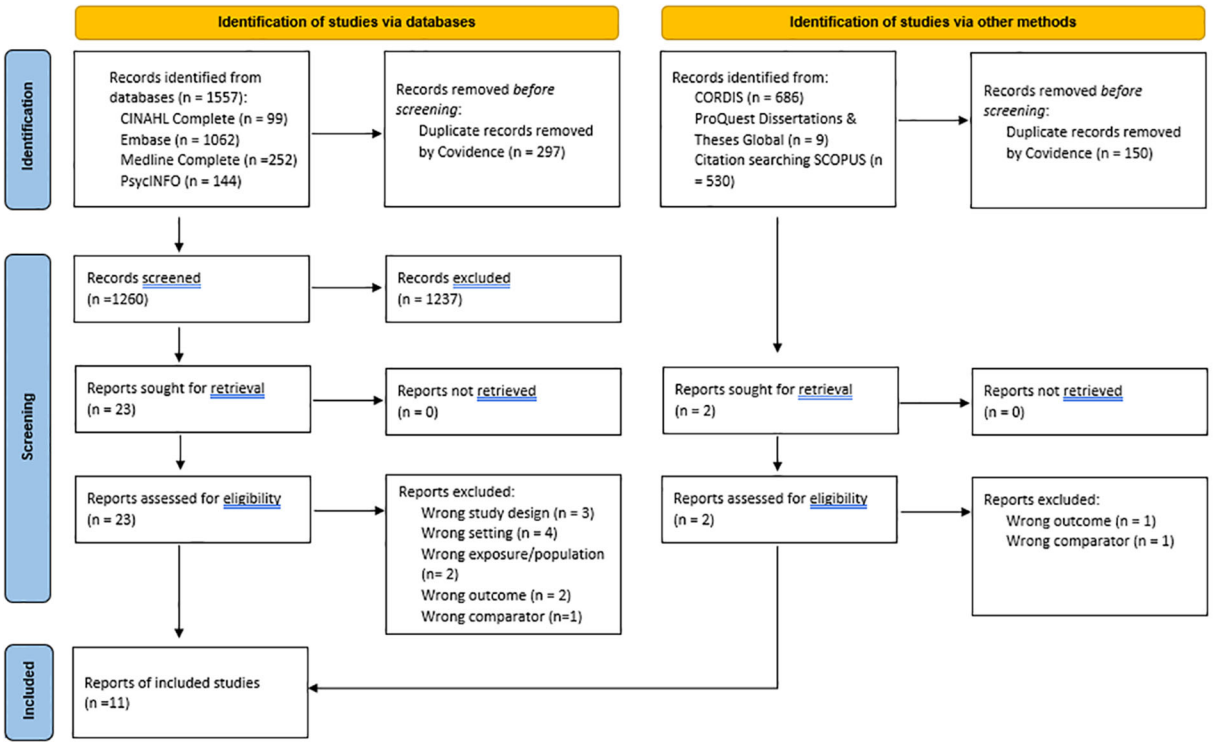

FIGURE 1
PRISMA 2020 flow diagram adapted from "Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

The critical appraisal tools assess pertinent biases in observational studies, including potential selection bias, information bias, and confounding, according to the relevant study design (36). Specifically, for the cross-sectional studies, we rated seven items concerning a) the inclusion/exclusion criteria, b) the description of the sample/representativeness, c) reliability and validity of the exposure(s), d) whether confounding factors were identified and measured, e) whether confounding factors were accounted for in study design/analysis, f) reliability and validity of the outcome(s), and g) appropriateness of statistical analyses. For the case-control studies identified, nine items were rated regarding a) comparison group representativeness (of source population), b) appropriateness of recruitment/matching of cases and controls, c) appropriateness of criteria to identify cases and controls, d) reliability and validity of the exposure(s), e) measurement of exposure(s) for cases and controls, f) whether confounding factors were identified and measured, g) whether confounding factors were accounted for in study design/analysis, h) reliability and validity of the outcome(s), and i) appropriateness of statistical analyses (36). The items were rated as follows: 0) did not satisfy the criteria (i.e., no) and 1) satisfied the criteria (i.e., yes). We summed the ratings to derive a critical appraisal score for each study (0–7 for cross-sectional studies; 0–9 for case-control studies.) This method was similarly applied in a separate published review on the prevalence of PDs in the community (2). The results of the critical appraisal are presented in Table 2.

2.4.2 Data extraction

A data extraction form was developed in consultation with a statistician (MM) using Microsoft Excel. One reviewer (SEQ) extracted the data, and another (ALS) validated the data with discrepancies resolved in one meeting. The primary outcome(s) were the presence of each MSD (categorical: yes/no). Models with the highest number of confounding adjustments were extracted. Where analyses addressed the reverse association, the outcome was presence of PD or probable PD (any, Clusters, and/or specific PDs). The odds ratio (OR) and 95% confidence interval (95% CI) were the principal summary measures. For regression analyses, b values were used as the summary measure.

2.4.3 Reporting of results

The MOOSE and PRISMA guidelines were considered for the reporting of results (40). The characteristics and results from individual studies, including critical appraisal scores, are presented in Tables 2, 3, respectively. We determined levels of evidence for associations based on an adapted method previously published by Lievense et al. in the rheumatological setting (41) and in other published reviews (42, 43). This is presented in Box 1 (below). There were too few studies with appropriately comparable study populations and groupings of PD to undertake meta-analyses.

3 Results

The results of the study identification and selection process are presented in Figure 1. Via the EBSCOhost platform, the searches from APA PsycINFO yielded 143 citations (additional n = 1 from the updated search), 94 from CINAHL Complete (additional n = 5 from updated search), 948 from Embase (additional n = 114 from updated search), and 236 from Medline Complete (additional n = 16 from updated search). After duplicates (n = 297 total) were removed, the total search yield included 1,260 citations. Of the 1,260 citations screened, 23 underwent full-text review, and 12 were excluded with reasons. No further citations were yielded from searching the other evidence sources. Thus, 11 peer-reviewed published articles were included in this review.

3.1 Characteristics

The characteristics of the included studies and summary of results are presented in Tables 2, 3. The reports of the identified studies were published between 2008 and 2020. Of the 11 studies included, nine were cross-sectional and two were case control. Seven out of the 11 studies were conducted in the United States (US) (28–32, 38, 39), with two studies each from Norway (34, 37) and Australia (25, 33). Epidemiological data sources included Waves I/II/III of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (29–31, 38, 39), the National Comorbidity Survey—Part II (28), and The St. Louis Personality and Aging Network (SPAN) study (32) each from the US; the Oslo Health Study (HUBRO) from Norway (34, 37), and the Geelong Osteoporosis Study (GOS) located in Australia (25, 33). Participant samples ranged from n = 696 in the GOS study from Australia (25) to n = 43,093 in two studies utilizing data from the NESARC (30, 31); two studies utilized samples comprising only women (25, 33).

Eight studies used semi-structured interviews to identify PDs including the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV)/AUDADIS-5 (29–31, 38, 39) performed by trained lay interviewers, the Structured Interview for DSM-IV Personality (SIDP-IV) (32) and the Structured Clinical Interview for DSM-IV (SCID-II) by trained interviewers (25, 33). Two studies identified probable PDs using The Iowa Personality Disorder Screen (IPDS) (34, 37) with another using the borderline PD scale from the International Personality Disorder Examination (IPDE) Screening Questionnaire (28). Majority (10/11) of studies utilized self-report of MSDs including arthritis (28, 29, 31–33, 38), fibromyalgia/muscular pain (37, 39), and spinal pain (28). One study determined osteoporosis (yes/no) by a BMD T-score of <–2.5 at the spine and/or hip using dual-energy X-ray absorptiometry (Prodigy; GE Lunar, Madison, WI, USA) (25). There were no studies identified that classified PD using measures based on the ICD-11 classification system.

The median critical appraisals score was 6, and thus, the reporting quality of most studies were considered high. In terms of the cross-sectional studies, the most common reason for not achieving a total sum score of 7 concerned the quality of describing the study population and setting, and/or the use of a reliable and valid measure of the study exposure (i.e., use of an adapted measure to assess PD). Regarding the case-control studies (whereby a total possible score is 9), a lack of information or unclear descriptions of the methodology (i.e., appropriate matching of cases and controls, validity and reliability of the exposure measure, and details concerning the appropriateness of the statistical analyses) resulted in a lower critical appraisal score.

TABLE 2 Characteristics of included studies.

Citation and country	Study and population characteristics			PD assessment		MSD assessment		Critical appraisal score
	Study design (data collection/ follow-up period)	Study population; sample size (*n*)	Mean age (SD)/ median (IQR)/age range Sex: % female	PD	Assessment • Classification • Tool • Administration	MSD	Assessment • Tool • Administration	
El-Gabalawy et al. (29) USA	Cross-sectional (NESARC Wave 2; 2004-2005)	Wave 2 NESARC participants N: 34,653	Aged 18+ Sex: 52.1%	• Borderline PD	• DSM-IV • AUDADIS-IV • Lay interviewer	Arthritis	• AUDADIS-IV • Self-reported	7/8
Goldstein et al. (30) USA	Cross-sectional (NESARC Wave 1; 2001–2002)	Wave 1 NESARC participants N: 43,093	48 (13.3) Sex: nr	• Antisocial PD	• DSM-IV • AUDADIS-IV • Lay interviewer	Arthritis	• AUDADIS-IV • Self-reported	6/8
McWilliams et al. (31) USA	Cross-sectional (NESARC Wave 1; 2001–2002)	Wave 1 NESARC participants N: 43,093	Aged 18+ Sex: nr	• Paranoid, schizoid, histrionic, antisocial, avoidant, dependent, obsessive–compulsive PDs	• DSM-IV • AUDADIS-IV • Lay interviewer	Arthritis	• AUDADIS-IV • Self-reported	7/8
McWilliams & Higgins (28), USA	Cross-sectional (NCS Part II; 2001–2003)	Community-based respondents enrolled in Part II of the NCS-R N: 5,692	Aged 18+ Sex: nr	• Borderline PD criteria mean scores	• ICD-10 • IPDE screener using borderline PD items • Self-report	• Arthritis • Chronic spinal pain	• Questionnaire • Self-reported	6/8
Olssøn & Dahl (37), Norway	Case-control (HUBRO; May 2000–September 2001)	Community-based respondents to the HUBRO study health Survey N: 2,214 Cases: 369 Controls: 1,845	Aged 30+ Sex: 48%	• PD-positive screen*	• DSM-IV • 5 items from the IPDS • Method nr	• Fibromyalgia • Muscular pain	• Questionnaire • Self-reported	9/10
Olssøn & Dahl (34), Norway	Case-control (HUBRO; May 2000–September 2001)	Community-based respondents to the HUBRO study health Survey N: 280 (cases) N: 1,400 (controls)	Aged 30+ Sex: 65%	• Avoidant PD-positive screen†	• DSM-IV • Avoidant PD items of IPDS • Method nr	Muscular pain (affecting work ability)	• Questionnaire • Self-reported	4/10
Powers & Oltmanns (32), USA	Cross-sectional (SPAN; dates nr)	Community-based residents aged 55–64 years enrolled in the SPAN N: 1,051	59.4 (2.7) Sex: 53%	• Borderline PD	• DSM-IV • SIDP-IV • Trained interviewer (clinician reported);	Arthritis	• Health section of the DIS • Self-reported	6/8

(Continued)

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TABLE 2 Continued

Citation and country	Study and population characteristics			PD assessment		MSD assessment		Critical appraisal score
	Study design (data collection/ follow-up period)	Study population; sample size (*n*)	Mean age (SD)/ median (IQR)/age range Sex: % female	PD	Assessment • Classification • Tool • Administration	MSD	Assessment • Tool • Administration	
					informant-reported, self-reported			
Quirk et al. (38) USA	Cross-sectional (NESARC pooled; Wave 1 2001–2002 and Wave 2 2004–2005)	Wave I and 2 NESARC participants N: 34,653	Aged 20+ Sex: 52.1%	• Any PD • Clusters A, B, and C PDs • Paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, obsessive–compulsive PDs	• DSM-IV • AUDADIS-IV • Lay interviewer	Arthritis	• AUDADIS-IV • Self-reported	7/8
Quirk et al. (33) Australia	Cross-sectional (GOS; 2011–2014)	Community-based women enrolled in the GOS in southeastern Australia N: 765	56.8 (42.7–68.9) Sex: 100%	• Any PD • Cluster A, B & C PDs	• DSM-IV • SCID-II • Trained interviewer	Arthritis (grouped): osteoarthritis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, or treated gout (medications used for gout or hyperuricemia)	• Questionnaire • Self-reported and/or medication use history	6/8
Sleurs et al. (39) USA	Cross-sectional (NESARC Wave 3 (2012-2013)	Wave III NESARC participants N: 36,309	18+ Sex: 51.16% (no fibromyalgia); Sex: 87.48% (fibromyalgia present)	• Schizotypal, borderline, and antisocial PDs	• DSM-5 • AUDADIS-5 interviewer	Fibromyalgia	• AUDADIS-5 • Self-reported	6/8

(Continued)

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TABLE 2 Continued

Citation and country	Study and population characteristics			PD assessment		MSD assessment		Critical appraisal score
	Study design (data collection/ follow-up period)	Study population; sample size (*n*)	Mean age (SD)/ median (IQR)/age range Sex: % female	PD	Assessment • Classification • Tool • Administration	MSD	Assessment • Tool • Administration	
Williams et al. (25) Australia	Cross-sectional (GOS; 2011–2014)	Community-based women enrolled in the GOS in southeastern Australia N: 696	56.8 (42.7–68.9) Sex: 100%	• Any PD • Clusters A, B, and C PDs	• DSM-IV • SCID-II • Trained interviewer	• Osteoporosis • BMD	• Dual-energy X-ray absorptiometry • Areal BMD (g/cm^2) measured at the posterior–anterior spine, femoral neck (hip), and total body including head • Osteoporosis (yes/no) defined as BMD T-score of <-2.5 at the spine and/or hip	6/8

AUDADIS, Alcohol Use Disorder and Associated Disabilities Interview Schedule; BMD, bone mineral density; Critical appraisal score, undertaken using the Joanna Briggs Institute checklists for systematic reviews of etiology and risk; DIS, Diagnostic Interview Schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ICD, International Classification of Diseases; IPDE, International Personality Disorder Examination; IPDS, Iowa Personality Disorder Screen; SCID-II, Structured Clinical Interview for DSM Axis II Disorders; SIDP-IV, Structured Interview for DSM-IV Personality; nr, not reported.*Cut-off ≥6. †Endorsement on two avoidant PD items of the Iowa Personality Disorder Screen plus the Social Phobia Inventory (short version) for generalized social anxiety disorder (sum score ≥6).

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TABLE 3 Summary of associations for included studies.

Citation and country	Study and population characteristics			Analytic approach	Summary of main findings
	Study design (data collection/ follow-up period)	Study population; sample size (*n*)	Mean age (SD)/ median (IQR)/age range Sex: % female		
Personality disorders and arthritis					
El-Gabalawy et al. (29) USA	Cross-sectional (NESARC Wave 2; 2004-2005)	Wave 2 NESARC participants N: 34,653	18+ Sex: 52.1%	Logistic regression, odds ratios (ORs) and 95% confidence intervals (CIs) • Adjusted for sex, ethnicity, education, marital status, income, age, lifetime mood disorder, lifetime anxiety disorder, lifetime substance disorder, and lifetime personality disorders (PDs) except borderline PD (i.e., antisocial, avoidant, dependent, obsessive–compulsive, paranoid, schizoid, histrionic, schizotypal, and narcissistic)	• Compared to those without, borderline PD was associated with increased odds of past-year arthritis (OR 1.56, 95% CI = 1.31, 1.85)
Goldstein et al. (30) USA	Cross-sectional (NESARC Wave 1; 2001–2002)	Wave 1 NESARC participants N: 43,093	48 (13.3) Sex: nr	Logistic regression, ORs, and 95% CI • Adjusted for age, sex, race/ethnicity, marital status, education, past-year personal income, health insurance coverage, region and urbanicity of respondent residence, body mass index, comorbid, lifetime diagnoses of nicotine dependence, any mood, anxiety, alcohol use, and drug use disorders, pathological gambling, lifetime PDs except antisocial PD (i.e., avoidant, dependent, obsessive–compulsive, paranoid, schizoid, and histrionic), average daily ounces of ethanol during period of heaviest lifetime drinking, frequency of use of most frequently used drug during period of heaviest lifetime use, and number of cigarettes smoked per day during most recent year of smoking	Compared to those with no history of antisocial behavioral syndromes: • Antisocial PD in men was associated with increased odds of past-year arthritis (OR 2.20, 95% CI = 1.69, 2.76) • Antisocial PD in women was associated with increased odds of past-year arthritis (OR 1.40, 95% CI = 1.03, 1.96) • Antisocial behavioral syndromes in men was associated with increased odds of past-year arthritis (OR 1.40, 95% CI = 1.20, 1.73) • Antisocial behavioral syndromes in women were not significantly associated with past-year arthritis (OR 1.20, 95% CI = 0.95, 1.42) • History of conduct disorder (only) in men was not significantly associated with past-year arthritis (OR 1.30, 95% CI = 0.66, 2.34) • History of conduct disorder (only) in women was not significantly associated with arthritis (OR 0.50, 95% CI = 0.26, 1.04)
McWilliams et al. (31) USA	Cross-sectional (NESARC Wave 1; 2001–2002)	Wave 1 NESARC participants N: 43,093	Aged 18+ Sex: nr	Logistic regression, ORs, and 95% CI • Adjusted for gender, marital status, income, age, and the presence of 1 or more health conditions other than arthritis, 1 or more past-year depressive disorders, 1 or more past-year anxiety disorders, and 1 or more past-year alcohol- or substance-related disorders	Compared to those without, past-year arthritis was associated with increased odds of: • Antisocial PD (OR 2.06, 95% CI = 1.72, 2.48) • Avoidant PD (OR 1.62, 95% CI = 1.27, 2.06) • Obsessive-compulsive PD (OR 1.41, 95% CI = 1.23, 1.62) • Paranoid PD (OR 1.40, 95% CI = 1.17, 1.67) • Schizoid PD (OR 1.79, 95% CI = 1.48, 2.17) • Histrionic PD (OR 1.80, 95% CI = 1.36, 2.39) Past-year arthritis was not significantly associated with dependent PD (1.49, 95% CI = 0.82, 2.70)
McWilliams & Higgins (28), USA	Cross-sectional (NCS Part II; 2001–2003)	Community-based respondents	Aged 18+ Sex: nr	Regression, *b* values • Adjusted for sex, marital status, race, age,	• Compared to those without, lifetime arthritis was associated with higher

(Continued)

TABLE 3 Continued

Citation and country	Study and population characteristics			Analytic approach	Summary of main findings
	Study design (data collection/ follow-up period)	Study population; sample size (*n*)	Mean age (SD)/ median (IQR)/age range Sex: % female		
Personality disorders and arthritis					
		enrolled in Part II of the NCS-R N: 5,692		education level, past-year mood disorders, anxiety disorders, and externalizing disorders	borderline PD symptomology (0.19, p ≤ 0.01)
Powers & Oltmanns (32), USA	Cross-sectional (SPAN; dates nr)	Community-based residents aged 55–64 years enrolled in the SPAN N: 1,051	59.4 (2.7) Sex: 53%	Logistic regression, ORs, and 95% CI • Adjusted for: sex, age, race, marital status, education, any lifetime MDD, alcohol dependence or drug dependence, and any PD except borderline PD • BMI as "mediator"	• Compared to those without, interviewer-reported borderline PD features was associated with increased odds of arthritis (OR 2.64, 95% CI = 1.06–6.57) • Compared to those without, informant-reported borderline PD features was associated with increased odds of arthritis (OR 1.76, 95% CI = 1.05–2.95) • Compared to those without, self-reported borderline PD features were not significantly associated with increased odds of arthritis (1.41, 95% CI = 0.74, 2.68) • Full mediating effect of body mass index (BMI) on the association between borderline PD features and all three sources of PD assessment
Quirk et al. (38) USA	Cross-sectional (NESARC pooled; Wave 1 2001–2002 and Wave 2 2004–2005)	Wave I and 2 NESARC participants N: 34,653	Aged 20+ Sex: 52.1%	Logistic regression, ORs, and 95% CI • Adjusted for sex, race/ethnicity, marital status, education, income, age, past-year mood, anxiety and substance use disorders	Compared to those without, PD Clusters were associated with increased odds of past-year arthritis among people of all ages: • Cluster B PDs (OR 1.38, 95% CI = 1.18, 1.60) • Cluster C PDs (OR 1.35, 95% CI = 1.08, 1.69) Compared to those without, specific PDs were associated with increased odds of past-year arthritis among people of all ages: • Paranoid PD (OR 1.28, 95% CI = 1.02, 1.61) • Antisocial PD (OR 1.61 95% CI = 1.24, 2.07) • Borderline PD (OR 1.59, 95% CI = 1.27, 1.98) • Avoidant PD (OR 1.47, 95% CI = 1.11, 1.96) In subgroup analyses among those under <55 years, PDs were associated with increased odds of past-year arthritis for those with: • Any PD compared to without (OR 1.36, 95% CI = 1.13, 1.64) • Cluster A PDs compared to without (OR 1.39, 95% CI = 1.11, 1.75) • Schizoid PD compared to without (OR 1.62, 95% CI = 1.16, 2.26) • Schizotypal PD compared to without (OR 1.58, 95% CI = 1.18, 2.13) • Obsessive–compulsive PD compared to

(Continued)

TABLE 3 Continued

Citation and country	Study and population characteristics			Analytic approach	Summary of main findings
	Study design (data collection/ follow-up period)	Study population; sample size (*n*)	Mean age (SD)/ median (IQR)/age range Sex: % female		
Personality disorders and arthritis					
					without (OR 1.41, 95% CI = 1.12, 1.79) In subgroup analyses among those ≥55 years, PDs were associated with increased odds of past-year arthritis for those with: • Any PD (OR 1.22, 95% CI = 1.03, 1.43) • Cluster C PDs (OR 1.28, 95% CI = 1.02, 1.61) PDs were not significantly associated with arthritis for all ages with: • Dependent PD (OR 1.39, 95% CI = 0.68, 2.85) • Histrionic PD (OR 1.17, 95% CI = 0.81, 1.7) • Narcissistic PD (OR 1.19, 95% CI = 0.98, 1.44) PD Clusters and specific PDs were not significantly associated with arthritis for those over 55 years with: • Any Cluster A PD (OR 1.15, 95% CI = 0.89, 1.48) • Schizoid PD (OR 1.18, 95% CI = 0.83, 1.68) • Schizotypal PD (OR 1.16, 95% CI = 0.78, 1.72) • Obsessive-compulsive PD (OR 1.11, 95% CI = 0.85, 1.45) Any C Cluster PD was not significantly associated with arthritis among those under 55 years (OR 1.20, 95% CI = 0.93, 1.54).
Quirk et al. (33) Australia	Cross-sectional (GOS; 2011–2014)	Community-based women enrolled in the GOS in southeastern Australia N: 765	56.8 (42.7–68.9) Sex: 100%	Logistic regression, ORs, and 95% CI • Adjusted for age, BMI, SES, physical activity, smoking status, and psychiatric disorder (ever), and interactions of IRSAD* smoking status, physical activity* psychiatric disorder (ever)	• Cluster B PDs were associated with increased odds of lifetime arthritis (OR 4.25, 95% CI = 1.34, 13.44) Grouped PDs were not significantly associated with arthritis: • Any PD (OR 1.07, 95% CI = 0.65, 1.75) • Cluster A PDs (OR 1.36, 95% CI = 0.53, 3.45) • Cluster C PDs (OR 1.04, 95% CI = 0.62, 1.75)
Personality disorders and spinal pain					
McWilliams & Higgins (28), USA	Cross-sectional (NCS Part II; 2001–2003)	Community-based respondents enrolled in Part II of the NCS-R N: 5,692	Aged 18+ Sex: nr	Regression, b values • Adjusted for sex, marital status, race, age, education level, past-year mood disorders, anxiety disorders, and externalizing disorders	• Compared to those without, past-year spinal pain was associated with higher borderline PD symptomology (0.38, $p \leq 0.001$) • Compared to those without, remitted spinal pain was associated with higher borderline PD symptomology (0.31, $p \leq 0.001$) • No significant differences in borderline PD symptomatology between past-year spinal pain and remitted spinal pain

(Continued)

TABLE 3 Continued

Citation and country	Study and population characteristics			Analytic approach	Summary of main findings
	Study design (data collection/ follow-up period)	Study population; sample size (*n*)	Mean age (SD)/ median (IQR)/age range Sex: % female		
Personality disorders and fibromyalgia/muscular pain					
Olssøn & Dahl (37), Norway	Case-control (HUBRO; May 2000–September 2001)	Community-based respondents to the HUBRO study health Survey N: 2,214 Cases: 369 Controls: 1,845	Aged 30+ Sex: 48%	χ^2 -tests; 2 × 2 contingency tables were calculated as effect sizes with Cohen's *d* • Matched on age and gender • Adjusted for education and employment status	*Personality problems predicting fibromyalgia/muscular pain:* • 33% of people with personality problems had past-year muscular pain versus 22% of controls ($p < 0.001$) • 4% of people with personality problems had lifetime fibromyalgia versus 2% of controls ($p < 0.001$)
				Logistic regression, ORs and 95% CI • Matched on age and gender • Adjusted for education and employment status	*Fibromyalgia/muscular pain predicting personality problems:* • Past-year *muscular* pain was associated with increased odds of personality problems (OR 1.4, 95% CI = 1.1, 2.9) • Lifetime fibromyalgia was not significantly associated with personality problems
Olssøn & Dahl (34), Norway	Case-control (HUBRO; May 2000–September 2001)	Community-based respondents to the HUBRO study health Survey N: 280 (cases) N: 1,400 (controls)	Aged 30+ Sex: 65%	χ^2 tests; 2 × 2 contingency tables were calculated as effect sizes with Cohen's *d* • Matched on age and gender Adjusted for education and employment status	*Personality problems predicting muscular pain:* • 37% of people with probable avoidant PD had muscular pain versus 20% of controls ($p < 0.001$; ES 3.8)
				Logistic regression, ORs and 95% CI • Matched on age and gender Adjusted for demographic impairment, somatic impairment, frequent use of analgesics, ≥4 past-year visits to GP, mental impairment, insomnia affecting work ability, frequent use of psychotropics, ≥4 past-year visits to psychiatrist/psychologist	*Muscular pain predicting personality problems:* • Muscular pain was not significantly associated with probable avoidant PD
Sleurs et al. (39) USA	Cross-sectional (NESARC Wave 3 2012–2013)	N: 36,309	18+ Sex: 51.16% (no fibromyalgia); 87.48% (fibromyalgia present)	Logistic regression, ORs, and 95% CI • Adjusted for sex, race, nativity, age, education, income, marital status, urbanicity and region	Compared to those without, fibromyalgia was associated with increased odds of PDs: • Any PD (OR 2.91, 95% CI = 2.32, 3.65) • Schizotypal PD (OR 3.57, 95% CI = 2.72, 4.67) • Borderline PD (OR 2.86, 95% CI = 2.32, 3.52) • Antisocial PD (OR 3.06, 95% CI = 1.93, 4.85)
Personality disorders and bone health					
Williams et al. (25) Australia	Cross-sectional (GOS; 2011–2014)	Community-based women enrolled in the GOS in southeastern Australia N: 696	56.8 (42.7–68.9) Sex: 100%	χ^2 tests	• 6.1% of people with any PD had osteoporosis versus 8.7% without ($p = 0.335$)
				Regression, b values • Adjusted for age and sex (female only)	• Cluster A PDs were associated with lower BMD at the hip (−0.057, $p = 0.027$) • Trend for association between Cluster A PDs and lower total body BMD (−0.037, $p = 0.056$) No significant association between:

(Continued)

TABLE 3 Continued

Citation and country	Study and population characteristics			Analytic approach	Summary of main findings
	Study design (data collection/ follow-up period)	Study population; sample size (*n*)	Mean age (SD)/ median (IQR)/age range Sex: % female		
Personality disorders and bone health					
					• Clusters B and total body BMD ($p > 0.05$) • Cluster B PDs and hip BMD ($p > 0.05$) • Cluster C PDs and total body BMD ($p > 0.05$) • Cluster C PDs and hip BMD ($p > 0.05$) • C PDs not significantly associated with total body or hip BMD ($p > 0.05$) • Cluster A PDs and spine BMD ($p > 0.05$) • Cluster B PDs and spine BMD ($p > 0.05$) • Cluster C PDs and spine BMD ($p > 0.05$)

3.2 Descriptive synthesis

The following sections present the findings from the descriptive synthesis and evidence gap analysis in text and tables. Specifically, Table 3 presents the results from all individuals studies/analyses with the evidence gap analysis shown in Supplementary Tables 7-14.

3.2.1 Personality disorders and arthritis

In the literature, associations between PDs and arthritis were examined in seven cross-sectional studies (28–33, 38). Of these, four utilized data from the NESARC (29–31, 38); the remaining three presented analyses from Part II of the NCS (28), the SPAN (32), and the GOS (33).

In Wave I of the NESARC, Goldstein et al. examined antisocial PD, antisocial PD features, and history of conduct disorder and the association with past-year arthritis, compared to people with no history of these PDs/features, and according to sex (30). Men and women with antisocial PD had increased odds of arthritis compared to those without a history (30). Separately, in Wave II of the NESARC, El-Gabalawy et al. reported an association between borderline PD and increased odds of past-year arthritis (29). In a further study using data from both waves I and II, Quirk et al., examined all PDs and PD Clusters in relation to past-year arthritis considering the role of age in these associations (38). Across all specific PDs and PD groupings, individuals with grouped Cluster B PDs had the highest odds of arthritis compared to those without these PDs. In addition, for those in the younger age group (*under 55 years*), any PD, schizoid, schizotypal, and obsessive–compulsive

BOX 1 Criteria for levels of evidence derived from Lievense et al. (41).

Strong evidence
Generally consistent findings in:
Multiple high-quality cohort studies
Moderate evidence
Generally consistent findings in:
1 high-quality cohort study and ≥2 high quality case-control studies
≥3 high-quality case-control studies
Limited evidence
Generally consistent findings in:
1 high-quality cohort study
<2 high-quality cross-sectional, case-control studies
Inconsistent evidence
If ≤75% studies reported consistent findings
No evidence
No evidence was identified

PDs were each associated with increased odds of arthritis compared to younger individuals without these PDs (38). Of the analyses deriving from the NESARC, all accounted for pertinent sociodemographics and at least mood, anxiety, and substance use disorders (29, 30, 38). In addition, the separate analyses presented in the reports by El-Gabalawy et al. and Goldstein et al. also adjusted for PDs other than the exposure (29, 30). Finally, in the GOS, Quirk et al. reported increased odds of a history of arthritis among women with Cluster B PDs compared to women without these PDs after adjustment for sociodemographic information, lifestyle behaviors, lifetime history of any mood, anxiety, substance use, or eating disorders (and the interactions of these) (33).

In terms of the reverse association, in Wave I of the NESARC, McWilliams et al. examined associations between past-year arthritis and odds of several specific PDs (avoidant, dependent, obsessive–compulsive, paranoid, schizoid, histrionic, and antisocial PDs) (31). Compared to people without, people with arthritis had increased odds of paranoid, schizoid, histrionic, antisocial, avoidant, and obsessive–compulsive PDs—analyses accounted for pertinent sociodemographic factors (31). In addition, in Part-II of the NCS, McWilliams reported that, compared to people without, those with lifetime arthritis had higher BPD symptomatology scores after accounting for sociodemographics, past-year mood disorders, anxiety disorders, and externalizing disorders (28). Separately, in the SPAN, Powers et al., reported increased odds of arthritis among people with interviewer- and informant-rated borderline PD features, but not self-reported borderline PD features, among adults aged 55 to 64 years. However, the association between all three types of assessment modes (of borderline PD features) and arthritis was fully mediated by BMI (32).

Also, non-significant findings for associations between PDs and arthritis were also observed. Analyses deriving from Wave I of the NESARC revealed that dependent PD was not significantly associated with greater odds of arthritis (31) with further analyses from pooled Waves I and II of the NESARC showing non-significant results for associations between histrionic and narcissistic PDs and arthritis (38). In subgroup analyses deriving from Wave I of the NESARC, antisocial behavioral syndromes were not significantly associated with arthritis among women, nor was a history of conduct disorder for both women and men (30). Also in the NESARC (Waves I and II pooled), those aged over 55 years, having any grouped Cluster A PDs, or the specific PDs of schizoid, schizotypal, or obsessive–compulsive were not significantly associated with greater odds of arthritis; being in the younger age group (under 55 years) and having any C Cluster PD was not significantly associated with arthritis (38). Finally, in the GOS (women only), any PD grouped, Cluster A PDs, and Cluster C PDs were not significantly associated with arthritis (25).

3.2.2 Personality disorders and spinal pain

In analyses utilizing data from Part-II of the NCS, McWilliams et al. examined associations between a history of spinal pain, as the exposure, and borderline PD symptomatology (28). Compared to people without, people with past-year spinal pain had higher borderline PD symptomatology following adjustment for pertinent sociodemographics, past-year mood disorders, anxiety disorders, and externalizing disorders (28). This association was similarly observed among people with remitted spinal pain compared to people without remitted spinal pain (28). However, in further analyses, people with past-year spinal pain did not report significantly different borderline PD symptomatology compared to people who had remitted (28).

3.2.3 Personality disorders and fibromyalgia/muscular pain

Two separate reports of studies utilizing data from the HUBRO (34, 37) and one from Wave III of the NESARC examined associations between PDs and fibromyalgia/muscular pain (39). Olssøn and Dahl examined both directions of associations between personality problems and fibromyalgia and muscular pain, respectively. First, a higher proportion of people with probable PD had past-year muscular pain and lifetime fibromyalgia compared to controls (age–gender matched), respectively (37). Moreover, muscular pain, but not fibromyalgia, was associated with increased odds of probable PD after additional adjustments for education and employment status (37). Next, Olssøn and Dahl examined avoidant personality problems specifically and found that a higher proportion of people with probable avoidant PD had muscular pain compared to controls (age and gender matched). In reverse, muscular pain was not significantly associated with probable avoidant PD (adjusted further for education and employment status) (34). Elsewhere, in Wave 3 of the NESARC, Sleurs et al. reported that compared to those without, people with fibromyalgia have increased odds of "any" PD as well as each schizotypal, borderline, and antisocial PDs (39); analyses accounted for sociodemographic information.

3.2.4 Personality disorders and bone health

In one study using the GOS data, associations between any PD and osteoporosis among women were not statistically significant (25). However, in analyses examining associations between PD Clusters and BMD, women with Cluster A PDs, but not Cluster B or C PDs, had lower hip BMD (i.e., poorer bone health) compared to women without these PDs (25). Women with Cluster A, B, or C PDs did not have significantly reduced total body BMD or spine BMD.

3.2.5 Levels of evidence

Overall, our evidence gap analysis (see Supplementary Tables 7-14) revealed that there was either conflicting or limited evidence for associations between PDs and arthritis, spinal pain, fibromyalgia, and BMD. In addition, there was currently no evidence (i.e., these studies have not yet been conducted) for associations between a range of specific PDs in regard to these MSDs especially concerning BMD.

4 Discussion

This review had two aims: 1) to evaluate the evidence for associations between PDs and MSDs including arthritis, back/

spinal pain, fibromyalgia/muscular pain, and aspects of bone health; to explore potential sources of heterogeneity in the results including study and population characteristics and the assessment of PD and 2) ascertain the quality and levels of evidence for these associations.

Overall, our descriptive synthesis revealed that there is currently limited and conflicting levels of evidence for associations between PDs and each of the MSDs. While 10 of the 11 studies reviewed were considered of "high quality," we identified several methodological factors that might contribute to the limited evidence base for these associations. First, the evidence identified was derived primarily from cross-sectional studies, and thus, evidence from case-control and cohort studies are needed to ascertain moderate or strong evidence for these associations if evident. In addition, we identified heterogenous groupings of PD as the exposure of interest—particularly for "any" PD—and the extent to which the full range of specific PDs were examined also varied. Considering the relatively small number of studies identified, the numerous PD groupings, and number of participants, the comparisons of alike studies were limited.

In terms of specific MSD outcomes, we identified conflicting evidence for associations between Cluster A PDs and arthritis. To illustrate, in the NESARC, paranoid PD among all ages was associated with increased odds of arthritis with schizoid and schizotypal PDs each being associated with arthritis among those *under* 55 years (not among those *over 55 years*.) When examined as a "Cluster" in relation to arthritis, the association with these PDs were attenuated (although remained significant). Separately, in the GOS, these PDs were examined as a Cluster among women with an average age of approximately 57 years; in this study, Cluster A PDs were not significantly associated with increased odds of arthritis. Similarly, in pooled Waves 1 and 2 of the NESARC, Quirk et al. reported no significant associations between Cluster C PDs (grouped) and increased odds of arthritis among individuals of all ages or those *aged under 55 years*. However, in separate analyses from the same report, people *over the age of 55 years* with Cluster C PDs were found to have significantly increased odds of arthritis; in the GOS, Cluster C PDs were not significantly associated with arthritis. Thus, the conflicting evidence for associations between Cluster A and C PDs and arthritis appears to be influenced by how these PDs are grouped and the nature of the study populations including age and sex factors.

There is a need to improve the evidence base on population-based associations between PD and MSDs. This expansion would contribute to a more comprehensive understanding of the interplay between these conditions and encourage investigation into potential shared etiological pathways, common risk factors, and consideration of therapeutic implications.

4.1 Mechanisms

In a recent scoping review, we highlighted that the mechanisms underlying potential associations between PDs and MSDs could be understood from the perspective of the biopsychosocial model (9). To date, biopsychosocial models have been employed to understand how the interaction of psychological, social, and biological factors operate in the etiology and maintenance of pain specifically (44–46). Thus, the biopsychosocial models provides a transdiagnostic lens to conceptualize how mechanisms might operate in concert across PD and MSDs.

To illustrate, exposure to early stress, trauma, and other forms of adversities in childhood and adolescence—critical periods for personality development and the acquisition of adaptive self-regulatory processes—are understood to alter stress mechanisms. These mechanisms are understood to have a role in vulnerability to PD via alterations in the hypothalamic–pituitary–adrenal (HPA) axis and morphological changes in brain areas involved in the stress response (47). Childhood adversity and types of trauma have been separately linked to PD (48–50) and to MSDs including arthritis (51) and chronic back pain (52). Alterations in the stress response can also lead to increased vulnerability of a range of physical disorders (45, 46). Moreover, a recent study reported associations between childhood adversity/trauma and borderline PD symptomatology among patients with chronic pain including pain related to MSDs (53).

Of interest, we observed several analyses showing associations between Cluster B PDs and arthritis specifically. There is evidence that stress is associated with emotional dysregulation, which often presents as hypersensitivity and reactivity and difficulty coping among people with these PDs (54). Stress is also associated with immune dysregulation and inflammation in the body (55). Acute stress arising as a symptom or consequence of PD may "trigger" or exacerbate MSDs that have inflammatory origins such as conditions of the joints through immune dysregulation and inflammatory responses. Separately, Turk and Monarch explained that intense emotions, such as anger, may interfere with help seeking and willingness to engage with treatment recommendations among people with psychiatric disorders and thus minimize the opportunity for effective rehabilitation (44). Others have highlighted the complexity of the experience of pain among people with borderline PD. For example, it is suggested that, as a consequence of self-regulation difficulties, the experience of endogenous pain may be felt as more intense and less tolerable, compared to self-inflicted pain; pain is also understood to serve an affect-regulating function for people with borderline PD, which can, in turn, lead to pain attenuation and tolerance (56, 57). To substantiate, previous experimental research has uncovered that modulating pain can regulate affect in patients with PD (58), which is reduced following treatment with DBT (59).

In this review, there was mixed evidence for associations between "Cluster C" PDs and MSDs. "Cluster C" PDs are traditionally conceptualized to manifest the behaviors of extreme avoidance of social interaction, which are motivated by feelings and fears of perceived inadequacy and rejection (5). People with features of these disorders may experience anxiety associated with pain leading to types of avoidance coping or safety behaviors. These may manifest externally through the avoidance of social interactions/situations or internally to avoid experiencing distressing thoughts, feelings, or sensations concerning pain (60). In addition, a recent review has summarized that features of these disorders tend to be more stable over time (61), and thus, avoidance styles of coping may became more entrenched and operate in the maintenance of comorbidities.

Given the plausible biopsychosocial factors linking PDs and MSDs, we have previously suggested that a multidisciplinary approach to identifying and treating comorbidities in clinicals settings may be needed (9). However, there is a lack of research into, and targeted measures and interventions for, each psychiatric and musculoskeletal medicine settings to identify and concurrently manage PDs and MSDs.

4.2 Strengths and limitations of this review

In terms of strengths, we developed and implemented a comprehensive search strategy including a thorough search for evidence from gray literature sources, which enabled a complete synthesis of the existing literature. We reported on the current levels of evidence for associations between PDs and revealed where evidence gaps exist, which will prompt and guide further research on this topic. We also provided a conceptual description of the possible mechanisms that might underly associations between PDs and MSDs—ideas to be further investigated and empirically tested in clinical settings.

In terms of the limitations, most notably was the paucity of data for each outcome. The evidence gap analysis revealed "no evidence" for a number of specific PDs and MSDs particularly in relation to BMD. Thus, the authors suggest that a call to action is needed to address the evidence gap and understand if people with PDs may be more susceptible to MSDs for which clinical monitoring and management may be required. In addition, the outcomes were chiefly assessed using self-reported measures (except for one study, which also utilized clinical measures of BMD). Recent evidence from a population-based study comparing self-report to register data in Finland (women only) reported that self-reported measures may be insufficient for accurately identifying MSDs (62). Thus, MSDs may be underrepresented in the reviewed studies.

A significant proportion of the studies utilized data from Waves of the NESARC (5 of the 11 studies), and there were few opportunities to synthesize the evidence examining associations between PDs and MSDs from varied studies and settings. In addition, this review included eligible analyses, which involved multiple comparisons of the same data source, which may be considered a limitation. Similarly, in terms of the assessment of PD, we note that multiple comparisons, that is, the number of possible PD groupings (i.e., 3 PD Clusters, 10 specific PDs, and pooled PDs) in relation to MSDs within and across studies, has limited what conclusions can be drawn about associations between PDs and MSDs. It is suggested that derivation of an "any PD" may assist in overcoming this methodological issue in future research. However, it is acknowledged that traditionally, these specific PDs vary in clinical presentation and severity, and thus, meaningful, and sensitive data may be lost if any one or more PDs are grouped as a unitary variable.

In terms of study designs, the available evidence was derived chiefly from cross-sectional studies, and no longitudinal studies were identified. Therefore, it is not presently possible to determine the direction of causality among associations between PDs and MSDs. There was also insufficient evidence sources to complete planned meta-analyses on associations between PDs and MSDs.

Therefore, considerably expanding the evidence base on the longitudinal course of PD and MSDs would facilitate a thorough exploration of the underlying mechanisms and understanding of potential clinical implications. For example, a burgeoning evidence base might lead to a greater focus in both psychiatric and musculoskeletal medicine settings to identify and concurrently manage PDs and MSDs. In addition, an evolving evidence base would allow for a deeper and more nuanced interpretation of synthesized evidence in future reviews on this important topic. Future research should also consider the application of the ICD-11 classification of PD in relation to these comorbidities.

5 Conclusions

To conclude, the quality of most studies included in this review that examined associations between PD and MSDs in general population adults was high. However, the results demonstrated limited and conflicting evidence for these associations—in part due to a lack of comparable cross-sectional studies and no detected longitudinal evidence, which is now needed.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

SQ: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. HK: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. RH: Writing – original draft, Writing – review & editing. MM: Methodology, Writing – original draft, Writing – review & editing. AS: Methodology, Writing – original draft, Writing – review & editing. JH: Writing – original draft, Writing – review & editing. LW: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1288874/full#supplementary-material

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Borderline personality disorder and risk of atrial fibrillation: insights from a bidirectional Mendelian randomization study

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Background: Atrial fibrillation (AF) is one of the most common form of arrhythmia. Previous studies have shown a link between AF and mental illness. However, the causal relationship between mental illness and AF remains unclear. The purpose of this study was to investigate the bidirectional causal relationship between borderline personality disorder (BPD) and AF.

Method: We used the bidirectional Two-sample Mendelian randomization (TSMR) method to evaluate the causal relationship between BPD and AF. Instrumental variables associated with BPD were derived from a genome-wide association study involving 214,816 Europeans (2,637 cases and 212,179 controls). We then obtained atrial fibrillation data from the GWAS meta-analysis (60,620 cases and 970,216 controls). The TSMR analyses were performed in five methods, namely fixed-effect inverse-variance weighted (IVW) method、random-effect IVW method, MR Egger regression method, Weighted median method and Simple mode method. Several sensitivity analyses are used to test the robustness of positive results.

Results: The fixed-effect inverse-variance weighted model [Odds ratio (OR), 1.033, 95% confidence interval (CI), 1.011-1.056, P = 0.0031], random-effect inverse-variance weighted model (OR, 1.033; 95%CI, 1.005-1.062; P = 0.0191) and Weighted median (OR, 1.034; 95%CI, 1.002-1.068; P = 0.0394) all showed that genetically predicted BPD was associated with an increased risk of AF. Sensitivity analysis using other MR Methods, including the MR-Egger intercept, MR-Presso method, and leave-one-out analyses, showed that the results were robust. In reverse MR analysis, there was no causal relationship of AF on BPD.

Conclusion: Our study provides a causal relationship between BPD and AF. This means that patients with BPD should be monitored for the occurrence of AF. Early screening and proper management of BPD may show anti-arrhythmic benefits.

KEYWORDS

borderline personality disorder, atrial fibrillation, casual association, bidirectional, Mendelian randomization

1 Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinic. It is characterized by rapid and disordered atrial electrical activity. AF can be divided into first diagnosed AF, paroxysmal AF, persistent AF, and permanent AF (1). AF can make people experience a variety of uncomfortable symptoms such as panic, fatigue, sweating, which seriously affect their quality of life (2). The purpose of AF treatment is to prevent thromboembolic complications, restore and maintain sinus rhythm, and control ventricular rate during AF (3). The most important thing in the treatment of AF is to actively search for the primary disease and inducing factors, and make corresponding treatment. Studies have shown that male sex, advancing age, and Caucasian ancestry are important risk factors for developing AF (4). Controllable risk factors for AF include smoking (5), alcohol use (6), high blood pressure (7), diabetes (8), obesity (9), obstructive sleep apnea (10), and a sedentary lifestyle (11), among other factors. Previous studies have shown that AF and psychiatric disorders are inextricably linked. It is important to note that patients with AF often exhibit one or more negative emotions, such as anxiety, depression, reactive instability, and high neuroticism under the influence of severe stressors (12). It has been demonstrated that depression significantly increases the cumulative incidence of atrial fibrillation (from 1.92% to 4.44% at 10 years), and 20-40% of AF patients are found to have high levels of depression (13). Similarly, Kim et al. found that depression was associated with a significantly increased risk and cumulative incidence of new-onset AF (14). A meta-analysis of cohort studies demonstrated that anxiety was independently associated with an increased risk of recurrence of AF after catheter ablation (adjusted relative risk, 2.3; 95%CI, 1.710-3.260; $P < 0.001$) (15). One study demonstrated that the level of anxiety before coronary artery bypass surgery is an important factor in the development of AF after surgery (16). Studies have shown that severe psychological distress (35%) and suicidal ideation (20%) were prevalent in the tertiary population with AF (17).

Mental illness causes serious social and economic burden, and it is difficult to accurately identify its pathogenesis and risk factors (18). Due to the complex pathogenesis of mental diseases, the reverse causality between risk factors and mental diseases is easily confused, which makes MR analysis become an important tool in the study of mental diseases. A previous review of 50 MR articles showed a causal relationship between a particular psychiatric disorder and its causative factors (19). This review is divided into four groups based on the mental disorders assessed: schizophrenia, major depressive disorder, attention deficit and hyperactivity disorder, and autism spectrum disorder or other mental disorders. BPD, though one of the screening criteria in this review, was not included in the target article. It can also be seen that the number of MR articles on BPD is relatively small. To some extent, our paper can fill the gap in the study of MR of BPD. Borderline personality disorder (BPD), also known as emotionally unstable personality disorder, is characterized by widespread instability in interpersonal relationships, emotional regulation, impulse control, and self-image management (20). Patients with BPD often suffer from depression, anxiety, impulsivity, anger and other negative emotions, and even have self-harm and suicidal tendencies (21). Emotional instability is the main characteristic of BPD. BPD is a serious mental disorder that can have a significant impact on an individual's quality of life, mental health and social interactions. We hypothesize that there may be a causal relationship between BPD and AF.

Mendelian Randomization (MR) is a data analysis technique used to evaluate causal inference in epidemiological studies. In MR analysis, genetic variants are used as Instrumental Variables (IVs) to estimate the causal relationship between the exposure factor of interest and the outcome of concern (22). We conducted a two-sample bidirectional MR study to estimate the causal relationship between BPD and AF. This paper expounds the causal relationship between BPD and AF, and provides the basis for early prevention and detection of arrhythmia in patients with BPD.

2 Method

2.1 Study design and data sources

In this study, bidirectional two-sample Mendelian randomization (TSMR) was used to evaluate the causal relationship between BPD and AF.

The summary data for BPD were derived from a recently published genome-wide association study (GWAS) that included 2,637 patients with BPD and 212,179 control patients (https://gwas.mrcieu.ac.uk/datasets/finn-b-F5_EMOPER/). We used the most recent GWAS meta-analysis of AF by Nielsen et al., which included 60,620 patients with AF and 970,216 controls of European ancestry (https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006414/). The analysis pooled six contributing studies [The Michigan Genomics Initiative (MGI), deCODE, the Nord-Trøndelag Health Study (HUNT), DiscovEHR, UK Biobank, and the AFGen Consortium] (23). Detailed information about the data sources is shown in Table 1.

2.2 Three core assumptions

In MR analysis, three core assumptions must be satisfied in order to obtain valid results (24), as shown in Figure 1. Specifically, multiple genetic variants must satisfy: (1) the correlation assumption: IVs are closely related to exposure; (2) the independence assumption: IVs are not associated with other confounding factors; (3) the exclusion assumption: IVs only affect the outcome through the exposure.

2.3 Selection and validation of SNPs

In this study, in order to obtain more screening data, we used $P < 5\times10^{-6}$ as the criterion for screening SNPs for BPD at the genome-wide level (25). In the genome range, 16 gene loci were identified that were significantly associated with BPD. Similarly, we found 111 independent genetic loci for AF that achieved genome-

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TABLE 1 Detailed information of studies and datasets used for analyses.

	Exposure (outcome): BPD	Outcome (exposure): AF
Year	2021	2018
Data source	FinnGen	Nielsen et al.
Ethnicity	European	European
Sample size	214,816	1,030,836
cases	2,637	60,620
controls	212,179	970,216
Number of SNPs	16,380,456	33,519,037
GWAS ID	finn-b-F5_EMOPER	ebi-a-GCST006414
Web source	https://gwas.mrcieu.ac.uk/datasets/finn-b-F5_EMOPER/	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006414/

BPD, borderline personality disorder; AF, atrial fibrillation.

wide significance ($P < 5\times10^{-8}$). Linkage disequilibrium (LD) refers to a nonrandom association between allele of different loci, measured using two parameters, r^2 and kb. The LD window is set to 10000kb, $r^2 > 0.001$ to ensure the independence of the selected genetic variation. F-statistic of genetic variation 10, the genetic tool is considered to be effective, that is, it is not affected by weak instrument bias (26). The calculation formula is: $F=R^2*(N-2)/(1-R^2)$. $R^2=2*(1-MAF)*MAF*\beta^2$. R^2 is the degree of variation explained by each SNP, EAF is the minor allele frequency, β is the beta coefficient associated with exposure, and N is the total sample size. Prior to MR analysis, we performed effective allelic comparisons to remove all SNPs with palindromic structures. This gives us a standard instrumental variable that conforms to MR analysis.

2.4 MR analysis and sensitivity analysis

Two-sample Mendelian randomization (TSMR) method was used in this study. TSMR analysis methods include fixed-effect inverse-variance weighted (IVW) method、random-effect IVW method, MR Egger regression method, Weighted median method and Simple mode method. IVW is the most important method. Heterogeneity among genetic variants was examined by heterogeneity statistics. By analyzing the p-value of the Q test of Cochrane, when $P > 0.05$, there was no significant heterogeneity. Through the MR-Egger intercept test, the horizontal multiplicity of the data can be detected, and the robustness of the results can be evaluated (27). An outlier test examines whether there are SNPS that differ significantly to further reduce this level of multiplicity. Finally, the leave-one-out method is used to determine whether the selected SNPs is reliable and stable. The results were described by odd ratio (OR) and 95% confidence interval (CI). The overall process of MR Analysis in this study is shown in Figure 2. In our study, R software package "TwosampleMR" was used for MR Analysis.

3 Result

3.1 The choice of SNP

SNPs for BPD and AF were derived from European studies involving both men and women. We selected 16 SNPs that met the criteria when BPD was used as exposure. We got 111 SNPs when AF was the exposure factor. Details can be found in the Supplementary Material.

3.2 Genetic liability to BPD with AF

Our findings suggest that BPD is associated with an increased risk of AF. An observed $P < 0.05$ is considered significant evidence of causality. IVW is the main method of our research. Based on the random-effects model IVW approach, we found that an increase in BPD determined by the one standard deviation (SD) gene was causally associated with a 3.3% increase in the relative risk of AF (N = 16 SNPs; OR, 1.033; 95%CI, 1.005-1.062; $P = 0.0191$). By IVW method of fixed effect model (OR, 1.033; 95%CI, 1.011-1.056; $P = 0.0031$) and Weighted median analysis (OR, 1.034; 95%CI, 1.002-1.068; $P = 0.0394$),We also found a causal relationship between BPD and AF risk. The specific causal relationship between BPD and AF is shown in Figure 3. The standard forest plot shows the effect size of each SNP and its 95% confidence interval (CI) (Figure 4A). The leave-one-out method was used for sensitivity analysis to evaluate the reliability of the results (Figure 4B). Each point in the scatter plot corresponds to a SNP, showing the association between this genetic variation and BPD and AF (Figure 4C). Funnel plot is used to detect heterogeneity among genetic variants (Figure 4D).

3.3 Genetic liability to AF with BPD

In reverse MR analysis, none of the five MR methods supported a causal relationship between AF genetic susceptibility and BPD (Figure 5). Details of MR Estimates and sensitivity analyses can be found in Figure 6.

3.4 Sensitivity analysis

We used mr_pleiotropy_test as the core analysis method to detect horizontal pleiotropy. The intercept term of the MR-Egger method was statistically tested. If there was no statistical difference, that is, $P > 0.05$, horizontal pleiotropy could not be considered. We also used the MR-PRESSO global test to detect horizontal pleiotropy. The leave-one-out method was applied to remove each SNP one by one, and then the meta effect of the remaining SNPs was calculated to observe whether the results would change significantly after the removal of a particular SNP. In the MR study of AF as an outcome, the sensitivity analysis is detailed in Table 2. Sensitivity analysis of AF as exposure in MR study is detailed in Supplementary Materials.

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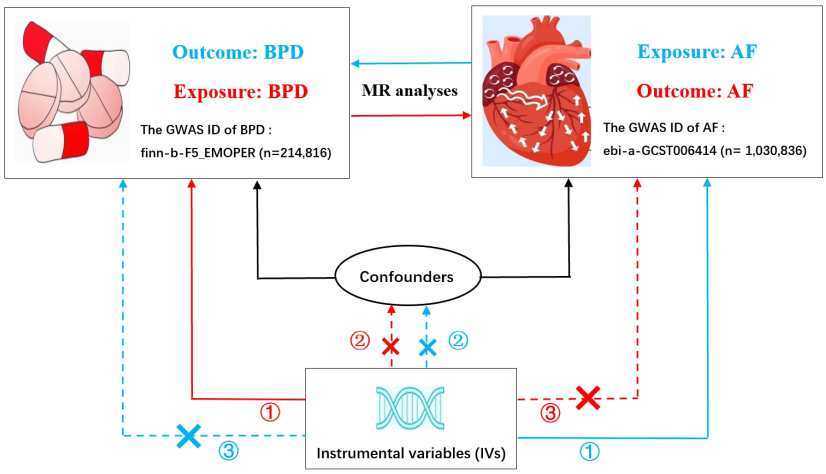

FIGURE 1
Bidirectional Mendelian randomization model of BPD and AF. (The red line represents BPD as exposure and AF as outcome; The blue line represents AF as exposure and BPD as outcome.) BPD, borderline personality disorder; AF, atrial fibrillation; GWAS, genome-wide association study. Three crucial hypotheses of the Mendelian randomization study: ① the correlation assumption; ② the independence assumption; ③ the exclusion assumption.

4 Discussion

To our knowledge, this is the first MR analysis to assess the causal relationship between BPD and the risk of AF. We have two new findings in European populations. On the one hand, our study suggests a causal relationship between genetic susceptibility to BPD and an increased risk of AF. On the other hand, there is no evidence to support a causal relationship between AF and the risk of BPD. However, due to certain limitations of MR studies, these results must be interpreted with caution.

AF is one of the most common persistent arrhythmia. Mental disorders such as anxiety, depression and stress may activate the autonomic nervous system, which may be closely related to the development of AF. Previous studies have systematically and prospectively revealed that negative emotions such as stress, sadness, anger, and anxiety can induce AF, while happiness has a protective effect on AF (28). A systematic review noted that AF imposes significant psychosocial burdens on individuals, including depression and anxiety, as well as impaired quality of life in people with AF (29). A meta-analysis of 2017,276 participants (222,253 with anxiety disorders) from 46 cohorts showed that anxiety was not associated with AF [relative risk(RR), 1.27; 95%CI, 0.90-1.80] (30). Studies have confirmed that 20-40% of AF patients are found to have high levels of depression. Depression significantly increased the 10-year cumulative incidence of AF (from 1.92% to 4.44%) (13). A descriptive study involving 126 patients undergoing coronary artery bypass grafting (CABG) found that the mean trait anxiety scale score of patients with postoperative atrial fibrillation was 40.2 ± 7.8, with a statistically significant difference (16). A meta-analysis involving 5,329,908 participants clearly indicated that anxiety increased the risk of AF by 10% [hazard ratios(HRs) 1.10; 95%CI, 1.02-1.19; P = 0.013; N = 235,599 in 6 studies]. Anger increased the risk of AF by 15% (HR, 1.15; 95%CI 1.04-1.26; P = 0.04, N = 21,791 in 3 studies). Depression increased the risk of AF by 25% (HR, 1.25; 95%CI, 1.12-1.39; P < 0.001; N = 5,160,247 in 6 studies). Work stress increased the risk of AF by 18% (HR, 1.18; 95%CI,1.05-1.32; P = 0.004; N = 51,664 in 4 studies) (31). At the same time, many studies have shown how to influence the negative

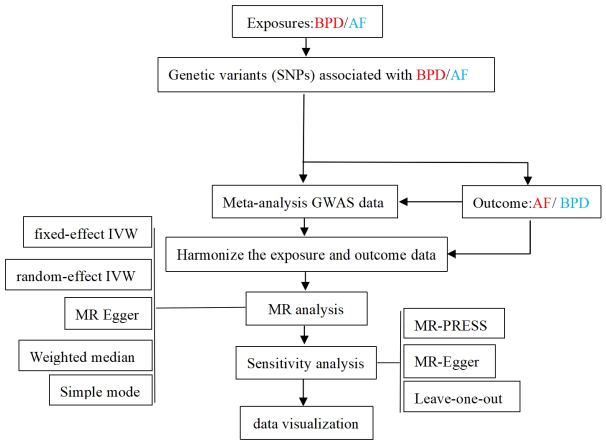

FIGURE 2
Flow chart of the overall design of the MR Analytical framework for this study. BPD, borderline personality disorder; AF, atrial fibrillation; GWAS, genome-wide association study.

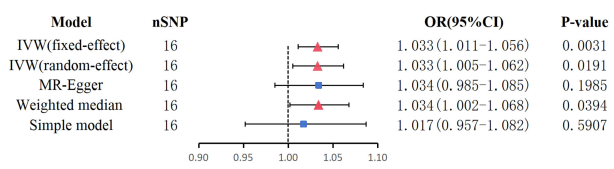

FIGURE 3
Mendelian randomization estimates of BPD on AF.

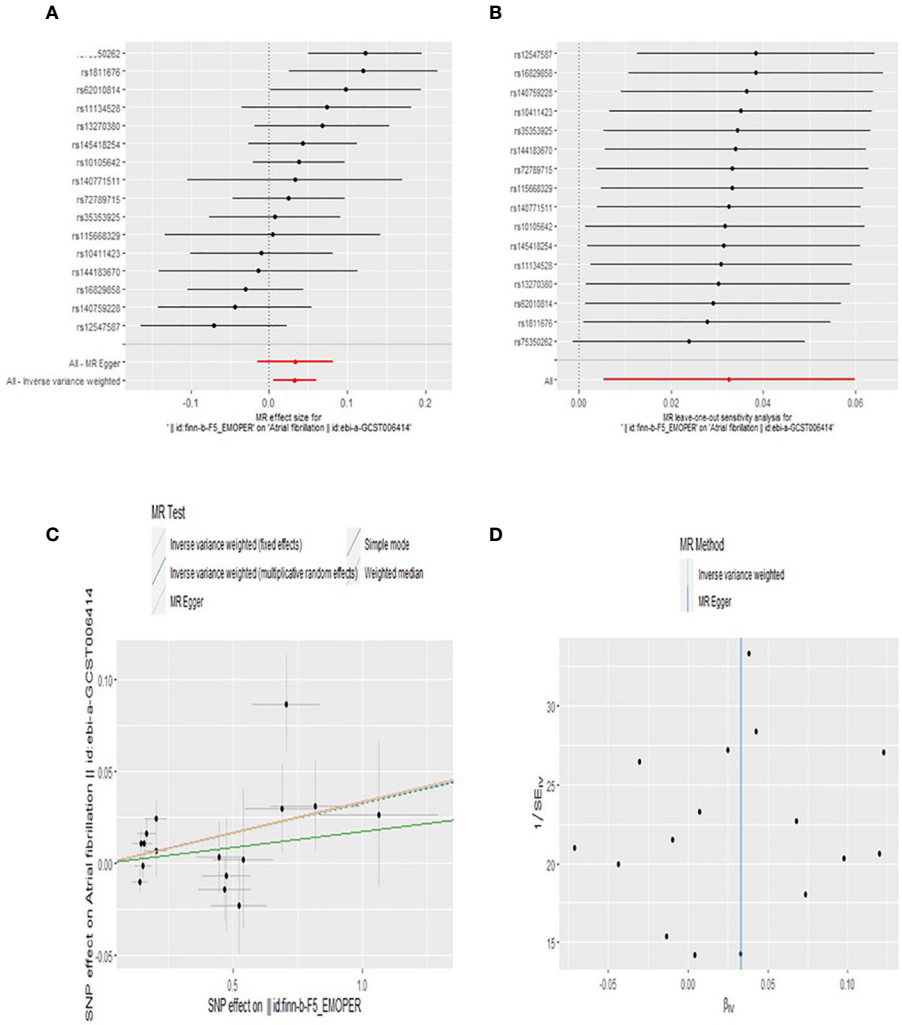

FIGURE 4
Forest plot **(A)**, sensitivity analysis **(B)**, scatter plot **(C)**, and funnel plot **(D)** of the effect of BPD on AF levels.

emotions of patients with AF to improve the prognosis and improve the quality of life of patients. Randomized studies in Australia have reported that improvement in psychological symptoms of anxiety and depression can be observed in patients with symptomatic AF treated with catheter ablation (32). Lakkireddy et al. have shown that yoga therapy improves depression, anxiety, blood pressure and resting heart rate, as well as quality of life in patients with paroxysmal AF (33). While several past observational studies have found a link between mental disorders and AF, the findings have been inconsistent. A large population survey suggests otherwise, that symptoms of depression and anxiety are not associated with an increased incidence of AF (34).

As mentioned above, there have been numerous studies that have linked AF to negative emotions such as depression and anxiety or psychiatric disorders, but the specific nature of their relationship is unclear. The current study also could not shed light on a key question: whether the mental disorder occurred before or after AF, or whether they affected each other at the same time. BPD, centered on emotional dysregulation, can be composed of many symptoms such as depression, anxiety, stress, and suicidal tendencies (20, 35, 36). The multiple manifestations of these unstable personality traits are similar to many mental disorders of AF. Our study specifically identified BPD as an exposure factor and concluded that BPD may predate and lead to AF.

Several studies have shown that patients with BPD exhibit fewer Respiratory sinus arrhythmia (RSA) than healthy individuals, a result that can be explained by reduced parasympathetic activity in BPD patients (37–39). We found that no experts had conducted systematic studies on the relationship between BPD and other arrhythmias. Our study was a MR study of the causal relationship between BPD and AF at the genetic level. It has been documented that inflammation is a

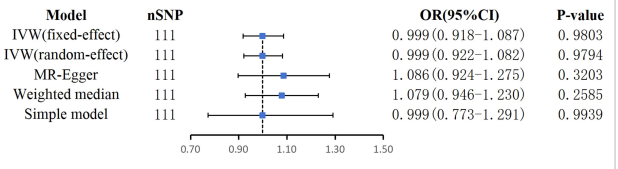

FIGURE 5
Mendelian randomization estimates of AF on BPD.

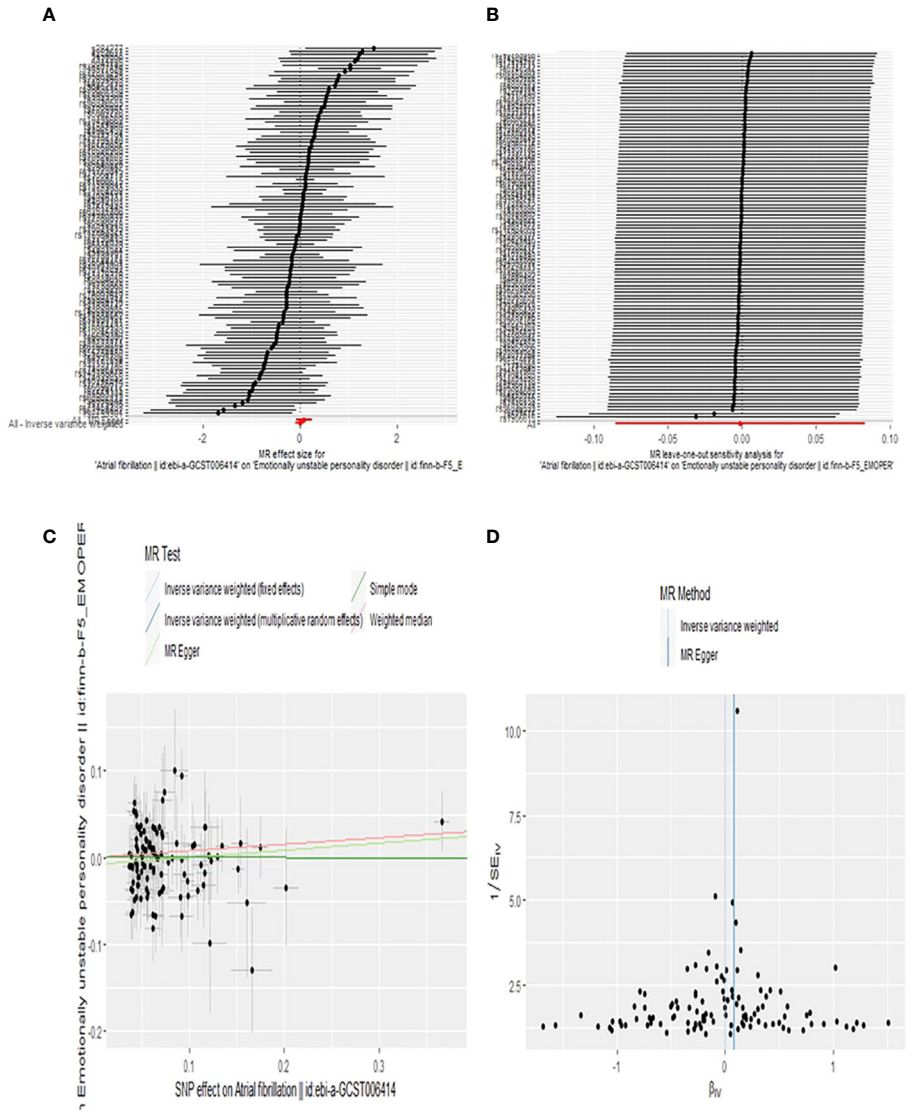

FIGURE 6
Forest plot **(A)**, sensitivity analysis **(B)**, scatter plot **(C)**, and funnel plot **(D)** of the effect of AF on BPD levels.

driver of AF (40). Similarly, some experts believe that BPD may exhibit a pro-inflammatory state (41). Inflammation may be a mediating factor between BPD and AF. The TSMR analysis we performed was sufficient to validate the most direct causal relationship between BPD and AF, without further exploring how this causal relationship is affected step by step.

Finally, it should be noted that in the course of our study, we used a more relaxed threshold ($P < 5\times10^{-6}$) to select instrumental variables for BPD. Although this improves the statistical efficiency, it is more likely to introduce multi-effect instrumental variables. Although we performed multiple sensitivity analyses, each SNP independently affected BPD and AF, which reduced the reliability of the results.

TABLE 2 Sensitive analyses for the Mendelian randomization analysis between BPD and AF.

Outcomes	Heterogeneity test (outliers-corrected)						Pleiotropy test (outliers-corrected)		Outiler
	MR Egger			IVW (Inverse variance weighted)			MR-PRESSO global test P-value	MR-Egger intercept test P-value	
	Cochran's Q	Degrees of Freedom	Cochran's Q P-value	Cochran's Q	Degrees of Freedom	Cochran's Q P-value			
AF	23.928	14	0.047	23.930	15	0.066	0.075	0.975	NA

BPD, borderline personality disorder; AF, atrial fibrillation; NA, not applicable.

5 Strengths and limitations

To our knowledge, our study is the first to use MR Analysis to explore the causal relationship between BPD and AF. TSMR analysis has several advantages (1): Compared with traditional observational studies, MR Method reduces the influence of confounding factors and reverse causality (2); We have strictly identified the SNPs selection to reduce the sampling bias; (3) The data we used are all from European populations, which reduces the influence of population stratification to a certain extent.

Our study also has some limitations: (1) Due to the lack of individual information in the samples, we could not stratify the analysis of age, and AF subtypes; (2) BPD is more common in women, and we did not stratify our study subjects by gender;(3) The samples we studied were all of European ancestry, and the conclusions cannot be generalized to all populations; (4) Not all data employed in the GWAS diagnosed BPD patients according to Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria, together with the lack of adjustment for comorbidities, it is difficult to be sure that the results are specific to BPD and not just common to psychiatric disorders in general.

6 Conclusion

Our TSMR analysis provides genetic evidence of a causal relationship between BPD and an increased risk of AF. On the contrary, no causal relationship of AF on BPD risk was observed. Our study enhances the current understanding of the role of psychiatric disorders in AF. Our study provides evidence to support early prevention of arrhythmias in patients with BPD. Further research is now needed to explore strategies for detecting and treating BPD.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Author contributions

WZ: Methodology, Supervision, Writing – review & editing, Validation. ZW: Conceptualization, Data curation, Methodology, Writing – original draft. HH: Formal analysis, Investigation, Project administration, Writing – review & editing. YS: Resources, Software, Writing - original draft. QW: Project administration, Supervision, Validation, Writing – original draft. MX: Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1392605/full#supplementary-material

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The interplay between borderline personality disorder and oxytocin: a systematic narrative review on possible contribution and treatment options

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Background: Borderline personality disorder (BPD) is a complex mental health condition marked by instability in mood, relationships, self-image, and behavior. Individuals with BPD often struggle with intense emotions, impulsivity, and maintaining stable relationships. Oxytocin, known as the "love hormone" or "bonding hormone," plays a crucial role in social bonding, trust, empathy, and emotional regulation and its dysregulation may contribute to BPD difficulties. This systematic review aims to analyze existing literature, examining the intricate interplay and encouraging future research and treatment strategies.

Methods: A systematic search of Literature in PubMed, Embase and Psychinfo, without any language or time restriction, was performed until March 2024 combining thesaurus and free-search indexing terms related to “borderline personality disorder” and “oxytocin”, producing 310 results (77 in PubMed, 166 in Embase and 67 in Psychinfo). Ninety-four full texts were analyzed, and 70 articles were included in qualitative analysis.

Results: Oxytocin may influence attachment styles, parental behaviors, and stress responses, particularly in individuals with a history of childhood trauma. The interaction between oxytocin, genetics, early life experiences, and environmental factors contributes to the complexity of BPD. Genetic variations in the oxytocin receptor gene may influence social and emotional abilities and contribute to the development of psychopathology. Additionally, early adverse experiences, such as childhood maltreatment, can alter oxytocin functioning, impacting social cognition and emotional regulation.However, oxytocin's role in BPD treatment remains uncertain, with some studies suggesting potential benefits for specific symptoms like social threat avoidance, while others indicate adverse effects on nonverbal behavior and mentalizing.

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Conclusion: Understanding oxytocin's role in BPD offers insights into potential therapeutic interventions. While oxytocin-based treatments may hold promise for addressing specific symptoms, further research is needed.

KEYWORDS

borderline personality disorder, oxytocin, empathy, emotional regulation, social cognition, child maltreatment

1 Introduction

Borderline personality disorder (BPD) is a complex mental health condition characterized by pervasive instability in mood, interpersonal relationships, self-image, and behavior. Individuals with BPD often struggle with intense emotions, impulsivity, and difficulties in maintaining stable relationships. Over the years, researchers have explored various biological factors contributing to the development and manifestation of BPD symptoms, and one such area of interest is the role of oxytocin (1).

Oxytocin (OXT), often referred to as the "love hormone" or "bonding hormone," is a neuropeptide that plays a crucial role in social bonding, trust, empathy, and emotional regulation. It is released in response to social interactions, particularly those involving intimacy, nurturing, and positive social affiliations. Given its involvement in regulating emotional responses and social behavior, researchers have hypothesized that dysregulation in the oxytocin system may contribute to the emotional instability and interpersonal difficulties observed in individuals with BPD (2–4).

In recent years, studies investigating the relationship between oxytocin and BPD have yielded intriguing findings, although the exact nature of this relationship remains complex and multifaceted. Some research suggests that individuals with BPD may have alterations in oxytocin levels or sensitivity, which could influence their ability to form and maintain healthy social connections and regulate emotions effectively. Additionally, there is growing evidence that oxytocin-based interventions, such as intranasal oxytocin administration, may have therapeutic potential in alleviating some symptoms of BPD, particularly those related to interpersonal functioning and emotional dysregulation.

However, the relationship between oxytocin and BPD is not without controversy, as studies have yielded inconsistent results, and the precise mechanisms underlying oxytocin's effects on BPD symptoms remain poorly understood. Furthermore, the interplay between oxytocin and other neurobiological, psychological, and environmental factors in the development and progression of BPD requires further exploration.

This systematic review aims to analyze and critically evaluate the existing literature on the relationship between borderline personality disorder and oxytocin. By synthesizing findings from neurobiological, clinical, and therapeutic studies, we seek to enhance our understanding of the complex interplay between oxytocin function and BPD symptomatology, ultimately highlighting potential avenues for future research and therapeutic interventions aimed at improving outcomes for individuals affected by this challenging disorder.

2 Methods

Our review was performed in accordance with the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

2.1 Literature sources and search

A systematic search of Literature was performed in three main databases (PubMed, Embase and PsychInfo) until March 2024. This preliminary exploratory analysis was conducted without any language or time restriction. Search phrases combined thesaurus and free-search indexing terms related to “borderline personality disorder” and “oxytocin”.

2.2 Eligibility and exclusion criteria

Studies were considered eligible if analyzing any relationship between borderline personality disorder and oxytocin.

Exclusion criteria were applied to the recruitment and diagnosis of borderline personality disorder which must be through standardized tests. No restriction on OXT detection and biological analysis methods was established.

2.3 Data collection process

Three authors (E.d.G., E. A., and A.A.) preliminarily reviewed titles and abstracts of traced articles.The initial screening was followed by the analysis of full texts to check compatibility regarding inclusion and exclusion criteria. Discordances were

analyzed and disagreements were resolved by discussion among all the authors.

When reported information was unclear or ambiguous the relevant corresponding author was contacted for clarification.

2.4 Data extraction

A standardized form was used to extract data, including information on year of publication, country, setting, characteristics of each study (sample size, age, gender and oxytocin administration or dosage). Two authors (E.A. and A.A.) conducted data extraction independently; extraction sheets for each study were cross-checked for consistency, and any differences were resolved by discussion among the coauthors.

3 Results

3.1 Literature search and basic information

The analysis of existing Literature produced 310 results (77 in PubMed, 166 in Embase and 67 in PsychInfo). Ninety-four full texts were analyzed, and 70 articles were included in qualitative analysis. (see Figure 1)

Table 1 provides an overview of the papers included in the qualitative analysis. Papers were sorted in two different categories to facilitate in-depth analysis: correlation between OXT and BPD, and new implications for the BPD treatment.

Most of the manuscripts were published in the last 15 years, except for one article released in 2006.

3.1.1 A psychoanalytic perspective

Bidirectional influences between maternal and infant OXT systems begin when the newborn is about 3 months old, enhancing both maternal care, infant social and emotional development and are essential to the development of attachment. Furthermore, the quality of parental care (warmth and availability) controls and modulates the development of a child's physiological and psychological infrastructures, as well as their gene expression. BPD is a disease characterized by difficulties and in attachment, a possible disruption in neuropeptides that regulate that system, such as oxytocin, are plausible and under investigation (5).

3.1.2 Different attachment styles and oxytocin

Juraś-Darowny et al. found that oxytocin plasma levels did not differentiate by attachment style in healthy individuals, while it is different in BPD patients. OXT plasma levels in the anxious-avoidant style were significantly higher than in the anxious-preoccupied style (5, 6). Furthermore, as the majority of BPD patients exhibit unresolved (disorganized) attachment representations, this subset of patients expressed significantly lower baseline OXT plasma levels compared to BPD patients with organized attachment (7).

Interestingly, in borderline patients, especially those with unresolved attachments, oxytocin levels were shown to decrease significantly after separation and not increase normally as in controls. This evidence highlights the role of oxytocin in higher rejection susceptibility due to greater efforts to avoid denial which is an epitome of BPD (7, 8).

3.1.3 An implication for compassion

These results have significant ramifications for therapeutic environments as well. The attachment system is stimulated in therapy and may elicit emotional memories. Research on the function of resistance to these emotions and relationships is crucial in the treatment of BPD patients.

It became evident, during the clinical development of compassion-focused therapy, that many clients had significant avoidance of self-compassion (with feelings of anger and anxiety, feeling alone and yearning for closeness, fear) and resistance to be open and responsive to compassion from others (Fear Of

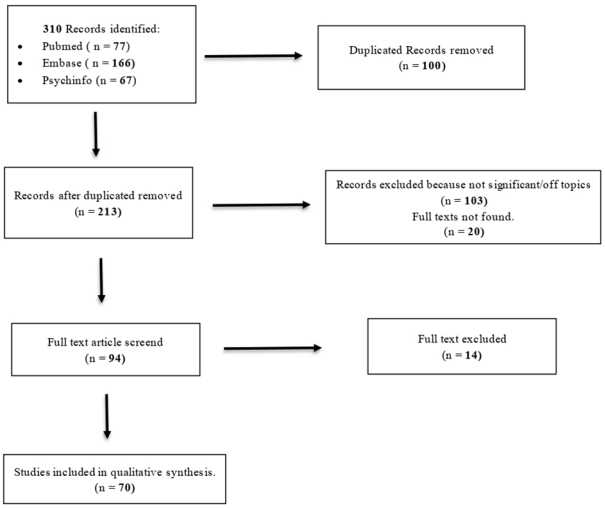

FIGURE 1
PRISMA flowchart.

TABLE 1 Sudy characteristics.

Authors	Year	Title	Theme	Country	Journal
Aboulafia-Brakha, T., Perroud, N., Suchecki, D., Nicastro, R., Dieben, K., & Curtis, L.	2023	Hypomodulation of salivary oxytocin in patients with borderline personality disorder: A naturalistic and experimental pilot study	Correlation	Brazil	*Psychiatry Research Communications*
Back SN , M Schmitz, J Koenig, M Zettl, N Kleindienst, SC Herpertz, K Bertsch	2022	Reduced vagal activity in borderline personality disorder is unaffected by intranasal oxytocin administration, but predicted by the interaction between childhood trauma and attachment insecurity	Treatment	Germany	Journal of Neural Transmission
Bartz J , D Simeon, H Hamilton, S Kim, S Crystal, A Braun, V Vicens, E Hollander	2011	Oxytocin can hinder trust and cooperation in borderline personality disorder	Treatment	USA	Social cognitive and affective neuroscience
Bartz JA, E Hollander	2006	The neuroscience of affiliation: Forging links between basic and clinical research on neuropeptides and social behavior	Correlation	USA	Hormones and behavior
Bertsch K , SC Herpertz	2017	Oxytocin and borderline personality disorder	Correlation /Treatment	Germany	Behavioral pharmacology of neuropeptides: Oxytocin
Bertsch Katja , Ph.D., Matthias Gamer, Ph.D., Brigitte Schmidt, M.D., Ilinca Schmidinger, M.D., Stephan Walther, Ph.D., Thorsten Kästel, M.S., Knut Schnell, M.D., Christian Büchel, M.D., Gregor Domes, Ph.D., and Sabine C. Herpertz, M.D.	2013	Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder	Treatment	Germany	*American Journal of Psychiatry*
Bertsch, K., Schmidinger, I., Neumann, I. D., & Herpertz, S. C.	2013	Reduced plasma oxytocin levels in female patients with borderline personality disorder	Correlation	Germany	*Hormones and behavior*
Bomann AC, MB Jørgensen, S Bo, M Nielsen, LB Gede, B Elfving, E Simonsen	2017	The neurobiology of social deficits in female patients with borderline personality disorder: The importance of oxytocin	Correlation	Denmark	Personality and Mental Health
Bonfig J, SC Herpertz, I Schneider	2022	Altered hormonal patterns in borderline personality disorder mother-child interactions	Correlation	Germany	Psychoneuroendocrinology
Brüne M	2016	On the role of oxytocin in borderline personality disorder	Correlation /Treatment	Germany	British Journal of Clinical Psychology
Brüne M , A Ebert, M Kolb, C Tas, MA Edel, P Roser	2013	Oxytocin influences avoidant reactions to social threat in adults with borderline personality disorder	Treatment	Germany	Human Psychopharmacology: Clinical and Experimental
Brüne, M., & Ebert, A.	2012	Does oxytocin have a role in borderline personality disorder?	Treatment	Germany	*International Journal of Neuropsychopharmacology*
Brüne, M., Kolb, M., Ebert, A., Roser, P., & Edel, M. A.	2015	Nonverbal communication of patients with borderline personality disorder during clinical interviews: a double-blind placebo-controlled study using intranasal oxytocin	Treatment	Germany	*The Journal of nervous and mental disease*
Byrd, A. L., Tung, I., Manuck, S. D., Vine, V., Horner, M., Hipwell, A. E., & Stepp, S. D.	2021	An interaction between early threat exposure and the oxytocin receptor in females: Disorder-specific versus general risk for psychopathology and social-emotional mediators	Correlation	USA	*Development and psychopathology*
Carrasco J. L. , E. Buenache, K. S. MacDowell, I. De la Vega, J. M. López-Villatoro, B. Moreno, M. Díaz-Marsá, J. C. Leza	2020	Decreased oxytocin plasma levels and oxytocin receptor expression in borderline personality disorder	Correlation	Spain	*Acta Psychiatrica Scandinavica*

(Continued)

TABLE 1 Continued

Authors	Year	Title	Theme	Country	Journal
Cataldo, I., Azhari, A., Lepri, B., & Esposito, G.	2017	Oxytocin receptors (OXTR) and early parental care: An interaction that modulates psychiatric disorders	Correlation	Italy	Research in developmental disabilities
Cicchetti, D., Rogosch, F. A., Hecht, K. F., Crick, N. R., & Hetzel, S.	2014	Moderation of maltreatment effects on childhood borderline personality symptoms by gender and oxytocin receptor and FK506 binding protein 5 genes	Correlation	USA	*Development and psychopathology*
Cochran, D. M., Fallon, D., Hill, M., & Frazier, J. A.	2013	The role of oxytocin in psychiatric disorders: A review of biological and therapeutic research findings	Treatment	USA	*Harvard review of psychiatry*
Debbané, M.	2018	Treating borderline personality disorder with oxytocin: An enthusiastic note of caution. Commentary to Servan et al. "The effect of oxytocin in borderline personality disorder.	Treatment	France	*L'encephale*
Diaz-Marsá M , J M López-Villatoro, A De la Torre-Luque, K S MacDowell, A Galvez-Merlin, A Gómez Del Barrio, F Ruiz-Guerrero, L Beato-Fernández, F Polo-Montes, M León-Velasco, D Martín-Hernández, A Carrasco-Diaz, J C Leza, J L Carrasco	2024	Decreased oxytocin plasma levels and oxytocin receptor expression associated with aggressive behavior in aggressive-impulsive disorders	Correlation	Spain	Journal of Psychiatric Research
Domes Gregor , Nicole Ower, Bernadette von Dawans, Franny B. Spengler, Isabel Dziobek, Martin Bohus, Swantje Matthies, Alexandra Philipsen & Markus Heinrichs	2019	Effects of intranasal oxytocin administration on empathy and approach motivation in women with borderline personality disorder: a randomized controlled trial	Treatment	Germany	Translational Psychiatry
Ebert A , MA Edel, P Gilbert, M Brüne	2018	Endogenous oxytocin is associated with the experience of compassion and recalled upbringing in Borderline Personality Disorder	Correlation	Germany	Depression and Anxiety
Ebert, A., Kolb, M., Heller, J., Edel, M. A., Roser, P., & Brüne, M.	2013	Modulation of interpersonal trust in borderline personality disorder by intranasal oxytocin and childhood trauma	Treatment	Germany	*Social neuroscience*
Fineberg SK , DA Ross	2017	Oxytocin and the Social Brain	Correlation	USA	Biological psychiatry
Fisher, Amanda M., et al.	2016	Intranasal oxytocin modulates social cognitive errors in borderline and schizotypal personality disorders	Treatment	UK	Biological Psychiatry
Flasbeck V , D Moser, R Kumsta, M Brüne	2018	The OXTR Single-Nucleotide Polymorphism rs53576 Moderates the Impact of Childhood Maltreatment on Empathy for Social Pain in Female Participants: Evidence for Differential Susceptibility	Correlation	Germany	Frontiers in psychiatry,
Ha, C.	2016	The effects of intranasal oxytocin on social cognitive functioning in adolescents with borderline personality disorder compared to a sample of non-clinical adolescents	Treatment	USA	*Book*
Hammen, C., Bower, J. E., & Cole, S. W.	2015	Oxytocin receptor gene variation and differential susceptibility to family environment in predicting youth borderline symptoms	Correlation	USA	*Journal of personality disorders*
Heinrichs M , B von Dawans, G Domes	2010	Oxytocin, vasopressin, and human social behavior	Correlation /Treatment	USA	Frontiers in neuroendocrinology,
Heinrichs Markus , Frances S. Chen, Gregor Domes	2012	Social neuropeptides in the human brain: oxytocin and social behavior	Correlation /Treatment	Germany	*book*

(Continued)

TABLE 1 Continued

Authors	Year	Title	Theme	Country	Journal
HerpertzSC, I Schneider, C Schmahl, K Bertsch	2018	Neurobiological Mechanisms Mediating Emotion Dysregulation as Targets of Change in Borderline Personality Disorder	Treatment	Germany	Psychopathology
Jain, S	2014	Journal Watch review of Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder.	Treatment	USA	Journal waTch review
Jawad MY , B Ahmad, AM Hashmi	2021	Role of oxytocin in the pathogenesis and modulation of borderline personality disorder: A review	Correlation	Pakistan	Cureus
Jobst Andrea , Frank Padberg, Maria-Christine Mauer, Tanja Daltrozzo, Christine Bauriedl-Schmidt, Lena Sabass, Nina Sarubin, Peter Falkai, Babette Renneberg, Peter Zill, Manuela Gander, Anna Buchheim	2016	Lower Oxytocin Plasma Levels in Borderline Patients with Unresolved Attachment Representations	Correlation	Germany	Frontiers in Human Neuroscience
Jobst Andrea ; Anna Albert; Christine Bauriedl-Schmidt; Maria Christine Mauer; Babette Renneberg; Anna Buchheim; Lena Sabass; Peter Falkai; Peter Zill; Frank Padberg	2014	Social exclusion leads to divergent changes of oxytocin levels in borderline patients and healthy subjects	Correlation	Germany	*Psychotherapy and psychosomatics*
Jurań-Darowny, D Strzelecki, M Talarowska	2023	Borderline personality - from psychoanalysis to epigenetics. Biological basis of attachment	Correlation	Poland	Psychiatria Polska
Kartal F, K Uğur, B Mete, ME Demirkol, L Tamam	2022	The Relationship Between the Oxytocin Level and Rejection Sensitivity, Childhood Traumas, and Attachment Styles in Borderline Personality Disorder	Correlation	Turkey	Psychiatry Investigation
Kirsch P	2015	Oxytocin in the socioemotional brain: implications for psychiatric disorders	Correlation /Treatment	Germany	Dialogues in clinical neuroscience
Kluczniok Dorothea , Katja Dittrich, Catherine Hindi Attar, Katja Bödeker, Maria Roth, Charlotte Jaite, Sibylle Winter, Sabine C. Herpertz, Stefan Röpke, Christine Heim & Felix Bermpohl	2019	Oxytocin and maltreatment potential. Influence of maternal depression, borderline personality disorder and experience of early childhood maltreatment	Correlation	Germany	*Der Nervenarzt*
Kohlhoff J , S Cibralic, DJ Hawes, V Eapen	2022	Oxytocin receptor gene (OXTR) polymorphisms and social, emotional and behavioral functioning in children and adolescents: A systematic narrative review	Correlation	Australia	Neuroscience & Biobehavioral Reviews
Leppanen J , KW Ng, YR Kim, K Tchanturia, J Treasure	2018	Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans	Tretment	Singapore/ Sud Korea/ UK/Georgia	Journal of Affective Disorders
Leppanen, J., Ng, K. W., Tchanturia, K., & Treasure, J.	2017	Meta-analysis of the effects of intranasal oxytocin on interpretation and expression of emotions	Treatment	UK	*Neuroscience & Biobehavioral Reviews*
Lischke A , SC Herpertz, C Berger, G Domes, M Gamer	2017	Divergent effects of oxytocin on (para-) limbic reactivity to emotional and neutral scenes in females with and without borderline personality disorder	Treatment	Germany	Social cognitive and affective neuroscience
Mancke F, SC Herpertz, K Bertsch - **Personality Disorders**	2015	Aggression in borderline personality disorder: A multidimensional model	Correlation	Germany	Personality Disorders: Theory, Research, and Treatment
Manuel C. D. Silva	2020	Oxytocin as a potential adjuvant treatment in borderline personality disorder – a review	Treatment	Spain	*European Neuropsychopharmacology*
Maoz H , A Grossman-Giron, O Sedoff, U Nitzan, H Kashua, M Yarmishin, O Arad, DT Bitan	2024	Intranasal oxytocin as an adjunct treatment among patients with severe	Treatment	Israel	Journal of affective disorder

(Continued)

TABLE 1 Continued

Authors	Year	Title	Theme	Country	Journal
		major depression with and without comorbid borderline personality disorder			
Meyer-Lindenber, A., Domes, G., Kirsch, P., & Heinrichs, M.	2011	Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine	Correlation /Treatment	Germany	*Nature Reviews Neuroscience*
Mielke Emilia L , Julian Koenig, Sabine C Herpertz, Sylvia Steinmann, Corinne Neukel, Pelin Kilavuz, Patrice van der Venne, Katja Bertsch, Michael Kaess	2023	Adverse childhood experiences mediate the negative association between borderline personality disorder symptoms and plasma oxytocin	Correlation	Germany	Progress in neuro-psychopharmacology and biological psychiatry
Patin, A., & Hurlemann, R.	2015	Social cognition	Correlation	Germany	*Cognitive enhancement*
Peled-Avron L , A Abu-Akel, S Shamay-Tsoory	2020	Exogenous effects of oxytocin in five psychiatric disorders: a systematic review, meta-analyses and a personalized approach through the lens of the social salience hypothesis	Correlation /Treatment	Israel	Neuroscience & Biobehavioral Reviews
Perez-Rodriguez M.M., Yuan Q., Zhou Z., Hodgkinson C.A., Bevilacqua L., Ripoll L., Goodman M., Koenigsberg H.W., Shen P.-H., Goldman D., Siever L., New A.S.	2013	Oxytocin genotype may modulate reactivity to the environment in borderline personality disorder	Correlation	USA	*Neuropsycopharmacology*
Perez-Rodriguez, M. D. L. M.	2014	Neuropeptides and BDNF and emotion dysregulation in borderline personality disorder	Correlation	USA	*Biological Psychiatry*
Perez-Rodriguez, M. M.	2014	Converging multimodal evidence of social cognitive abnormalities in borderline and schizotypal personality disorders: Circuits, modulators and mechanisms	Correlation /Treatment	Usa	*Neuropsychopharmacology*
Perez-Rodriguez, M. M., Bulbena-Cabré, A., Nia, A. B., Zipursky, G., Goodman, M., & New, A. S	2018	The Neurobiology of Borderline Personality Disorder	Correlation	Spain	*Psychiatric Clinics*
Plett O , V Flasbeck, M Brüne	2023	Effects of human and animal-assisted skills training on oxytocin und cortisol levels in patients with borderline personality disorder	Treatment	Germany	Journal of Psychiatric Research
Ramseyer, F., Ebert, A., Roser, P., Edel, M. A., Tschacher, W., & Brüne, M.	2020	Exploring nonverbal synchrony in borderline personality disorder: A double-blind placebo-controlled study using oxytocin	Treatment	Switzerland	*British Journal of Clinical Psychology*
Ripoll LH	2012	Clinical psychopharmacology of borderline personality disorder: An update on the available evidence in light of the Diagnostic and Statistical Manual of Mental Disorders-5	Correlation	USA	Current Opinion in Psychiatry
Ripoll, L. H.	2013	Psychopharmacologic treatment of borderline personality disorder	Treatment	USA	*Dialogues in clinical neuroscience*
Saeed, S. A., & Kallis, A. C.	2021	Borderline personality disorder: 6 studies of biological interventions	Treatment	USA	*Current Psychiatry*
Schmitz M , LE Müller, A Schulz, N Kleindienst, SC Herpertz, K Bertsch	2020	Heart and brain: Cortical representation of cardiac signals is disturbed in borderline personality disorder, but unaffected by oxytocin administration	Treatment	Germany	Journal of Affective Disorders
Schneider I , S Boll, I Volman, K Roelofs, A Spohn, SC Herpertz, K Bertsch	2020	Oxytocin Normalizes Approach–Avoidance Behavior in Women With Borderline Personality Disorder	Treatment	Germany/ UK/ Netherlands	Frontiers in Psychiatry
Servan A , J Brunelin, E Poulet	2018	The effects of oxytocin on social cognition in borderline personality disorder	Treatment	France	L'encephale

(Continued)

TABLE 1 Continued

Authors	Year	Title	Theme	Country	Journal
Siever, L. J., Hodgkinson, C. A., Weinstein, S., Shen, P. H., New, A. S., & Goldman, D.	2010	Opioids and oxytocin: Genotypes and phenotypes in BPD	Correlation	USA	*Biological Psychiatry*
Simeon D , J Bartz, H Hamilton, S Crystal, A Braun, S Ketay, E Hollander	2011	Oxytocin administration attenuates stress reactivity in borderline personality disorder: a pilot study	Treatment	USA	Psychoneuroendocrinology
Stanley B , LJ Siever	2010	The interpersonal dimension of borderline personality disorder: toward a neuropeptide model	Correlation	USA	American Journal of Psychiatry
Stevens, F. L., Wiesman, O., Feldman, R., Hurley, R. A., & Taber, K. H.	2013	Oxytocin and behavior: Evidence for effects in the brain	Correlation /Treatment	USA	*The Journal of neuropsychiatry and clinical neurosciences*
Stoffers JM , K Lieb	2015	Pharmacotherapy for borderline personality disorder–current evidence and recent trends	Treatment	Germany	Current psychiatry reports
Vancova Z	2021	Potential therapeutic possibility of oxytocin for borderline personality disorder	Treatment	Slovakia	Psychiatric Annals
Zhang M , N Liu, H Chen, N Zhang	2020	Oxytocin receptor gene, childhood maltreatment and borderline personality disorder features among male inmates in China	Correlation	China	BMC psychiatry

Compassion-FOC). Compassion is associated with caring motivations, which are neurochemically connected to the action of oxytocin.

Usually, for BPD patients, providing care for others was characterized by a lack of availability, neglect, emotional insensitivity, or even abuse and harm.

Ebert et al. discovered a negative correlation between OXT levels and FOC in individuals from the BPD group. In a recent study they showed that, in comparison to the control group, BPD patients exhibited noticeably greater fears and resistances to all forms of compassion. Additionally, BPD patients remembered their parents' actions from their childhood less favorably. Lack of emotional warmth may have an impact on a child's OXT system that is comparable to a mild trauma. This may suggest that this ìpopulation of patients would benefit from specialized focused treatment in this field (6).

3.1.4 OXT and mother-child interactions

Being a mother implies behavioral, physiological, and neurological changes that are crucial for successful mother-child interactions and sensitive caregiving OXT plays an essential role in those changes. Herpertz et al. state thatAfter interacting with their own child, mothers with BPD exhibited altered oxytocin and cortisol reactivity, with a decrease in oxytocin and an unchanged cortisol level; on the contrary, mothers without BPD displayed stable oxytocin levels and a decrease in cortisol after mother-child interaction (9).

According to the theoretical implications of this model on parent-child relationships, low parental oxytocin levels are linked to a decreased sense of reward during interactions with their offspring with poor importance given to the child's requests. These factors reduce parental sensitivity and may contribute to insecure attachment and poor parent-child bonding (9–11).

Furthermore, a child's oxytocin levels may be lowered as a result of the mother's decreased OXT levels (9, 10).

On the other hand, Kluczniok et al. tested OXT as a potential mediator for the association between maternal experience of early childhood maltreatment and potential abuse perpetrated against their own child in BPD. They found that early childhood maltreatment is associated with reduced plasma OXT in mothers with mental distress due to several factors (including BPD). Notwithstanding, OXT low level did not mediate the association with abusing of their own child (12).

3.2 A Biopsychosocial perspective

Finding specific factors linked to borderline personality disorder (BPD) and low plasma levels of oxytocin in BPD patients may help in the identification of those patients who would benefit from therapies with oxytocin (13–15).

3.2.1 OXT and early life stressful event

Unfavorable early life and childhood experiences, such as persistent rejection, maltreatment and abandonment are important environmental elements that may influence the oxytocin system (11). Early stress can modify the activity of the oxytocin receptors and interfere with both its binding properties and the neuropeptide system's development (16).

BPD is associated with lower levels of oxytocin as well as decreased expression of the oxytocin receptor (OXTR), indicating

the involvement of both oxytocin and its receptor in this disorder (17).

As a possible consequence, brain altered neurodevelopment in BPD patients with a history of trauma and early life stress may be related to an impairment in the oxytocin system. The amygdala, which is responsible for the emotional regulation which is lacking in BPD patients, may suffer from the interaction between the OXTR gene and childhood maltreatment.

According to research by Bartz et al., severe early stress and maltreatment can affect the oxytocin–vasopressin stress–response system, which, in turn, can alter brain development and cause a variety of disorders, such as BPD and Post Traumatic Stress Disorder (PTSD). Prolonged early stress modifies the release of corticotropin, which then modifies the binding of the oxytocin and vasopressin receptors. Some authors have also proposed that gonadal steroids and oxytocin may play a role in the way that stress in early life influences affiliative behaviors in adults (18–21).

3.2.2 The interaction between gene and environment in BPD

The interaction between the gene and environment (G × E) may play a role in the development of BPD (22–24). It is important to view OXTR from the perspective of "differential susceptibility" since a reduced protein expression due to different genotypes may be a biological mediator of some aspects of the psychogenesis and psychopathology of BPD. OXTR is on chromosome 3p25.3 of the human genome. A growing number of researches, including reports of both direct effects and gene-environment interactions, points to the possibility that single nucleotide polymorphisms (SNPs) of the OXTR gene might be linked to individual variations in social and emotional abilities as well as to the genesis of psychopathology (25).

The OXTR's rs53576, a SNP in the third of four introns, is the most thoroughly studied single-nucleotide polymorphism (SNP) (26, 27). Since the frequency of rs53576 varies according to ethnicity, genetic susceptibility may also differ between racial groups. Another explanation for these contradictory effects of genetic susceptibility could be gender differences, which has been extensively documented in the literature.

Moreover, according to a recent study, females with the A allele were more likely to experience maltreatment as children. This could indicate that different genders have distinct patterns of interaction between the OXTR gene and childhood maltreatment (22).

Furthermore, Kohlhoff and colleagues found that BPD-OXTR rs53576 moderate the interaction between child maltreatment and BPD traits, with varying effects in each genders, but it did not directly predict BPD traits.

In particular, girls who had suffered abuse and belonged to the AG-AA group (presence of minor allele A) showed more severe BPD traits compared to girls with the GG genotype who had not been abused.

Boys who were maltreated and had the GG genotype exhibited more BPD traits than boys who were not, with a specific gender-oriented model. On the contrary, there was no difference in the degree of BPD traits between boys with the AG-AA genotype and those who were not abused (2).

The OXTR gene is thought to contribute disproportionately to disturbed relatedness. When early parental warmth is present, AA/AG genotypes are less likely to develop BPD; however, when early childhood abuse occurs, they are more likely to develop psychopathology (28, 29).

Studies examining polymorphisms in OXTR revealed that multiple variants of the gene are linked to empathic concern for other people as well. The goal of Jawad et al. study was to investigate how oxytocin receptor gene variants interact with childhood trauma, detected with the Childhood Trauma Questionnaire (CTQ), and affect a person's capacity for BPD empathy in case of painful experiences. They discovered that low scores on the CTQ were linked to less empathy for psychological pain, while childhood maltreatment in A-allele carriers was associated with higher empathy for psychological pain. According to this evidence, people who have at least one A-allele are more vulnerable to environmental variation, which may have a secondary role in the onset of emotional instability (26, 28).

3.2.3 Phenomenology of borderline personality disorder and oxytocin

In current literature, the three main psychopathological domains of borderline personality disorder (BPD) are Behavioral dysregulations—impulsivity (suicidal thoughts and behaviors, and self-mutilation), affective dysregulation (which includes inappropriate anger and attempts to prevent abandonment) and disturbed relatedness (unstable relationships, identity disorders, and a persistent sense of emptiness) (2). A reduced protein expression may be a biological mediator of some aspects of the psychogenesis and psychopathology of BPD (17).

3.2.4 The “threat hypersensitivity” as the core of BPD symptoms

The "threat hypersensitivity", thought to be a common trait in people who experienced interpersonal maltreatment in their early childhood, is closely linked to the three domains of BPD psychopathology.

Furthermore, “threat hypersensitivity” is linked to amygdala hyperactivity, which is the salience network activated in response to threatening social stimuli. This phenomenon is known as enhanced emotional dysregulation or "bottom up emotion generation."

According to the social salience theory, OXT makes people more sensitive to social cues and intrapersonal and interpersonal variables determining if a person to react positively or negatively.

In particular, the abnormal stress response and the top-down and bottom-up dysregulation of emotional systems that characterize Borderline Personality Disorder might be influenced by oxytocin deficiencies.

Due to inadequate prefrontal cortex modulation, low oxytocin action on the limbic system would cause an abnormally high amygdala activation, leading to interpersonal hypersensitivity, emotional dysregulation, and impulsive behavior (17).

These results are also consistent with a process of down-regulation of the oxytocin system in BPD patients as a reaction to early adverse experiences linked to disordered attachment styles, as previously reported by Jobst et al. (7)

Bomann et al. described positive correlations between plasma OXT levels and exposure to uncontrollable noise, various social stressors, and attachment anxiety, suggesting that oxytocin has a calming and stress-relieving effect. This suggested relationship between serum OXT and BPD symptomatology is thus demonstrated by this evidence (2, 30).

3.2.5 Emotional and behavioral dysregulations

Reduced basal levels of oxytocin cause the amygdala to become more activated in BPD patients, impairing their ability to comprehend social cues and resulting in aberrant behaviors and emotional dysregulation (31). This theory is further supported by the discovery of a strong negative correlation between psychological self-reported stress, anxiety, anger traits and OXT (32).

Byrd et al. described an intriguing link between early threat experiences, oxytocin receptor genetic assets in BPD females and traumatic childhood exposure. Women who carry at least one copy of the rs53576 gene and A allele, showed increased levels of emotion dysregulation in adolescence. This evidence was predictive of psychopathology in general, including BPD traits and diagnosis, in all women (20, 25).

3.2.6 Aggressive behaviors

Similarly, reactive aggression has been negatively related to the oxytocin system (33). Trait aggressiveness and self-reported aggressiveness were inversely correlated with oxytocin plasma concentrations in BPD patients (34), confirming the possibility that abnormal impulsive-aggressive behavior, which is typical of BPD patients, is strictly related to oxytocin system dysfunction (15).

Considering possible genetic implications, De Las Mercedes Perez-Rodriguez et al. discovered a risk linked to haplotype CT of the oxytocin gene (rs877172 C rs3761248 T), which is associated with increased aggression and anxious attachment (31). Furthermore, Siever et al. found a link between four OXT SNPs and inappropriately high levels of anger in BPD patients (35).

A recent study (36) attested a correlation between OXT SNPs and the Personal Distress subscale of the Interpersonal Reactivity Index (a measure of dispositional empathy) in adults with personality disorders, as well as irritable aggressive anger dysfunction. According to this data, the oxytocin system may modulate reactivity to the environment in BPD.

3.2.7 Suicidal and self-harming behaviors

BPD is frequently associated with emotional,behavioral dysregulation andimpulsive aggression as welland suicidal and self-harming behaviors in response to perceived rejection and loss,.

In BPD, there is a clear correlation between self-harm and reduced pain sensitivity. Oxytocin modulates pain by interacting with the opiate and cannabinoid systems. According to literature, oxytocin-positive parvocellular neurons in the hypothalamus project directly to the brainstem, where they may work with modulatory signals from peripherally released oxytocin to reduce both physical and psychological pain (37).

3.2.8 Interpersonal dysfunction and social cognition

Patients with borderline personality disorder may have relational difficulties, which have been explained by social deficits and emotional dysregulation.

In order to examine the acknowledged role of OXT in attachment, especially in romantic partner bonding, Bomann et al. investigated potential associations between serum OXT and marital status in BPD.

The mean serum OXT level of patients in romantic relationships was 599 pg/ml, while the mean level of single patients was 374 pg/ml. This disparity represented a significant difference between the two groups.

These findings could reinforce the evidence that OXT is a crucial mediator of romantic attachment. However, since BPD patients frequently suffer significant emotional distress and intense fear of being abandoned, it is plausible that their elevated OXT serum levels reflect a higher level of stress than among singles. Higher OXT plasma levels, in this study, have been linked to self-reports of relationship distress and relationship anxiety, supporting this theory (30).

Affective dysregulation alone cannot fully account for low interpersonal functioning while social cognition impairment may also be a factor. These deficits in social cognition are supposed to be associated with unfavorable early life experiences and are primarily mediated by the oxytocin system, which has been demonstrated to be controlled by epigenetic modifications (22, 34). In response to a scenario of social exclusion, which is a powerful negative bonding stimulus in BPD, Jobs et al. found that female BPD patients had lower OXT plasma levels than healthy individuals (7, 32).

Jobst et al. examined the plasma levels of oxytocin in both borderline patients and healthy controls (HC) following Cyberball, which is based on social exclusion and causes social pain in people. They showed that there was no difference in oxytocin levels despite attachment representations. Similar OXT variations following social exclusion were detected in BPD patients with organized attachment as well as in those with unresolved attachment representations. However, OXT plasma levels were lower in the latter group (7).

When OXT plasma levels were directly compared between the BPD and HC groups following social exclusion, a significant difference was observed. BPD patients' OXT plasma levels tended to decrease, while HC patients tended to increase. OXT plasma levels were consistently lower in BPD patients than in HC.

Such results indicate that BPD and HC have distinct emotional reactions to social exclusion. In this particular situation, OXT release may encourage prosocial behavior and lessen social discomfort. This OXT response to social exclusion may be compromised in BPD patients, which may be related to their overall difficulty in mending damaged cooperation skills (7).

Interestingly, the OXT system grows as a result of experiences that occur during sensitive developmental periods, and it might be particularly affected by traumatic childhood experiences. Epigenetic modifications of genes implicated in OXT signaling may be involved in the mechanisms mediating the long-term influence of early adverse experiences on socio-behavioral outcomes.

On the one hand, "Low OXT state" could refer to a protective state where negative emotions are less perceived and social pain might be easier tolerated. In this special context, early childhood maltreatment and the formation of insecure attachment representations might be linked to the development of borderline personality disorder and may contribute to the symptoms of BPD behavior in adulthood (38).

3.3 Oxytocin as a treatment for BPD

The role of Oxytocin in the treatment of BPD is complex, ambivalent and still under investigation. Several studies have been conducted in the last years aiming to discover the therapeutic potential of this hormone for this specific disease.

Some studies demonstrated promising results for a possible treatment of some key symptoms of the BPD with Intranasally administration of Oxytocin.

3.3.1 Social threat

Oxytocin have an impact on social threat avoidance and in social threat hypersensitivity in subject affected by BPD, As attested by Schneider et al. (39) oxytocin normalizes the threat-avoidance behavior in patients with BPD by enhancing reaction times in affect-incongruent (approach angry and avoid happy faces) conditions. The results of the study by Bertsch et al. (40) showed beneficial effects from administration of oxytocin stressing a decreasing social threat hypersensitivity and reducing eventually anger and aggression in patients with BPD. Similarly, according to the results of the study by Brüne et al. (38) oxytocin modifies the avoidant response to social threat in BPD patients, probably lowering stress level and inhibiting social withdrawal from distressing social stimuli.

3.3.2 Stress reactivity

Patients diagnosed with borderline personality disorder often describe their lives as stressful and unpredictable. In the study by Simeon et al. (16) a single-dose OXT administration in a group of BPD patients attenuated dysphoric emotional response and lowered the cortisol response to stress. Lischke et al. (41) showed that oxytocin decreased amygdala and insula reactivity in BPD patients, suggesting that oxytocin may be capable of attenuating BPD patients' stress and hypersensitivity for complex scenes, irrespective of their valence.

3.3.3 Empathy and approach motivation

Dysfunction of empathy and related processes in patients with BPD has been widely suggested. Domes et al. (42) give evidence of a beneficial effect of a single dose of oxytocin on affective empathy and approach motivation in women with BPD adapting their level of social functioning to healthy controls with important clinical implications for the future treatment of the disease.

Although promising results that can lead to further investigations on oxytocin as a possible treatment for BPD, OXT didn't show an impact on other elements of the disease.

3.3.4 Nonverbal behavior

Nonverbal behavior consists of actions that can indicate an individual's attitudes or feelings without speech. Nonverbal behavior can be apparent in facial expressions, gaze direction, interpersonal distance, posture and postural changes, and gestures. It serves several functions, including providing information to other people (if they can detect and understand the signals), regulating interactions among people, and revealing the degree of intimacy among them. Nonverbal behavior is often used synonymously with nonverbal communication, even though nonverbal actions are not always intended for, or understood by, other people.

Oxytocin seems to have a negative impact on nonverbal behavior, an important factor in interpersonal relationships.

Brüne et al. (43) analyzed the impact of OXT in modifying non-verbal signs in BPD patients and they didn't find any positive change in their non-verbal communication after OXT administration. Instead, oxytocin acted in a pro-social way in clinically healthy subjects. Oxytocin administration seems also to worsen non-verbal synchrony in BPD patients, while OXT administration enhances non-verbal synchrony in mentally health subjects.

3.3.5 Mentalizing

Mentalizing -the accurate understanding of mental states- is a domain belonging to social cognition. Two types of mentalizing errors have been described: Hypo-mentalizing errors are simplistic interpretations of social cues, likely due to deficits in social information processing. Hyper-mentalizing errors are distorted misinterpretations of social cues, likely due to hypersensitivity to social stimuli. As demonstrated by the results of Fisher et al. (44) and Ha et al. (45) OXT doesn't positively affect the hyper-mentalizing phenomenon in BPD patients; instead OXT seems to worsen it due to intensifying.

3.3.6 Trust and cooperation

Oxytocin, although it has been regarded colloquially as a prosocial hormone, has a trust-lowering effect in BPD, which was correlated with patients' history of childhood trauma (46). The study by Bartz et al. (18) highlights the effect on trust in BPD patients and agrees with previous studies that OXT does not uniformly facilitate trust and pro-social behavior in humans; in fact, OXT may impede trust and pro-social behavior depending on psychiatric diagnosis (e.g. BPD) and/or chronic interpersonal

insecurities combined with situational factors that heighten those insecurities.

3.3.7 Cardiac alterations in BPD

Heart rate variability (HRV) is the physiological phenomenon of variation in intervals between heartbeats. It is measured by the variation in the beat-to-beat interval. HRV is related to emotional arousal and alterations of HRV is related to many psychiatric disorders.

Reduced heart variability (HRV) is associated with self-regulatory deficit in BPD. Back et al. (47) investigated the possibility of modification of HRV in the resting state of BPD patients by oxytocin. Their results showed OXT did not have a significant effect in the modification of the HRV. Furthermore, oxytocin administration, according to the study by Schmitz et al. (48), doesn't modify heartbeat-evoked potentials (HEPs) as a marker of the cortical representation of cardiac signals in BPD.

4 Discussion

This is, to our knowledge, the first extensive review about the role of oxytocin in borderline personality disorder and its possible contribution as a treatment.

The interplay between maternal and infant oxytocin (OXT) systems highlight their crucial role in attachment development (5, 9–11). The quality of parental care is impacted, as it modulates a child's physiological and psychological infrastructures, potentially influencing gene expression. In patients with Borderline Personality Disorder (BPD), disruptions in the oxytocin system are implicated in attachment difficulties and resistance to compassion.

The findings suggest that attachment styles might be linked to oxytocin plasma levels, particularly in BPD patients. Those with anxious-avoidant attachment styles exhibit higher oxytocin levels compared to those with anxious-preoccupied styles. Furthermore, individuals with unresolved attachment representations show lower baseline oxytocin levels. This supports the hypotheses that oxytocin may play a role in susceptibility to rejection and avoidance behaviors, an epitome of BPD. Furthermore, early life stress, including maltreatment, can influence oxytocin levels and its receptor expression, potentially contributing to BPD development.

Therapeutically, the comprehension of the role of oxytocin in attachment and compassion could support interventions like Compassion-Focused Therapy (CFT). Addressing oxytocin-related deficits in BPD patients may be crucial for improving their responsiveness to compassionate care (5).

Moreover, oxytocin's influence on mother-child relationship underscores its importance in sensitive caregiving. BPD mothers show altered oxytocin and cortisol reactivity after interacting with their children, which may influence parent-child bonding.

Early life stress and genetic factors influence oxytocin levels and receptor expression, impacting BPD development (17, 22, 24–26, 29). Research suggests that childhood maltreatment may lead to oxytocin system alterations, contributing to BPD symptoms.

Genetic variations in the oxytocin receptor gene (OXTR) are linked to social and emotional skills, as well as psychopathology. Gender differences and gene-environment synergy further complicate the relationship between OXTR polymorphisms, childhood maltreatment, and BPD traits. The "threat hypersensitivity" core of BPD symptoms is associated with oxytocin deficiencies, affecting emotional regulation and social cognition. Research indicates correlations between oxytocin levels and emotional dysregulation, aggression, and interpersonal dysfunction in BPD patients.

Studies highlight oxytocin's modulation of stress reactivity, empathy, and approach motivation in BPD patients. However, oxytocin administration doesn't improve all BPD symptoms. It may exacerbate non-verbal communication deficits, hyper-mentalizing, and trust issues in BPD patients, potentially due to their history of childhood trauma.

The therapeutic potential of oxytocin for BPD is complex and varied. While some studies suggest benefits in reducing emotional dysregulation, aggression, and stress reactivity, others indicate no significant effects or even negative impacts on trust, empathy, and non-verbal behavior.

5 Conclusion

In conclusion, this comprehensive overview provides valuable insights into the intricate role of oxytocin in borderline personality disorder (BPD) and its potential as a treatment option.

Attachment styles appear to correlate with oxytocin plasma levels, particularly in BPD patients, suggesting a potential role for oxytocin in susceptibility to rejection and avoidance behaviors typical of this disorder. Moreover, early life stress, including maltreatment, can influence oxytocin levels and receptor expression, contributing to BPD development. Genetic polymorphisms in the oxytocin receptor gene (OXTR) make the relationship between oxytocin, childhood maltreatment, and BPD traits more complicated, suggesting a potential gene-environment interaction in BPD development.

From a therapeutic point of view, while studies indicate correlations between oxytocin levels and emotional dysregulation, aggression, and interpersonal dysfunction in BPD patients, the therapeutic promise of oxytocin for BPD remains challenging and varied. While some studies suggest benefits in reducing emotional dysregulation, aggression, and stress reactivity, others show no

significant effects or even negative impacts on trust, empathy, and non-verbal behavior.

Overall, this review highlights the multifaceted nature of oxytocin's involvement in BPD and emphasizes the need for further research to clarify its therapeutic potential and mechanisms of action in treating BPD symptoms.

Author contributions

EdG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EA: Data curation, Formal analysis, Investigation, Writing – original draft. JS: Funding acquisition, Visualization, Writing – review & editing. AA: Data curation, Formal analysis, Investigation, Writing – original draft. MC: Funding acquisition, Supervision, Writing – review & editing.

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Personality disorders in individuals with functional seizures: a systematic review

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Functional seizures (FS) are classified as conversion disorders in the DSM-5 and dissociative disorders in the ICD-11, showing a multifactorial psychopathology with various psychiatric comorbidities, such as depression and anxiety. Several studies have found a correlation between FS and personality disorders, mainly those in cluster B. Within this cluster, borderline personality disorder (BPD) or borderline personality traits are the most prevalent in FS. Emotion dysregulation is a hallmark of BPD and is commonly reported in individuals with FS. Cluster C personality disorders, such as avoidant or obsessive-compulsive disorders, have also been reported in FS. In this review, we aim to evaluate the relationship between FS and personality disorders. Assessing personality disorders in the context of FS is relevant for determining the most appropriate intervention. Cognitive-behavioral therapy (CBT) is considered the first-line approach to treating FS. Among various CBT strategies, dialectical behavior therapy, which specifically targets emotion dysregulation, may be helpful for individuals with BPD. Future research should assess the advantages of systematically evaluating personality disorders in FS to address specific treatment planning and evaluate its effectiveness on seizure recurrence, psychological comorbidities, and quality of life.

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KEYWORDS

functional seizures, personality disorders, cluster B personality disorder, borderline personality disorder, emotion dysregulation, dialectical-behavior therapy

1 Introduction

Psychogenic nonepileptic seizures, also known as functional seizures (FS), are defined as paroxysmal altered motor, sensory, autonomic, and/or cognitive signs and symptoms that resemble an epileptic seizure but are not caused by ictal epileptiform activity (1). FS are classified as a subgroup of conversion disorders (functional neurological symptom disorder)

according to the DSM-5 (2) or as a dissociative neurological symptom disorder with non-epileptic seizures in the ICD-11 (3). The diagnosis reaches the highest certainty level recording a typical event at video-EEG (1). FS are frequently mistaken for epilepsy, delaying the correct diagnosis by an average of 7 years (4, 5). The misdiagnosis leads to inappropriate treatment, with a significant impact on quality of life, morbidity, and healthcare costs (1, 6). In the general population, FS have an estimated incidence of 1.4–4.9/100,000/year and a prevalence between 2 and 33 cases per 100,000 (7). Several theoretical models have been proposed to explain FS development (8, 9). Initially interpreted as a dissociative phenomenon, FS have been derived from a breakdown in psychological integration in response to intense stress or emotion, appearing as a sensorimotor flashback when traumatic dissociated material comes into consciousness (7). Accordingly, the prevalence of traumatic life events varied from 44% to 100% in FS. In particular, sexual abuse is three times more common among FS individuals, ranging from 6% to 85% (7, 10). In addition, childhood emotional neglect, defined as the carelessness of the affectional needs of a child, demonstrated a strong association with FS. Noteworthy, not all individuals reported past exposure to traumatizing events, configuring trauma as neither a necessary nor sufficient condition. Subsequent theory interpreted FS as avoidant/defensive reaction in response to overwhelming situations or traumatic experiences in individuals with low capacity for coping stressful life events (7). A variant of this model interprets FS as a physical component of emotional states not recognized or misinterpreted by individuals due to their inability to identify and/or name emotions (i.e., alexithymia) seen as unacceptable. A further model explains FS as learned behavior maintained by positive or negative reinforcement thanks to intrinsic/extrinsic benefits, like reducing anxiety, relieving duties, or getting attention (8). Recently, "integrative cognitive model" conceptualized FS as behavioral paroxysms resulting from automatic activation of learnt mental representations, defined "seizure scaffold" (7). In detail, an attack's semiology depends on the content of the scaffold, acquired from internal (as direct symptom experience) or external (as attendance of symptom) sources (11).

FS comprehend concomitant heterogeneous psychiatric disorders, ranging from 53 to 100% (12, 13), and being able to represent predisposing/precipitating factor, underlying etiology, or consequence (14). Depression demonstrated a prevalence rate varying between 8.9% and 100% (13). Suicide risk has been shown to be greater in people with FS compared to the general population (15). Furthermore, the prevalence of anxiety disorders varied between 4.5% and 70%, including panic disorder and generalized anxiety disorder. FS individuals meeting the criteria for post-traumatic stress disorder (PTSD) ranged from 7% to 100% (13). Personality disorders (PDs) demonstrated a high prevalence among people with FS, up to 75% in some reports (13). Within PDs, cluster B, mainly borderline PD (BPD), appears as the most common personality phenotype (15, 16). Interestingly, FS and BPD seem to have some mutually common aspects, sharing a history of traumatic experiences, depression, and PTSD (17). Moreover, emotional dysregulation, considered a BPD hallmark, is commonly described in FS (18). Likewise, cluster C PDs, such as avoidant or obsessive-compulsive, have also been reported in FS (9). Assessment of PDs in the context of FS could be particularly relevant in choosing therapeutic intervention.

As widely recognized, psychotherapy, including cognitive-behavioral therapy (CBT), is the most commonly used approach to treating FS (19). Dialectical-behavior therapy (DBT) is a form of CBT specifically developed for BPD targeting emotion dysregulation and has proved efficacy in FS (9, 20). Therefore, investigating BPD in FS individuals could be relevant to tailoring a therapeutic approach. Nevertheless, few studies evaluated the frequency of PDs in individuals with FS using DSM IV/V criteria. Moreover, systematic analysis of PD clusters found in FS is currently unavailable (13).

This systematic review aims to assess the following in the adult FS population: I) prevalence of PDs diagnosed according to DSM-IV/V or ICD-10/11; II) frequency of clusters A, B, and C in studies evaluating personality phenotypes; and III) PDs and their cluster rates compared to individuals with epilepsy across studies considering both groups.

2 Materials and methods

2.1 Search strategy and selection criteria

This review, following PRISMA guidelines (21), focuses on primary research articles published between 1950 and 2024. Studies excluded from this review include unpublished research, review articles, editorials, letters, case studies, case reports with less than five individuals, and meta-analyses. The protocol is available online on PROSPERO (https://www.crd.york.ac.uk/PROSPEROFILES/509286_STRATEGY_20240203.pdf) with registration number: CRD42024509286.

Databases PubMed, OVID Medline, and PsycINFO were searched, including the following terms:

("PNES" OR "psychogenic non-epileptic seizure*" OR "psychogenic non-epileptic seizure*" OR "psychogenic nonepileptic seizure*" OR "non-epileptic seizure*" OR "functional seizure*" OR "dissociative seizure*" OR "psychogenic seizure*" OR "pseudoseizure*" OR "pseudo-seizure*") AND ("personality disorder*" OR "personality disease*" OR "borderline personality disorder*" OR "cluster-a personality disorder*" OR "cluster-b personality disorder*" OR "cluster-c personality disorder*" OR "narcissistic personality disorder*" OR "avoidant personality disorder*" OR "dependent personality disorder*" OR "obsessive-compulsive personality disorder*" OR "passive-aggressive personality disorder*" OR "schizotypal personality disorder*" OR "schizoid personality disorder*" OR "paranoid personality disorder*" OR "depressive personality disorder*" OR "antisocial personality disorder*" OR "histrionic personality disorder*").

The * indicates that any combination of letters after the initial string was accepted. All search words were not case-sensitive.

This search, performed on 03 February 2024, returned 70 articles on PubMED, 19 on OVID Medline, and 82 on PsycINFO (Figure 1).

After the removal of duplicated articles, the combined searches produced 123 articles. No further papers were identified after searching the reference list of the included articles.

2.2 Papers' assessment for eligibility

Each qualifying article underwent a thorough evaluation based on the following inclusion and exclusion criteria: availability of the full text, written in English, primary research article (case reports with ≥5 individuals were included), related to humans with FS, studies enrolling individuals aged ≥18 years, and PDs diagnosed according to DSM-IV/V or ICD-10/11. Restrictions on the publication's year were not applied. Papers regarding PDs in infants or adolescents were not considered for this review because our aims included the frequency of all PDs, and the diagnosis of antisocial PD requires at least an age of 18 years in accordance with DSM-V criteria (2).

Three independent reviewers (IM, IS, and FF) assessed each article by title and abstract/full text to determine eligibility, comparing their results. Any discrepancies were resolved through consensus among the review team (IM, IS, FF, LM, and AG).

2.3 Data extraction

For each article, the following data were extracted: study setting; study population and participants' demographics and baseline characteristics; study design; year of publication; main outcome (frequency of PDs in individuals with FS); secondary outcomes (frequency of any PD phenotype in people with FS and, where available, in those with epilepsy); and information for risk of bias assessment. Three people independently extracted the data. Any disagreements were resolved by reaching a consensus within the review team.

2.4 Risk of bias

Two sources of bias were considered: inclusion bias and reporting bias in the included studies. To mitigate inclusion bias, each article was assessed by three independent and blinded reviewers. Any discrepancies between reviewers were resolved by reaching a consensus within the three-person review team. After the included articles were selected, the list was assessed by an additional reviewer (AG), and any problematic articles were thoroughly discussed within the team. We also rated each article according to the modified Newcastle-Ottawa Scale (NOS) for cross-sectional studies (22).

2.5 Statistical analysis (meta-analysis)

For articles that compared the prevalence of PDs and their relative clusters between FS and epileptic seizure groups, a meta-analysis was conducted using Cochrane's Review Manager Web tool (RevMan Web) (https://revman.cochrane.org) (23). As the considered variables are dichotomous outcomes, the Mantel-Haenszel method was used to provide the odds ratio (OR) along with its 95% confidence interval (CI) pooled in a forest plot. Heterogeneity across the analyzed studies was evaluated through the Cochrane Q test (χ^2 test) and the I-squared index (I^2). A p-value of <0.05 was considered statistically significant. Publication bias was assessed using funnel plots.

3 Results

3.1 Study selection

As reported in Figure 1, out of the 123 articles reviewed, 13 were excluded due to full-text unavailability, 6 articles were not in English, 42 were not classified as primary research articles, 8 articles regarded individuals with age <18 years, 34 had not been diagnosed with PDs according to DSM-IV/V or ICD-10/11, and 6 articles were not related to FS individuals.

After manual assessment, 14 (Table 1) articles met the inclusion criteria and were retained for further analysis. The scoring of all reviewed articles is detailed in Supplementary Table 1. At the risk of bias assessed through NOS, 4/14 (24–27) and 10/14 (17, 28–36) studies obtained medium-quality (4–6 stars) and high-quality (at least 7 stars) judgments, respectively (Table 2).

3.2 Features of the included studies

Table 1 summarizes the clinical characteristics of the enrolled individuals, the edition of the DSM or ICD used for PD diagnosis, the methods used for personality assessment, and the main results of all 14 studies included. In all papers included, participants have no intellectual disability, comorbidity, or other relevant conditions, such as epilepsy or drug abuse. Noteworthily, individuals with FS alone were considered for analysis. The sample size varied from 20 to 111 across studies. The age of FS participants ranged from 18 years to 65 years (mean age: 34.9). Concordantly to the literature, the female sex is preponderant across studies, reaching 65% of the study population. In 13/14 studies (17, 24–31, 33–36), the FS diagnosis required the recording of typical events on video-EEG, reaching the "documented" level in accordance with the latest diagnostic criteria (1). In one study (32), FS were determined according to the criteria of the Non-epileptic Seizures Task Force of the International League Against Epilepsy (ILAE), including individuals with diagnostic levels indicated as "probable," "clinically established," and "documented" (1). Groups used as FS comparisons were not homogenous among the included studies. In detail, 5/14 studies enrolled people with epilepsy (17, 28, 31, 33, 34), 2/14 individuals with FS plus epilepsy (29, 32), and 1/14 individuals with a diagnosis of a functional disorder different from FS (35); in two cases, individuals with FS and individuals with epilepsy were evaluated in comparison to healthy subjects (30) and people with FS plus epilepsy (36), respectively.

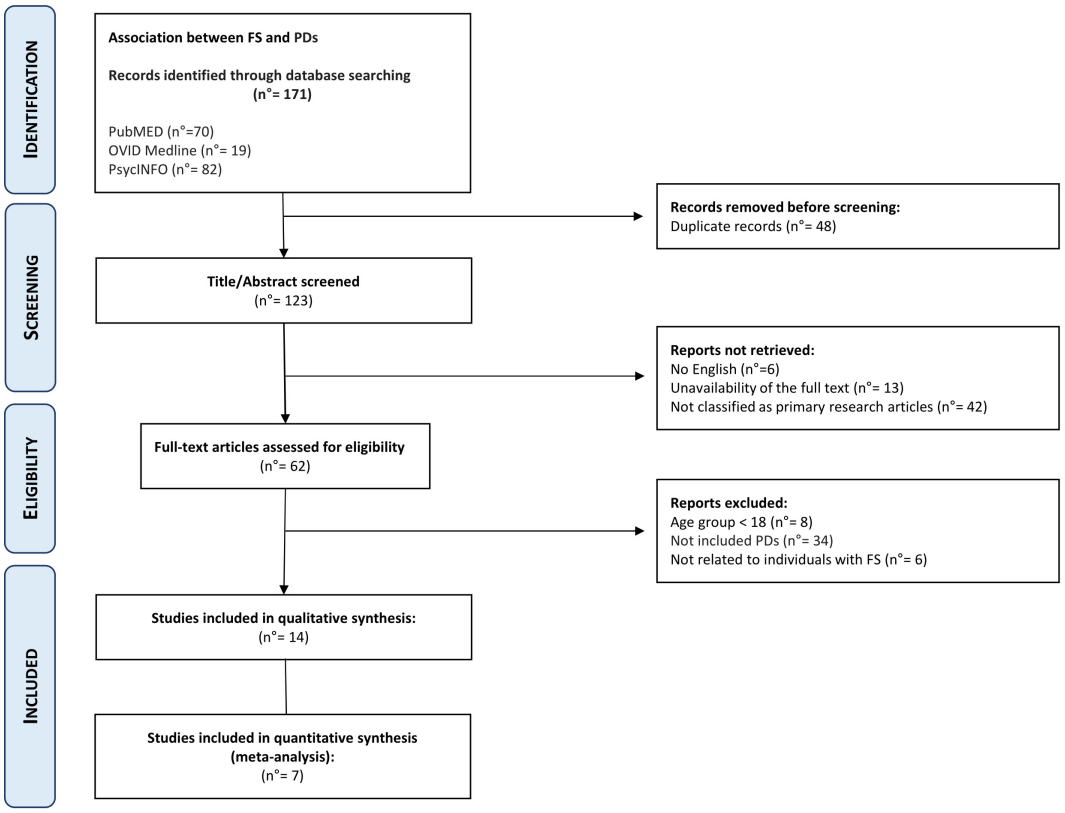

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) study flowchart.

3.3 Personality disorders in FS

The rate of PDs as comorbidity in FS ranged from 18% to 87%, with a mean of 53.7%. Diagnosis of PDs was made according to DSM-IV in 12/14 studies (17, 24, 26–31, 33–36) and ICD-10 in 2/14 (25, 32). In total, 12 out of 14 studies used the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID II) to assess PDs (17, 24, 26, 28–36), and in 2/14 cases, diagnosis was based on psychiatric evaluation (25, 27).

Ten out of 14 studies classified PDs in clusters (17, 24, 25, 27, 29–33, 36), and and in 3/14 cases only cluster B has been determined (26, 28, 35). Considering the 13/14 studies that analyzed cluster B, the rate of this personality phenotype varied between 41.7% and 84.6%, with a mean of 63.4% (26, 28, 35). Notably, 10 out of 14 studies assessed the prevalence of cluster A and cluster C. Cluster A subtype ranged from 0% to 48.3%, with a mean of 12.4%. Cluster C demonstrated a frequency between 7.7% and 75.9%, with a mean of 31.6% (17, 24, 25, 27, 29–33, 36). Four out of 14 studies described other PD phenotypes that did not meet the criteria for a specific personality cluster (24, 25, 27, 32). In detail, two studies described 12 individuals with organic PDs (5.1%) (25, 27), one reported three PDs not otherwise specified (1.3%) (24), the remaining counted seven personality changes after stress (3%) and two cases with combined PDs (0.9%) (32).

Moreover, 7 out of 14 studies differentiated subtypes of PDs within each cluster (24, 25, 27, 30, 32, 33, 36). Noteworthy, an individual could receive more than one PD diagnoses. Within cluster A, 11 individuals had paranoid PD (6.2%), 9 had schizoid PD (5.1%), and 7 had schizotypal PD (3.9%). Regarding cluster B, 2 individuals were diagnosed with antisocial PD (1.1%), 101 with BPD (56.7%), 19 with histrionic PD (19%), and 20 with narcissistic PD (11.2%). In relation to cluster C, 35 individuals had avoidant PD (35%), 24 dependent PD (13.5%) and 19 obsessive-compulsive PD (19%). One study reported 16 cases of passive-aggressive PD and 15 cases of depressive PDs, in accordance with the criteria reported in Appendix B of DSM-IV (33). These PDs are no longer listed in the DSM-V but fall under the category of other specified/unspecified personality disorder subclinical diagnoses (2).

Furthermore, 7 out of 14 studies used individuals with epilepsy as a comparison group to the FS cohort (17, 28, 30, 31, 33, 34, 36). Combining these studies suitable for meta-analysis, OR resulted greater than 1, indicating that individuals with FS have nearly three times the odds to have PDs than people with epilepsy (OR=2.81; 95% CI=1.86-4.25; I2=0%; p<0.00001), as reported in Figure 2. Testing Cluster B prevalence, individuals with FS demonstrated a four-time increased OR to have this PD phenotype compared to epilepsy population (OR= 4.61; 95% CI=2.43-8.74; I2=0%; p<0.00001), as displayed in Figure 3. Five out of 14 studies evaluated differences in cluster A and cluster B between FS individuals and people with epilepsy. In detail, people with FS demonstrated an OR less than 1 for cluster A PDs compared to the epilepsy population (OR=0.68; 95% CI=0.35–1.30; I^2 = 62%; p=0.024), as represented in Figure 4.

TABLE 1 Characteristics and results of the included studies.

Author	Year	FS, n°	Age	Diagnostic criteria	Other groups enrolled	Personality assessment	PDs, n° (%)	Cluster A, n° (%)	Cluster B, n° (%)	Cluster C, n° (%)	Other PDs, n° (%)
Bailles et al. (24)	2004	30	34.1 ± 12.7	DSM IV	None	SCID II	18/ 30 (60%)	1/18 (5.6%)	12/18 (66.7%)	2/18 (11.1%)	3/18 (16.7%)
Binzer et al. (28)	2004	20	27	DSM IV	20 with epilepsy	SCID II	13/ 20 (65%)	–	7/13 (53.8%)	–	–
D'alessio et al. (29)	2006	24	33.42 ± 14.08	DSM IV	19 with FS + epilepsy	SCID II	17/ 24 (71%)	1/17 (5.9%)	8/17 (47.1%)	8/17 (47.1%)	–
Direk et al. (30)	2012	35	29.1 ± 9.2	DSM IV	35 with epilepsy 37 healthy subjects	SCID II	26/ 35 (74%)	1/26 (3.8%)	21/26 (80.7%)	13/26 (37.1%)	–
Harden et al. (31)	2009	16	45	DSM IV	16 with epilepsy	SCID II	13/ 16 (81%)	4/13 (30.7%)	11/13 (84.6%)	1/13 (7.7%)	–
Hovorka et al. (25)	2007	56	29.6 ± 10,1	ICD-10	None	Structured psychiatric interview	25/ 56 (44.6%)	1/25 (4%)	18/25 (72%)	4/25 (16%)	2/25 (8%)
Labudda et al. (32)	2018	67	37.7 ± 12.3	ICD-10	42 with FS + epilepsy	SCID II	24/ 67 (35.8%)	–	10/24 (41.7%)	5/24 (20.8%)	9/24 (37.5%)
LaFrance et al. (26)	2010	38	36.2 ± 13.2	DSM IV	None	SCID II	20/ 38 (52.6%)	–	10/20 (50%)	–	–
Nez˘a´dal et al. (27)	2011	111	31.2 ± 9.7	DSM IV	None	Psychiatric evaluation	52/ 111 (46.8%)	1/52 (1.9%)	33/52 (63.5%)	8/52 (15.4%)	10/52 (19.2%)
Rady et al. (33)	2021	33	31.15 ± 7.92	DSM IV	33 with epilepsy	SCID II	29/ 33 (87.9%)	14/29 (48.3%)	23/29 (79.3%)	22/29 (75.9%)	–
Salinsky et al. (34)	2019	73	46	DSM IV	64 with epilepsy	SCID II	30/ 73 (41.8%)	–	–	–	–
Scévola et al. (17)	2013	35	37.54 ± 14.07	DSM IV	49 with epilepsy	SCID II	25/ 35 (71.43%)	5/25 (20%)	15/25 (75%)	11/25 (44%)	–
Stone et al. (35)	2004	20	27	DSM IV	30 with functional disorder different form FS	SCID II	13/ 20 (65%)	–	7/13 (53.8%)	–	–
Turner et al. (36)	2011	22	40.2 ± 14.5	DSM IV	21 with epilepsy 10 with FS + epilepsy	SCID II	4/22 (18%)	1/4 (25%)	2/4 (50%)	–	1/4 (25%)

DSM, Diagnostic and Statistical Manual of Mental Disorder; FS, functional seizures; ICD, International Classification of Disease; PDs, personality disorders; SCID-II, Structured Clinical Interview for DSM-IV Axis II disorders.

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TABLE 2 Quality assessment of included articles through the modified Newcastle-Ottawa Scale for cross-sectional studies.

References	Selection[a]				Comparability[b]	Outcome[c]		Total quality score
	(1) Representativeness of the sample	(2) Sample size	(3) Non-respondents	(4) Ascertainment of exposure	(1) Comparability of individuals based on the design or analysis	(1) Assessment of the outcome	(2) Statistical test	
Bailles et al. (24)	*	*	*	*		**		6
Binzer et al. (28)	*	*	*	*	**	**		8
D'alessio et al. (29)	*	*	*	*	**	**		8
Direk et al. (30)	*	*	*	*	**	**		8
Harden et al. (31)	*	*	*	*	**	**		8
Hovorka et al. (25)	*	*	*	*		**		6
Labudda et al. (32)	*	*	*	*	**	**		8
LaFrance et al. (26)	*	*	*	*		**		6
Nez˙a´dal et al. (27)	*	*	*	*		**		6
Rady et al. (33)	*	*	*	*	**	**		8
Salinsky et al. (34)	*	*	*	*	**	**		8
Scévola et al. (17)	*	*	*	*	**	**		8
Stone et al. (35)	*	*	*	*	**	**		8
Turner et al. (36)	*	*	*	*	**	**		8

[a]A maximum of 5 stars can be awarded for the selection.
[b]A maximum of 2 stars can be awarded for comparability.
[c]A maximum of 3 stars can be awarded for the outcome.

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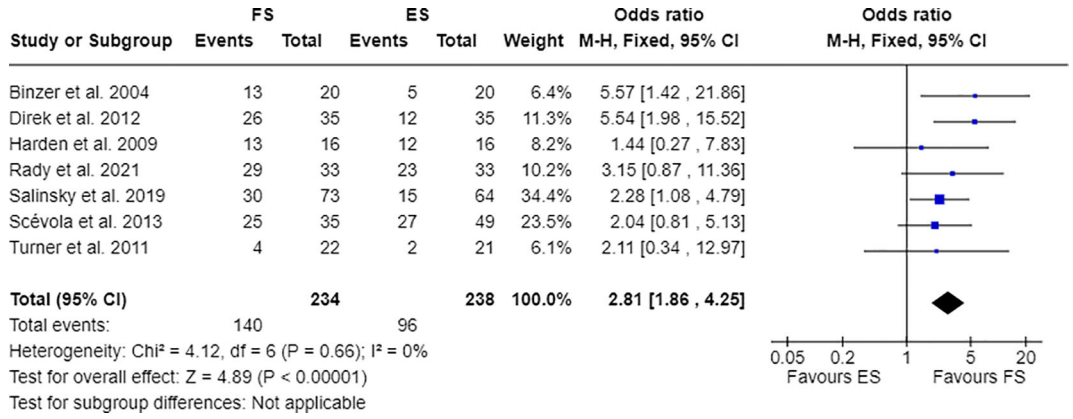

FIGURE 2
Meta-analysis of eligible studies comparing PDs between FS individuals and the epilepsy population (ES).

Similarly, FS individuals proved an OR less than 1 to present a cluster C in comparison with people with epilepsy (OR=0.63; 95% CI=0.34–1.16; I^2 = 52%; p=0.014), as delineated in Figure 5. The funnel plot displays a symmetric distribution of included studies, indicating no publication bias (Supplementary Figures 1–4).

4 Discussion

This systematic review illustrates that PDs represent a notable comorbidity in the FS population. When analyzing personality phenotypes, cluster B is the most common PD in FS, in accordance with previous literature data (9, 16). Although at inferior rates, cluster C and, even less, cluster A have been also attested. Among all PD phenotypes, BPD represents the most common diagnosis in FS, followed at an inferior rate by avoidant PD. In comparison to people with epilepsy, our meta-analysis demonstrated in FS individuals an increased risk of having concomitant PD, particularly those belonging to cluster B. At the same time, clusters A and C appear less likely to occur in people with FS than in those with epilepsy.

In the literature, the association between FS and PDs is well recognized (13, 16). A previous systematic review documented a PDs' rate between 5.4% and 74.3%, while in an earlier work this comorbidity varied from 10% to 86% in FS (16). In our analysis, the prevalence of PDs in FS falls subtly higher, ranging from 18% to 87%. Our slightly greater rate is likely due to mandatory criteria in including exclusively studies diagnosing PD in accordance with DSM-IV/V or ICD-10/11. Nonetheless, a wide disparity in PDs prevalence in FS population has been demonstrated among studies. In a previous review, this difference was attributed to a higher rate of PDs in individuals with a longer duration of FS (16). We did not confirm this trend in our work. It is not known whether differences in FS clinical semiology (such as motor and non-motor manifestations) or levels of dissociation could explain this disparity. Since not all studies included in the present review assessed these features, we were unable to conduct such an analysis. Cluster B PDs, particularly BPD, have been widely demonstrated as the most prevalent personality phenotype in FS (16). Our analysis confirmed BPD as the most frequent PD in FS, regarding more than half of this population. Other cluster B PDs have a lower frequency. In particular, although histrionic PD shares some traits with BPD, its frequency appears lower than that expected in FS, with a prevalence not exceeding 20%. Some reports describe cluster C subtypes of personality in FS.

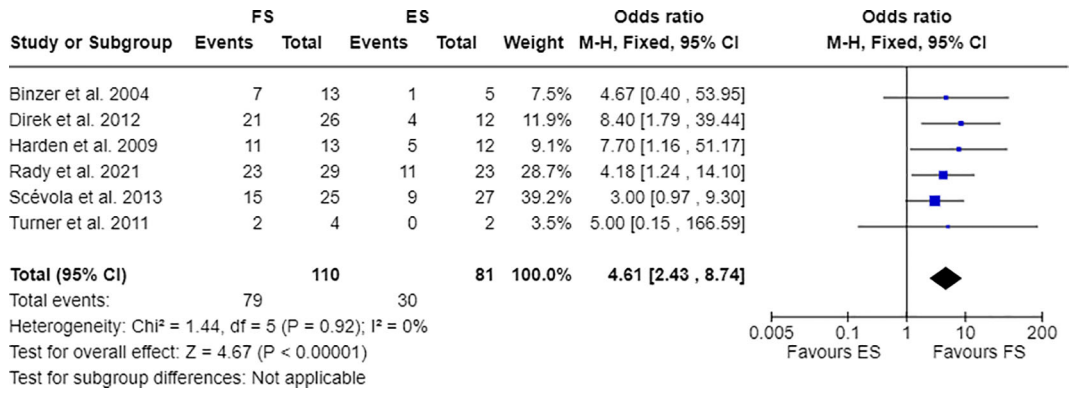

FIGURE 3
Meta-analysis of eligible studies comparing Cluster B PDs between FS individuals and the epilepsy population (ES).

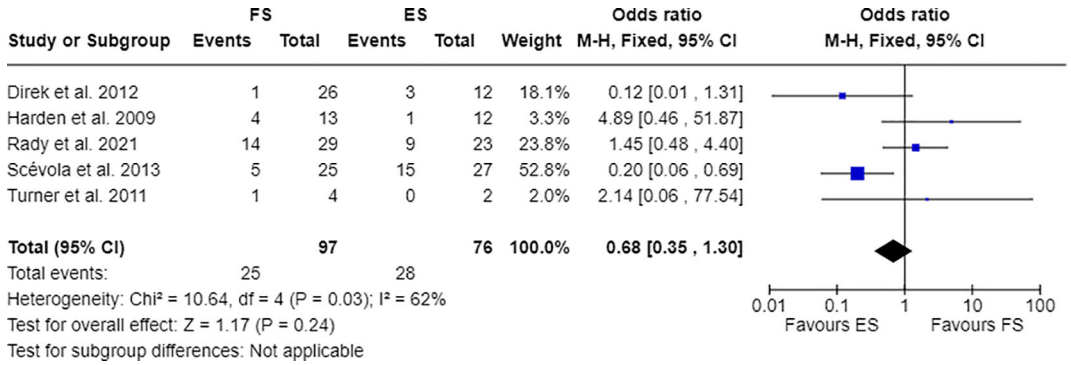

FIGURE 4
Meta-analysis of eligible studies comparing Cluster A PDs between FS individuals and the epilepsy population (ES).

According to our data, cluster C PDs, despite their prevalence can reach up to 75.9% in FS, proved a greater association to epilepsy. Similarly, a previous study reported cluster C more frequently in people with epilepsy than in those with FS (37).

BPD combines marked impulsivity, interpersonal relationships, self-image, and affects instability, consisting of rapidly shifts between extremely positive idealization and extremely negative devaluation about self and others (2, 20). The hallmark of BPD is emotional dysregulation, reflecting an inability to respond to and manage emotional transitions (16, 38). Notably, people with FS frequently exhibit emotional dysregulation and instability in interpersonal relationships (9, 16, 18). Additionally, individuals with BPD may commonly experience childhood sexual/emotional abuse or neglect and have higher rates of concurrent psychiatric disorders, such as depression or PTSD (20). Moreover, dissociative symptoms are included among the diagnostic criteria for BPD and may represent a psychological mechanism underlying FS development (7, 20). Likewise, the similarity between these conditions also includes anger problems, hostile coping styles and somatoform disorder in comorbidity. In this context, BPD might be interpreted as a predisposing etiological factor for FS (30). Interpreting psychiatric disorders in FS as mere comorbidities could be misleading (12). The high heterogeneity in FS clinical and psychiatric manifestations likely reflects the wide range of underlying psychopathologies (30). Conversely, psychiatric comorbidities might contribute to poor outcomes in FS, acting as perpetuating factors (6).

Regardless of their relationship, the identification of psychiatric disorders in FS, especially PDs, significantly impacts treatment choice. Currently, psychotherapy is the first-line therapy for both FS and BPD (19, 20). CBT has been widely demonstrated to reduce attack frequency and improve quality of life in individuals with FS (19, 26, 39). To date, two CBT approaches for FS have been evaluated through randomized controlled trials. The CBT developed by Goldstein targets factors involved in the development and maintenance of attacks, interpreting FS as dissociative responses. The CBT model reported by LaFrance promotes behavior and self-control, addressing both seizures and comorbidities (19). Among the psychotherapies available for BPD, DBT was developed in accordance with Linehan's biosocial theory, which conceptualizes BPD as a pervasive dysregulation disturbance with great emotional vulnerability and a deficient ability to modulate emotions (40). DBT includes skill modules such as mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance (20, 41). In this regard, mindfulness-based therapy has shown efficacy in FS. As mentioned above, individuals with FS could be overwhelmed by their emotions, becoming detached from them as an adaptive strategy. Mindfulness increases awareness of feelings and reinforces attention to body symptoms and their misattribution (42). In this light,

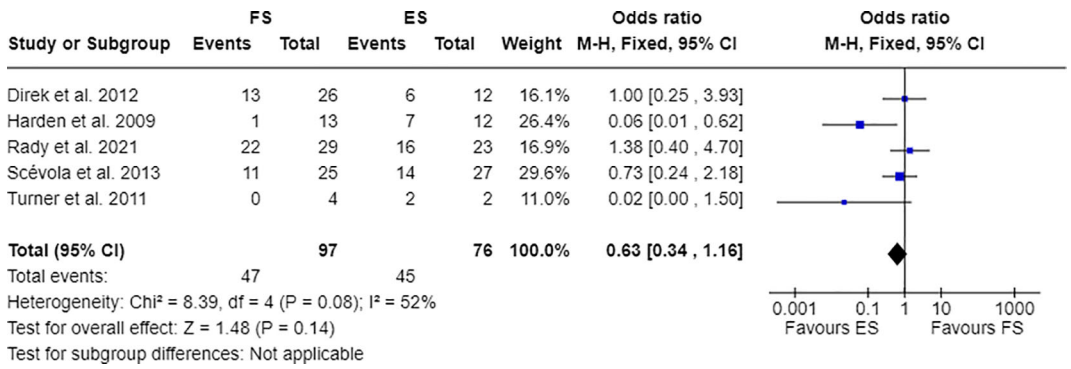

FIGURE 5
Meta-analysis of eligible studies comparing Cluster C PDs between FS individuals and the epilepsy population (ES).

characterizing concomitant psychiatric disorders allows for the individualization of treatment for FS. As mentioned above, individuals with FS may exhibit various psychopathologies, such as a dissociative response to a previous traumatic life event, a maladaptive response to overwhelming situations, or the automatic activation of learned mental representations. As expected, different etiopathologies and underlying defense mechanisms have been demonstrated to influence treatment. However, psychotherapy for FS tailored to concomitant psychiatric disorders has not yet been thoroughly investigated.

The present review has some limitations. The main limitation is the small FS sample size in each included study. Nevertheless, FS diagnosis appears quite homogeneous across studies, reaching the "documented" level in almost all cases (1). Moreover, half of the included studies evaluated the prevalence of each PD subtype, further restricting the data analysis. Additionally, the comparison groups to FS are sufficiently heterogeneous, comprising healthy subjects, people with epilepsy, and individuals with FS plus epilepsy. The epilepsy population was the most numerically represented across the included studies, allowing for a meta-analysis.

In conclusion, PDs have been shown to be a common comorbidity in FS. Cluster B, especially BPD, demonstrated a high prevalence in individuals with FS. Evaluating the presence of PDs, particularly BPD, may have relevance in personalizing FS treatment. Psychotherapy tailored to concomitant psychiatric disorders could be more effective in reducing the recurrence of attacks and improving quality of life. Systematic investigation of therapeutic approaches structured around psychiatric comorbidity is currently not available (39). Further studies are needed to clarify the potential benefits of selecting psychotherapy based on the psychiatric comorbidity of an individual, especially PDs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

IS: Conceptualization, Data curation, Formal analysis, Writing – original draft. IM: Conceptualization, Data curation, Writing – review & editing. LM: Conceptualization, Data curation, Writing – review & editing. FF: Conceptualization, Formal analysis, Methodology, Writing – review & editing. AG: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1411189/full#supplementary-material

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Clinical characteristics of adults with alcohol dependence syndrome comorbid with antisocial personality disorder: a cross-sectional study

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Introduction: Antisocial Personality Disorder (ASPD) is characterized by a pervasive pattern of disregard for and violation of the rights of others, typically emerging by age 15 years and involving behaviors such as deceitfulness, impulsivity, and aggressiveness. The present study sought to examine the prevalence of the comorbid ASPD in adult people with Alcohol Dependence Syndrome (ADS) and identify clinical characteristics associated with ASPD.

Methods: A cross-sectional study of 100 consecutive subjects diagnosed with ADS was conducted. Subjects were examined between August 2023 and September 2023. Various assessments and questionnaires were employed, including the Montreal Cognitive Assessment (MoCA), Alcohol Use Disorders Identification Test (AUDIT), and Structured Clinical Interview for DSM-IV (SCID-II). A computed tomography (CT) scan of the brain was performed on 47.5% participants.

Results: Out of the 100 individuals screened for the study, 20 were excluded. The study found that 35% of the examined study participants had a comorbid ASPD. Individuals with both ADS and ASPD were more likely to be younger, started drinking at an earlier age, had higher hospitalization rates, and scored higher on the AUDIT test (all $P < 0.05\%$). Also, they had lower education levels, higher rates of unemployment, and lower marriage rates (all $P < 0.05\%$). In addition, they reported more family members with ADS, incarceration, or mental illness and a higher frequency of traumatic experiences (all $P < 0.05\%$). Depression, anxiety, stress (all $P < 0.05\%$), and sleep problems ($P = 0.058$) were correlated with ASPD. Participants with the comorbid ASPD had lower MoCA scores ($P = 0.046$) and struggled with attention and linguistic subtests compared to subjects with ADS only.

Conclusion: The study highlights the high prevalence of comorbid ASPD in participants with ADS, shedding light on their demographic and psychometric characteristics. Individuals with the comorbid ASPD are more likely to face

cognitive deficits, especially in linguistic and attention-related tasks. The findings underline the importance of considering the comorbidity of ASPD in ADS subjects. The study implies that the understanding of the associated risk factors can aid in developing more targeted treatment interventions.

KEYWORDS

depression, anxiety, cognition, antisocial, alcoholism, trauma, sleep

1 Introduction

Antisocial Personality Disorder (ASPD) is a pervasive pattern of disregard for and violation of the rights of others, with the average age of onset being 15 years; the diagnosis is based on three or more of the following indicators: failure to conform to social norms concerning lawful behaviors, deceitfulness, impulsivity, irritability, and aggressiveness, reckless disregard for the safety of self or others, consistent irresponsibility, and lack of remorse (1). To meet the diagnosis criteria, an individual must be at least 18 years old and have evidence of a Conduct Disorder (CD) with onset before the age of 15 years (2). The requirement of this childhood criterion serves to portray ASPD as a persistent personality disorder with roots early in development (3). Individuals with ASPD are more prone to be violent; they tend to violate the rights of others, be manipulative, commit crimes, and the disease produces extraordinary societal costs and aggregate social burden (2, 4). The maladaptive behaviors may include suicidal behavior, self-harm, aggression, criminal behavior, and substance misuse (2, 4).

Goldstein et al. (5) also found that individuals with ASPD are more likely to have comorbid substance misuse and other psychiatric disorders. The ASPD is associated with greater odds of any substance use disorder (SUD), specifically alcohol, nicotine, and any drug use disorder (6). Similarly, data from cohorts of prisoners has shown that alcohol dependence syndrome (ADS) shows high comorbidity with ASPD, suggesting that there may be common biological risk mechanisms (7). Furthermore, individuals with ASPD, SUD, and their co-occurrence (ASPD/SUD) have similar personality traits (8). Low agreeableness, low conscientiousness, high impulsivity, high excitement-seeking, low deliberation, and low self-discipline were characteristic of these disorders (8). The ASPD exhibited lower neuroticism than SUD and ASPD/SUD, which is consistent with the high levels of mood and anxiety disturbance often reported in individuals with SUD (8).

Alcohol dependence syndrome is characterized by alcohol use that causes serious impairment. It is characterized by preoccupation with alcohol, impaired control over drinking, usage of alcohol despite adverse consequences, and distortions in thinking. Alcoholism is characterized by craving, loss of control, withdrawal symptoms, and tolerance (9). Alcohol use disorder (AUD) is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as "a problematic pattern of alcohol use leading to clinically significant impairment or distress." An alcohol dependence syndrome aligns symptomatically with the current diagnoses of moderate or severe AUD as per DSM-5. To diagnose a patient with AUD, the patient needs to meet at least two criteria: alcohol usage in larger amounts or for longer periods than intended, unsuccessful efforts to cut down or control alcohol use, spending a long time in obtaining alcohol, using alcohol, or recovering from its effects, failure to fulfil major role obligations due to alcohol, reduction in activities due to alcohol, continued alcohol use despite having persistent or recurrent problems due to alcohol, recurrent alcohol use in situations in which it is physically hazardous, craving, tolerance, and withdrawal. Alcohol Dependence Syndrome is a chronic, relapsing brain disease that presents a significant public health issue (1). There are links between developmental changes in personality and alcohol use (10). Across adolescence and early adulthood, individuals with steeper declines in impulsivity and neuroticism demonstrated steeper declines in problematic alcohol use (10). Individuals with a less substantial decline (or even an increase) in impulsivity and neuroticism had either increases or smaller decreases in problematic alcohol use (10). Similarly, increases in risk-taking behavior across development are associated with increased alcohol use among adolescents (11).

The ADS remains to be the actual topic in the field of psychiatry. Although its exact etiology remains unknown, susceptibility to the disorder is likely multifactorial. The cultural aspects are likely to play a very important role in the prevention and treatment of ADS. In Slovakia, 75% of adults consume alcohol occasionally or regularly. Alcohol is socially more accepted than other substances, and in Slovakia, its consumption is socially promoted (12). Alcoholism is the most commonly seen psychiatric diagnosis amongst Slovakians, and 26.5% of all psychiatric hospitalizations are due to alcohol (13). To our knowledge, the present study is a first study analyzing the prevalence of ASPD amongst the Slovak population. In the present study, we compared the characteristics of subjects with ADS and ADS comorbid with ASPD and compared their cognitive abilities. Knowledge of any cognitive deficits associated with ASPD would be valuable in working toward understanding the neurobiology of

this disorder and its relationship with other conditions and developing more targeted treatment interventions.

2 Materials and methods

2.1 Study design and setting

The present study was a cross-sectional pragmatic study of 100 consecutive adult research participants with a diagnosis of ADS who were hospitalized in the 1st Department of Psychiatry, University Hospital of Louis Pasteur in Kosice. The study was conducted between August 2023 and October 2023. The exclusion criteria were as follows: the diagnosis of intellectual disability, dementia, delirium tremens, substance use disorder (other than alcohol, nicotine, and/or caffeine), the presence of significant withdrawal symptoms (Brief Alcohol Withdrawal score> 3 points), and the subject's disagreement to participate in the study. Out of the 100 individuals screened for the study, 20 were excluded. The reasons for the exclusion were either meeting the exclusion criteria, not signing the informed consent, or not filling out one or more questionnaires during the examination. The final statistical analysis included only subjects with completed data (80 participants).

The study was reviewed and approved by the Ethics Committee of the University Hospital of Louis Pasteur Kosice (study protocol number: 2023/EK/08045). The participants provided their written informed consent to participate in this study.

2.2 Methods

For participants, we obtained sociodemographic and clinical characteristics, including age, sex, and the presence of comorbidities. The information was obtained through the subjects' clinical interviews and medical records. The study used the following questionnaires: the Brief Alcohol Withdrawal Scale (BAWS), Montreal Cognitive Assessment (MoCA), the Alcohol Use Disorders Identification Test (AUDIT), the Depression, Anxiety, and Stress Scale-42 (DASS-42), the Pittsburgh Sleep Quality Index (PSQI), Structured Clinical Interview for DSM-IV, axis-II (SCID-II), Multifactorial Memory Questionnaire (MMQ), and The Adverse Childhood Experiences - International Questionnaire (ACE-IQ). If patients underwent computed tomography (CT) examination, we obtained these data from their documentation.

2.2.1 Cognition assessment

The MoCA (Montreal Cognitive Assessment) includes tasks focused on attention, visual-constructive abilities, executive functions, immediate and long-term memory, naming, abstract thinking, speech, and orientation (14).

All points for subtasks are added to the total score (14). The maximum number of points is 30 (+ 1 for education) (14). It is also possible to calculate scores for individual cognitive domains, which can be used for differential diagnostic considerations (15). If the resulting score is 26-30, cognitive abilities are normal; if the score is 18-25, there is mild cognitive impairment present; if the participants reach a score of 10-17, we speak of moderate cognitive impairment, and with a score below 10, we diagnose subjects with severe cognitive impairment (14, 15).

2.2.2 Dependence on alcohol assessment

The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item test that asks about domains of alcohol use (16). The first three items refer to risky alcohol consumption, the following three determine the occurrence of possible symptoms of addiction, and the last four statements deal with indicators of harmful alcohol consumption (16). Individual statements are evaluated on a 5-point scale (16). The resulting raw score can be 0–40 points (16). In interpreting the scores obtained, a score of 0–7 indicates low-risk drinking, a score of 8–15 indicates high-risk drinking, a score of 16–19 represents harmful drinking, and a score of 20–40 indicates alcohol dependence (16).

2.2.3 Quality of sleep assessment

We measured sleep quality using the PSQI questionnaire that evaluates sleep quality during the last month (17). It is a 19-item questionnaire, where each item is assigned a possible score from 0-3, with a higher score indicating a greater problem with sleep (17). This questionnaire evaluates seven components: Subjective sleep quality, sleep latency, sleep duration, awakening during the night, sleep efficiency, medication use to improve sleep, and daytime dysfunction (17). Calculating the scores for all seven components gives us the so-called global PSQI score; if it is > 5, it can distinguish individuals with poor sleep from those with good sleep (17).

2.2.4 Depression, anxiety, stress assessments

In the present study, the DASS-42 was used to measure participant's affectivity (depression, anxiety, and stress) (18). Participants agree with 42 items on a 4-point Likert scale (18). The depression scale allows us to assess the degree of dysphoria, hopelessness, anhedonia, self-loathing, inactivity, or lack of interest (18). The items in the anxiety scale are mainly focused on physiological reactions but also on experiencing situational anxiety (18). The stress scale contains items measuring the degree of irritability, impatience, excitement, or tension (18). Adding up the points of these items gives us final scores for depression, anxiety, and stress (18). A score of 0-9 points indicates the absence of depression, 10-13 points indicate mild depression, 14-20 points indicate moderate depression, 21-27 points indicate severe depression, and a score above 28 indicates extremely severe depression (18). A score of 0-7 points suggests the absence of anxiety, 8-9 points indicate mild anxiety, 10-14 points indicate moderate anxiety, 15-19 points indicate severe anxiety, and a score above 20 points indicates extremely severe anxiety (18). A score of 0-14 points indicates the absence of stress, 15-18 points indicates mild stress, 19-25 points indicates moderate stress,

26-33 points indicates severe stress, and a score above 34 indicates extremely severe stress (18).

2.2.5 Withdrawal symptoms assessment

The Brief Alcohol Withdrawal Symptoms Scale (BAWS) consists of 5 items (tremor, sweating, agitation, orientation, and hallucinations), with each item rated on a scale from 0 to 3, with higher scores indicating more severe withdrawal symptoms (19).

2.2.6 Metacognition assessment

The Multifactorial Memory Questionnaire (MMQ) was developed to assess several aspects of mnestic functions: emotions associated with memory performance, memory failures, and strategies used in the memory process (20–22). By calculation, we can evaluate subjectively perceived cognition as very low, low, below average, average, above average, good, and very good (21, 22).

2.2.7 Traumatization in childhood assessment

The ACE-IQ (Adverse Childhood Experiences – International Questionnaire) detects traumatic childhood experiences and divides them into 13 categories: physical and emotional abuse, sexual abuse, violence between household members, caring for a family member who is physically or mentally ill, suicidal tendencies, incarceration of a household member, family dysfunction such as the death of one or both parents, divorce or parental separation, emotional and physical neglect, alcohol and drug abuse in the family, collective violence and bullying (23). The resulting score is from 0-13; the higher it is, the more trauma a person has experienced (23).

2.2.8 Antisocial personality disorder assessment

The Structured Clinical Interview for DSM-IV, axis-II (SCID-II, personality disorders) is a diagnostic methodology for ten personality disorders. In our study, we focused only on antisocial personality disorder (24). In a structured interview, we asked the participant 17 questions, some of which were about a social behavior disorder in childhood/adolescence. If the total score was at least 3 points, we asked 14 questions specific to antisocial personality disorder (24). If the subject had at least three symptoms, the diagnosis of antisocial personality disorder was established (24).

2.3 Statistical analyses

We analyzed the data using descriptive statistics and cluster analysis. We used the Shapiro-Wilk test to determine the normality of the data distribution. Continuous variables were expressed as medians (p50) and interquartile ranges (IQR = p25 - p75). Categorical variables were expressed as absolute and relative counts. The results of the ordinal logistic regression models are expressed as the probability value (*P*), odds ratio (OR) with 95% confidence interval (95% CI), and standard deviation of the regression coefficient (SD). Patterns between categorical variables were examined using the chi-squared test. A comparison of interval variables between the two groups was performed using the Wilcoxon rank-sum test. A value was considered statistically significant if the *P*-value was less than 0.05. Statistical analyses were performed using Stata Special Edition statistical software Version 13.1 (StataCorp LP, College Station, TX).

3 Results

3.1 Sample characteristics and univariate analyses

A computed tomography (CT) scan of the brain was performed on 38 (47.5%) participants. Cortical cerebral atrophy was described in 33.8% of participants, and vascular changes were verified in 18.8%. Regarding comorbidities, 31.25% of patients were diagnosed with depressive disorder (25% with the diagnose other depressive episode, 6.25% with Major depressive disorder, recurrent, moderate), 6.25% of patients were diagnosed with Other specific personality disorders, 2.5% of patients were diagnosed with other schizophrenia, 1.25% of patients were diagnosed with Insomnia, not due to a substance or known physiological condition, and 1.25% of patients were diagnosed with Mixed obsessional thoughts and acts. Antisocial personality disorder was found in 35% of participants. More than 46% had no detected cognitive impairment in MoCA, 27.5% had mild cognitive impairment, 21.3% had moderate cognitive impairment, and 5% had severe cognitive impairment. Seventy-five percent of ASPD participants had cognitive impairment in MoCA. Only 8.8% of participants reported subjective problems with cognitive abilities in the MMQ questionnaire. Nearly 65% of participants had the documented pathology in the PSQI questionnaire. More than half of the participants described experiences with emotional abuse (61.3%), the presence of a person addicted to addictive substances in the home environment (57.5%), and observing violence between parents (62.5%). In the DASS-42 Questionnaire, we measured degrees of depression, anxiety, and stress. More than 46% of all participants had no symptoms of depression, 7.5% had only mild symptoms, 10% had moderate symptoms, 10% had severe symptoms, and 26.3% had extremely severe symptoms. Thirty-one point three percent of all participants had no anxiety symptoms, 6.3% had mild symptoms, 16.3% had moderate, 11.3% had severe, and 35% had extremely severe symptoms. More than 46% of all participants had no symptoms of stress, 6.3% had mild, 15% had moderate, 16.3% had severe, and 16.3% had extremely severe symptoms. Depression was reported in 68% of ASPD participants, 64% of participants reported stress, and 79% of participants reported anxiety. Among participants without ASPD, depression was reported in 53.85% of participants, 51.92% of participants reported stress, and 36.54% of participants reported anxiety. Regarding traumatization of ASPD participants, 42.8% reported physical abuse, 75% emotional abuse, 14% contact with sexual abuse, 89% reported alcohol and/or drug abuse in the household, 75% reported witnessing household member treated violently, 54% reported having one or no parent, parental separation or divorce, 29% reported emotional neglect, 43% physical neglect and

32% of ASPD participants reported being bullied. Regarding alcohol withdrawal symptoms, 53.75% of patients had no withdrawal symptoms during the examinations, 12.5% of patients had 1 point, 30% had 2 points, and 3.75% had 3 points on the BAWS scale.

The sociodemographic characteristics of all subjects, with a comparison between the subgroup of subjects with ADS and those with ADS+ASPD, are reported in Table 1. The subjects with ASPD were younger, had a lower age of first hospitalization, were hospitalized more often, had a lower education grade, and were employed less frequently (all $P < 0.05$).

Psychological characteristics of all subjects with a comparison between subjects with ADS and subjects with ADS+ASPD are reported in Table 2. Subjects with ASPD had higher scores of stress in DASS-42, traumatic events in ACE-IQ, lower scores in MoCA, more often had an addicted family member according to ACE-IQ, mental illness in the household according to ACE-IQ and incarcerated household member according to ACE-IQ (all $P<0.05$).

3.2 Bivariate analyses

The results of bivariate analyses showed that the presence of ASPD was predicted by a higher number of hospitalizations (OR = 1.13, 95% CI = 1.03-1.23, $P = 0.007$) and by a lower grade of education (OR = 0.29, 95% CI = 0.11-0.76, $P = 0.012$).

In bivariate analyses, subjects with ASPD had lower MoCA scores (OR = 0.29, 95% CI = 0.11- 0.76, $P = 0.039$), their family members were more often addicted (OR = 12.30, 95% CI = 3.29-46.03, $P < 0.005$), had mental illness in the household (OR = 6.67, 95% CI = 1.85- 23.97, $P = 0.004$) and an incarcerated household member (OR = 4.78, 95%CI = 1.70-13.41, $P = 0.003$).

3.3 Multivariate analyses

Multivariate regression analyses were performed to examine whether significant results persisted after controlling for potential cofounders.

Multiple logistic regression models and results:

i. In a model adjusting for the presence of ASPD (SCID-II), cognitive impairment (in MoCA), sex, length of drinking, and depression (in DASS-42), the presence of ASPD was significantly predicted by depression (OR 1.6; 95% CI: 1.14-2.23; $P = 0.006$) and cognitive impairment (OR 6.18; 95% CI: 1.9- 20.15; $P = 0.003$).

TABLE 1 Demographic and clinical characteristics of study participants.

	All (*N*=80)	ADS (*N*=52)	ADS+ASPD (*N*=28)	*P*-value
Males	62 (77.5%)	38 (47.5%)	14 (17.5%)	0.19
Females	18 (22.5%)	24 (30%)	4 (5%)	
Age at first hospitalization, years	42.5 (34-55)	46 (34.5-57.5)	38.5 (30.5-45)	**0.04**
Current age, years	51.5 (38.5-58)	53.5 (39.5-59.5)	45 (36.5-55)	**0.04**
Length of drinking alcohol, years	4 (0.5-8)	3 (0-7)	6 (2-10)	0.127
Number of hospitalizations	4 (2-7)	2.5 (1.5-6)	6 (3.5-12.5)	**0.003**
General education	15 (18.75%)	6 (7.5%)	9 (11.25%)	**0.03**
High school education	55 (68.75%)	37 (46.25%)	18 (22.5%)	
University education	10 (12.5%)	9 (11.25%)	1 (1.25%)	
Unemployed	27 (33.75%)	15 (18.75%)	12 (15%)	**0.047**
Employed	32 (40%)	21 (26.25%)	11 (13.75%)	
Retired pensioners	10 (12.5%)	11 (13.75%)	0 (0%)	
Disability pensioners	11 (13.75%)	5 (6.25%)	5 (6.25%)	
Single	37 (46.25 %)	22 (27.5%)	15 (18.75%)	0.283
Married	25 (31.25 %)	18 (22.5%)	7 (8.25%)	
Widowed	8 (10%)	7 (8.25%)	1 (1.25%)	
Divorced	10 (12.5%)	5 (6.25%)	5 (6.25%)	
Without CT pathology	9 (23.68%)	6 (15.79%)	3 (7.89%)	0.431
Vascular changes in CT	15 (39.47%)	10 (26.32%)	5 (13.16%)	0.254
Atrophy in CT	27 (71.05%)	14 (36.84%)	13 (34.21%)	0.508

Data expressed as N (%) or medians and interquartile ranges (IQR).
ADS, Alcohol Dependence Syndrome; ADS+ASPD, Alcohol Dependence Syndrome with comorbid Antisocial Personality Disorder; CT, computed tomography; N, number.
Bold values are statistically significant ($p<0.05$).

TABLE 2 Psychometric characteristics of participants with ADS and with ADS-ASPD.

	All (*N*=80)	ADS (*N*=52)	ADS+ASPD (*N*=28)	*P*-value
Depression in DASS-42	11 (3-30)	8.5 (0.5-24.5)	21 (6.5-25.5)	0.38
Anxiety in DASS-42	13 (5.5-24)	12 (3-21.5)	15.5 (8.5-28)	0.63
Stress in DASS-42	17 (4.5-28)	10.5 (2.5-26.5)	20.5 (12.5-35.5)	**0.026**
Traumatic events in ACE-IQ	4 (2-6)	3.5 (1-5)	6 (4.5-7)	**0.015**
MoCA score	20.5 (17-26)	23 (18-26)	19 (14.5-22.5)	**0.046**
AUDIT score	26.5 (17-34)	22 (13-31)	33 (21.5-37.5)	0.052
PSQI score	7 (3-14)	6 (3-13.5)	7 (3-16)	0.058
MMQ score	100 (74-100)	100 (82.5-100)	79.5 (55-100)	0.073
Addicted family member in ACE-IQ	46 (57.5%)	21 (26.25%)	25 (31.25%)	**<0.001**
Mental illness in the household in ACE-IQ	23 (28.75%)	9 (11.25%)	14 (17.5%)	**0.002**
Incarcerated household member in ACE-IQ	14 (17.5%)	4 (5%)	10 (12.5%)	**0.002**

Data expressed as N (%) or medians and interquartile ranges (IQR).
ADS, Alcohol Dependence Syndrome; ADS+ASPD, Alcohol Dependence Syndrome with comorbid Antisocial Personality Disorder; DASS-42, Depression, Anxiety, and Stress Scale-42; ACE-IQ, Adverse Childhood Experiences – International Questionnaire; MoCA, Montreal Cognitive Assessment; AUDIT, Alcohol Use Disorders Identification Test; PSQI, Pittsburgh Sleep Quality Index; MMQ, Multifactorial Memory Questionnaire; N, number.
Bold values are statistically significant (p<0.05).

ii. In a model adjusting for the presence of ASPD (SCID-II), sex, length of drinking, both cognitive impairment (in MoCA) (OR 3.64; 95% CI: 1.24- 10.71; $P = 0.019$) and addicted family member (in ACE-IQ) (OR 5.76; 95% CI: 1.51- 21.99; $P = 0.01$) were independently associated with ASPD.
iii. In a model adjusting for the presence of ASPD (SCID-II), sex, length of drinking, both cognitive impairment (in MoCA) (OR 5.22; 95% CI: 1.62- 16.83; $P = 0.006$) and an incarcerated household member (in ACE-IQ) (OR 14.26; 95% CI: 3.49- 58.37; $P < 0.001$) were independently associated with ASPD.

4 Discussion

The primary finding of the present study is that 35% of study participants met the criteria for ASPD and featured distinct demographical, clinical, and psychological characteristics. Our findings are in line with previous reports suggesting that antisocial behavior is associated with an increased risk of alcohol use and predicts later problems with alcohol use (25). These findings also provide additional evidence for the high prevalence of ADS in individuals with ASPD (3). Data from a large epidemiological study of psychopathology highlights the intertwined nature of ADS and personality disorders (26). In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), 42% of individuals who met the diagnostic criteria for any personality disorder also fulfilled the criteria for DSM-IV alcohol dependence (26). Those with ASPD showed a notably higher likelihood, being 7 to 8 times more prone to meeting the criteria for alcohol dependence (26).

An existing personality disorder elicits environmental responses, such as interpersonal or occupational problems, that provoke the onset of ADS (10). The comorbidity may result from overlapping genetic and environmental underpinnings (10). Shared environmental risk factors such as childhood trauma, coercive parenting, and antisocial peer affiliation are associated with the ADS comorbid with ASPD (10). On the other hand, ASPD incapacitates one's ability to ignore the immediate reward offered by alcohol (10). This jeopardizes the ability to inhibit habitual use of alcohol regardless of the significant psychological and physical distress it causes, leading to the genesis of ADS (10). Conversely, excessive alcohol consumption may lead to a neuroadaptation that results in increased impulsivity or negative emotionality, as seen in ASPD (10).

On the other hand, earlier substance abuse causes aggression and/or antisocial behavior and may transform into ASPD later in life, further increasing aggression (27). Although the literature is limited in this aspect, it may be reasonable to suggest that the search for stimulus may be the initial reason that adolescents succumb to drug use, leading to antisocial/violent behavior and finally forming a vicious cycle embodied by ASPD (27). Findings indicate that proneness to act out aggressively may be linked to a reduced differentiation (at a neural and behavioral level) between threatening and non-threatening interpersonal cues, in line with the hypothesis of a hostile filter that biases the perception of the entire social environment, thus increasing the likelihood for aggressive encounters (28). Alterations of fronto-temporal-limbic regions and neuromodulatory systems, such as the serotonergic or endocannabinoid signaling systems, may also connect impulsive behavior to aggressive responding (28). Weaker cortico-striatal connectivity could relate to greater risk-taking and greater proclivity for violence (28).

Furthermore, we found that participants with ASPD had lower MoCA scores and had more problems with vigilance, attention, and

linguistic skills (Figure 1). This is in line with previous literature findings that antisocial symptoms have been significantly associated with cognitive control defects, attentional problems, abnormalities in decision-making, deficits in flexible responding, such as reversal learning, planning impairments, neural regions governing inhibitory control, and verbal deficits/delayed language development (29, 30). The young offenders scored approximately half a standard deviation lower on verbal domains of intelligence than on performance-related domains of general intelligence (31). Moreover, in subjects with ASPD, spatial convergence in brain regions belonging to ventral and dorsal attention networks (the anterior midcingulate cortex/the pre-supplementary motor area (aMCC/pre-SMA), superior parietal lobule (SPL), and premotor (frontal eye field, and the cuneus) were found (32). Indeed, the

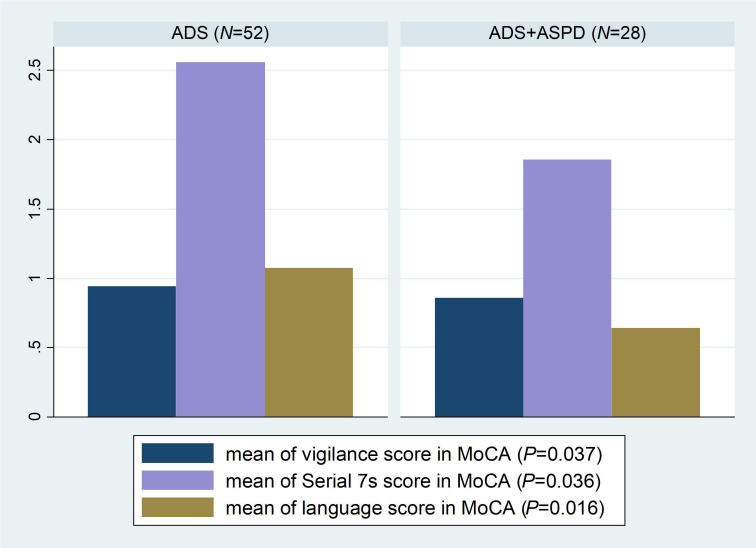

FIGURE 1
Boxplot of statistically significant MoCA subtests with a comparison between subjects with ADS and ADS+ASPD. ADS, Alcohol Dependence Syndrome; ADS+ASP, Alcohol Dependence Syndrome with comorbid Antisocial Personality Disorder; MoCA, Montreal Cognitive Assessment; N, number.

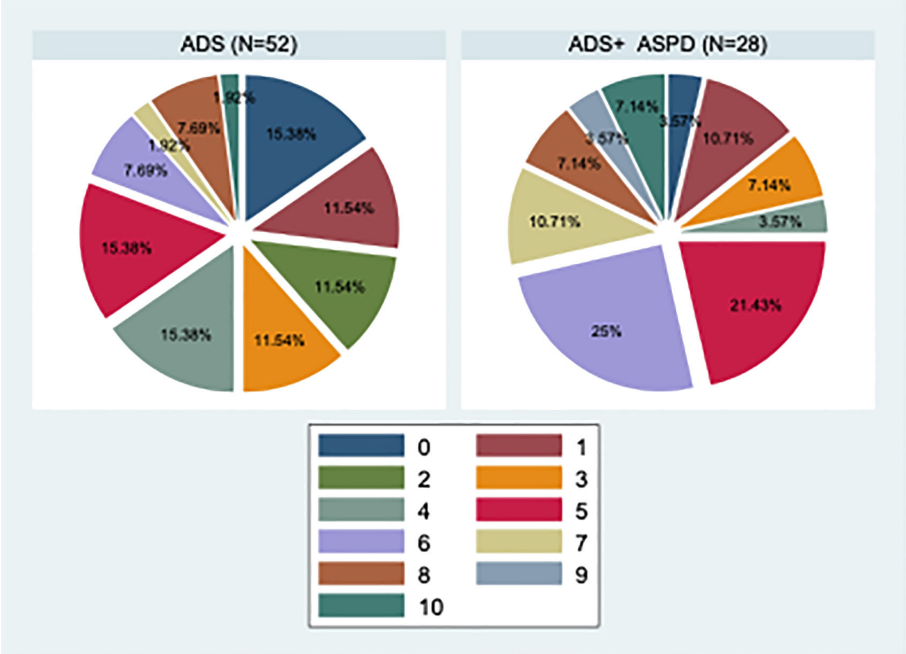

FIGURE 2
Pie graphs of the number of different types of traumatization in ACE-IQ with a comparison between subjects with ADS and ADS+ASPD. ADS, Alcohol Dependence Syndrome; ADS+ASPD, Alcohol Dependence Syndrome with comorbid Antisocial Personality Disorder; N, number.

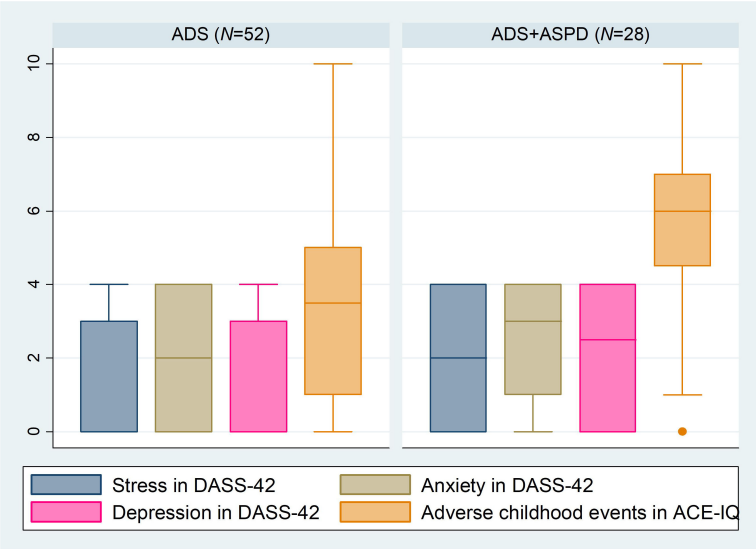

FIGURE 3
Boxplot of selected questionnaire results with a comparison between subjects with ADS and ADS+ASPD. ADS, Alcohol Dependence Syndrome; ADS +ASPD, Alcohol Dependence Syndrome with comorbid Antisocial Personality Disorder; DASS-42, Depression, Anxiety, and Stress Scale-42; ACE-IQ, Adverse Childhood Experiences - International Questionnaire; N, number.

aMCC/pre-SMA mainly corresponded to the ventral network, whereas the SPL and premotor cortex were associated with the dorsal network (32). These regions are frequently co-activated in tasks requiring attentional processes such as shifting: sustained, oddball, and working memory (32). Ventral network regions (e.g., aMCC/pre-SMA) may correspond to a stimulus-driven attentional system. In contrast, regions subserving the dorsal attentional network (e.g., SPL, premotor cortex) may play a crucial role in top-down or goal-driven attentional control (32). Subjects with ASPD have significant connectivity deficits in the amygdala, middle cingulate cortex, ventral posterior cingulate cortex-precuneus, ventromedial and dorsomedial prefrontal cortex, premotor cortex, and superior parietal lobule and increased connectivity in the ventral posterior cingulate cortex and decreased connectivity in the parietal operculum, calcarine cortex, and cuneus (32). There is a negative relationship between the severity of antisocial behaviors and connectivity with the ventromedial prefrontal cortex (32). These findings overlapped with socio-affective and attentional processes (32). The ASPD is associated with variability in neural functioning during reward and loss processing (33). In particular, impulsive-antisocial traits appeared to be specifically associated with hypersensitivity in the ventral striatum (VS) and prefrontal cortex (PFC) (VS reactivity or VS-PFC functional connectivity) during the anticipation, but not the receipt of rewards (33). Beyond VS reactivity, ASPD was related to the greater orbitofrontal cortex (OFC), medial PFC reactivity, and VS-dorsomedial PFC connectivity during reward processing (33). The ASPD was linked to greater reactivity in several regions, including the posterior cingulate, precuneus, and insula, during error-related loss receipt and decreased VS reactivity during loss anticipation (33).

Our finding of younger age among ADS participants with comorbid ASPD corresponds with the literature (34). In our sample, individuals diagnosed with ASPD tend to start drinking alcohol at younger ages, which is in line with literature findings (35), and were more likely to seek treatment at a younger age, which was previously described (10). Studies also reported that prevalence rates of ASPD steadily decline with age (36). Over the years, researchers have proposed multiple factors that may contribute to the decline in the prevalence of ASPD with age, including increased rates of mortality and incarceration and a change in personality traits over the lifespan (37).

We found that individuals with ASPD had more frequent hospitalizations and more problems with alcohol consumption, as shown in the AUDIT test, which aligns with literature findings - more than half of subjects dependent on alcohol relapse within a year (38). Relapse can be attributed to several psychosocial and biological factors. Among others, marital status, traumatic experiences, psychological distress, and the presence of co-existing psychopathology, including anxiety and depression, and alteration in the brain's dopamine system may influence relapse (10). If individuals with ASPD seek treatment, their chances of adhering to the treatment are low because they tend to violate rules (10). The comorbidity leads to poorer treatment outcomes, thereby increasing the chance of relapse or drop-out (10).

We reported that subjects with comorbid ASPD had lower education levels, tended to be unemployed more often, and tended to be married less often. The results align with the literature finding, which revealed significantly higher odds of a diagnosis among individuals with less than a high school education, lower income, and those not married (37). Using the NESARC-III data, Goldstein et al. (5) found similar results with adults of any age. In their study, individuals with ASPD were more likely to be 18-29 years old, widowed/separated/divorced, had less than a college degree and a lower family income (5). Also, more knowledge on the effect of education level on this relation is required since research suggests that school failure is overrepresented in offenders and related to aggressive

antisocial behaviors (39). It is hypothesized that behavioral disorders and impulsivity in individuals with ASPD negatively affect their academic and professional achievements, which results in lower income levels and employment compared to healthy individuals (40).

We reported that participants with ADS+ASPD more often have family members who suffer from ADS, are incarcerated, or are otherwise mentally ill. Similarly, a state hospital study (41) of 740 individuals admitted for alcoholism treatment concluded that ADS +ASPD subjects had a higher prevalence of familial alcoholism when compared with alcohol abusers without ASPD. This points us toward the etiopathogenesis of the disease, which combines genetic and environmental influences (42–44). Notably, Rhee and Waldman's (45) meta-analysis reported additive and non-additive genetic contributions to antisocial behavior (32% and 9%, respectively), 16% of the variance explained by shared environment, and 43% explained by individual-specific environmental influences. A genetic basis for ASPD is supported by the finding that a first-degree biological relative with ASPD constitutes a risk factor for the disorder (43). The ASPD, like most mental disorders, is thought to have a complex, multifactorial etiology characterized by polygenic inheritance and genetic heterogeneity across individuals. The genetic contribution is not stable over time, suggesting that partly different genes contribute to ASPD at different stages of the lifespan (44). Recently, GWAS meta-analysis identified a novel genome-wide significant signal with rs9806493 chromosome 15q26.1 close to SLCO3A1, possibly contributing to the genetic risk factor for ADS and ASPD (42). Many environmental risk factors were described in the literature. Of the prenatal risk factors, maternal smoking, alcohol use, drug use, and stress during pregnancy are among the best documented (44). Perinatal risk factors include obstetric complications, parental psychopathology, malnutrition, and exposure to heavy metals (44). Postnatal risk factors include more strained family relationships, child maltreatment, parental substance abuse, lower income, childhood residential mobility, and bullying (43).

Subjects with ASPD reported experiencing traumatic events more often (Figure 2), which is in agreement with previous literature findings (10). Adverse childhood experiences, which encompass various forms of abuse, neglect, and impoverishment during childhood, are prime examples of negative socialization experiences that engender antisocial traits and behaviors (2). Clinical evidence suggests that trauma may contribute to ASPD features such that the experience of trauma provides a template for which people who develop ASPD learn to interact with others (46). People with ASPD traits may use the betrayal trauma they experienced earlier in life as a template for perpetrating trauma on others later in life (2). One way of understanding the relationship between antisocial behaviors preceded by traumatic experiences is to suggest that individuals who have experienced severe trauma develop insensitivity to stressful situations. In addition to numbing reactions of sadness and fear, these individuals would tend to behave aggressively. Traumatic experiences compromise the functioning of neurotransmitters, the neuroendocrine, and the immune system, generating a dysfunction of the hypothalamic-pituitary-adrenal system affecting control and stress response (4). The average correlation between trauma and ASPD traits were both high. Exposure to traumas at all levels of betrayal predicts ASPD traits for women, but only exposure to high betrayal trauma predicts ASPD traits for men (2). Fergusson et al. (47) examined the association between childhood sexual abuse, childhood physical abuse, and ASPD and found that the prevalence of ASPD at ages 18–21 and 21–25 was two to four times greater among those who had been sexually abused compared to those who had not. Similarly, those who experienced regular physical abuse or severe physical abuse had ASPD at a prevalence that was two to seven times higher than those who were not physically abused. In multivariate models, sexual abuse predicted ASPD; however, physical abuse did not occur in the fully adjusted model (2).

Our next finding was that depression, anxiety, and stress were all statistically significantly correlated with ASPD) (Figure 3), which is in line with the literature findings (40). However, we failed to replicate this finding in a linear regression model, possibly due to the small sample size. Symptoms reflecting impulsivity and emotional dysregulation are found in ASPD, psychopathy, anxiety, and mood disorders. Interestingly, the relationship between psychopathy and ASPD with mood and anxiety disorders has been a controversial topic, as many experts associate ASPD and psychopathy with very low levels of anxiety and depression (3). In contrast, in the DSM-5, it is noted that those with an ASPD diagnosis may also experience anxiety disorders and/or depressed mood (1). Evidence from epidemiological samples indicates that individuals with ASPD are four times more likely to experience a mood disorder, and up to half of the individuals with ASPD may also experience an anxiety disorder in their lifetime, particularly posttraumatic stress disorder and social anxiety disorder. These individuals with comorbid ASPD and anxiety disorders were found to be at increased risk for major depression and substance dependence (48, 49). Drinking is sometimes used as a coping strategy and/or method of self-medication among individuals with substance abuse disorder before, during, and after anxiety-provoking events (3).

Our last finding was that individuals with ADS-ASPD reported worse sleep, which showed a statistical trend. Previous sleep problems were reported in individuals with ASPD and ADS (50). A similar relationship between sleep and ASPD was described in a study conducted by Van Veen in 112 patients with antisocial personality disorder and borderline personality disorder. The study found a relationship between behavioral disinhibition and/or emotional dysregulation and poor sleep. Poor sleep quality was reported in 53.6% of the patients, especially with problems falling asleep, and 22.3% suffered from severe chronic insomnia, which was particularly characterized by major problems with sleep initiation, resulting in much shorter total sleep times. Problems with sleep were significantly associated with greater impulsivity. Subjects with greater insomnia or lower sleep quality reported more difficulties with focusing and controlling their thoughts (51). However, to our knowledge, this is the first study comparing sleep problems in individuals with ADS with and without ASPD.

A recent meta-analysis on 24,801 subjects did not find enough evidence to determine whether or not medication is a helpful treatment for people with ASPD (52). There is also minimal evidence available on psychological interventions for adults with ASPD (53). A recent meta-analysis of 605 adults found that three interventions (schema therapy, contingency management, and

dialectic behavior therapy) may be more effective than other approaches (53). However, the certainty of the evidence was low or very low to recommend or reject any psychological treatment for people with a diagnosis of ASPD (53).

Our findings may not apply to all participants with alcohol dependence syndrome as the sample we studied was small. Nevertheless, the group was homogenous; all subjects were from the same region, and the same team of psychiatrists evaluated them. The results might differ in a sample of outpatients with the same problems and a sample of people recovering from ADS. Many of the participants in the present study were using benzodiazepines at the time of the examination, which can worsen some cognitive parameters.

Since this study extensively uses questionnaire methods, it was not possible to objectively evaluate variables such as sleep parameters or the incidence of traumatization. Specifically, in cases of memory decline, they may be unable to recall all the events. In addition, a limited insight into one's problems is very common in this population. The present results are preliminary, and the study is still ongoing. Further studies are warranted to evaluate the impact of various comorbidities and their treatment on cognitive skills.

The strength of the current study is that it provides a comprehensive analysis of comorbid ASPD among adults with ADS based on the in-depth analysis of the selected demographic and psychological variables controlling for key covariates in analyses. Another strength is that it explored familial psychopathology among subjects, providing deeper insights into their conditions. Overall, the study advances understanding of the complexities of comorbid ASPD in individuals with ADS, providing valuable insights for research and clinical practice.

The study demonstrated that more than one-third of the individuals with ADS met the criteria for ASPD. The prevalence of depression, anxiety, stress, traumatization, and sleep problems was high among all subjects. All these difficulties were closely related to ASPD. Participants with ADS+ASPD had lower MoCA scores and had more problems with attention and linguistic skills. The findings implicate that screening for ASPD might be helpful in the complex management of ADS.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of the University Hospital of Louis Pasteur Kosice (study protocol number: 2023/EK/08045). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DJ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. MP: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. SC: Investigation, Writing – review & editing. MF: Investigation, Writing – review & editing. JF: Investigation, Writing – review & editing. AB: Investigation, Supervision, Writing – review & editing.

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Conflict of interest

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

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Personality and help-seeking for psychological distress: a systematic review and meta-analysis

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Introduction: The effective management of depression, anxiety, and other forms of psychological distress depends on individuals' readiness to seek and accept help for their mental suffering. Understanding which personality traits relate to help-seeking can help better tailor mental healthcare to individual needs. However, findings regarding associations of personality traits with help-seeking have been inconsistent.

Methods: This systematic review and meta-analysis focused on English-language research studies on the association of personality (encompassing personality disorders, Five Factor –Big Five– dimensions, and other measures of personality) with depression, anxiety, or unspecified psychological distress in adults aged 18 years and older. Procedures followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy included two concepts: personality and help-seeking and was carried out on PubMed, Embase, Web of Science, and PsycINFO. Reference tracking and searches on Google Scholar were additionally performed. Sufficiently homogeneous subsections were analyzed by meta-analysis.

Results: A total of 48 studies described in 47 records reported on the association between personality and help-seeking. Nine assessed personality disorders, 29 Five Factor dimensions, and 13 other personality constructs. Twenty-three studies investigated attitudes towards help-seeking while 25 studies investigated help-seeking behaviors. Of the studies investigating behavior, three used external observations, the rest relied on self-reports/clinician-administered questionnaires. Evidence highlighted a dissociation between attitudes and behavior for schizotypal and borderline personality disorders, and neuroticism, which displayed negative help-seeking attitudes but more help-seeking behavior. By contrast, paranoid, schizoid and obsessive-compulsive personality disorders related to both negative help-seeking attitudes and behavior across studies. Limited evidence linked extraversion to social support seeking and conscientiousness to care seeking behaviors. Meta-analyses on the

Five Factor dimensions and help-seeking attitudes supported robust negative associations with neuroticism, as well as positive associations with agreeableness, albeit less reliably. Other personality traits mostly corroborated the above relationships, while also contributing new perspectives, such as help-seeking behavior's negative associations with reality weakness and cynicism, and positive associations with abasement and rigidity.

Discussion: Future research should investigate help-seeking behavior using external observations and longitudinal designs. Assessing personality in clinical settings can help identify populations at risk of keeping to themselves when mentally distressed.

KEYWORDS

personality, help-seeking, care seeking, treatment-seeking, social support seeking, depression, anxiety, psychological distress

1 Introduction

Mental disorders underlying psychological distress such as depression and anxiety are highly prevalent around the world and represent an important burden on populations in terms of role impairment and social costs (1). The effective management of depression, anxiety, and more general forms of psychological distress greatly depends on individuals' readiness to seek and accept help for their mental suffering in the form of professional care (2) and social support (3). In contrast, failing to seek help has been linked to serious mental illness (4). A tendency to keep one's psychological distress to oneself has been associated with various social and demographic factors, for instance gender roles (5–7) or racial/ethnic and cultural values (8, 9). However, findings have been inconsistent even regarding well-established sociodemographic determinants of help-seeking for psychological distress, such as gender (10), suggesting that sociodemographic factors do not provide the full picture. Personality has been hypothesized to also play a role in help-seeking (11).

Help-seeking can represent an open admission of dependence on others or of the failure to tackle one's problems on one's own, but can also be perceived as the only possible option in cases where one has little faith in one's own coping abilities (12). Hence, help-seeking may not be perceived as an acceptable solution in case of high individual need for control as in obsessive-compulsive personality disorder and high perfectionism (13), or in case of dominance-driven individual motivations as in narcissistic or antisocial personality profiles (14, 15). By contrast, it could become an overutilized behavioral response to difficulty in individuals who harbor persistent or recurring negative self-views, as in the case of high neuroticism (16) or borderline personality disorder (17). Personality traits may also improve individuals' help-seeking abilities. For example, extraversion, openness to experience, and agreeableness have been positively associated with communication competence (18), extraversion with seeking social support when facing a challenging task (19), and conscientiousness and openness with clients' engagement in psychotherapy (20).

Overall, help-seeking has been positively associated with mental health recovery (21), making it a promising strategy to prevent detrimental consequences of psychological distress, such as persisting mental health conditions (22), suicide (23), or long-term disability (24). Yet, randomized controlled interventions promoting help-seeking for psychological distress have shown little effect on objectively measured help-seeking behavior (25), which may be partly due to individual differences such as the above that were not taken into account. Personality-targeted approaches have shown promise in areas where personality risk factors have been consistently identified, such as alcohol use or internalizing and externalizing problems in adolescents (26, 27). Thus, gaining a clearer understanding of the role of personality with respect to help-seeking attitudes and behaviors can represent an essential first step to identify which individuals will spontaneously reach out to healthcare professionals or their social circle in times of difficulty, and which ones will need more proactive, targeted interventions to prevent isolation and downward spirals into more severe psychopathology.

The present systematic review and meta-analysis aims to integrate evidence about the personality disorders and traits associated with help-seeking attitudes and behaviors for psychological distress, defined as depression, anxiety, and unspecific acute psychological stress.

2 Methods

We synthesized the research evidence on the association between personality and help-seeking for psychological distress in adult populations. Methods followed the Preferred Reporting Items

for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (28). The review's protocol was preregistered on PROSPERO (29).

2.1 Eligibility criteria

2.1.1 Types of records

We included all peer-reviewed quantitative and qualitative studies reporting on original data that were published in English as journal articles or doctoral dissertations. The rationale behind including dissertations was that a majority of studies undertaken in the context of PhD projects in psychology do not get published in journals (30) even though they can be considered peer-reviewed by the thesis committee.

We excluded reviews, expert opinions, case studies, conference abstracts that did not have a full-text version, and records not reporting on original data. We also excluded studies that did not report on the association of interest, namely between personality and help-seeking, or that were not conducted in a human adult population (see below).

2.1.2 Participants

The population of interest was defined as adults of any age, with a cutoff for adulthood at ≥ 18 years of age. Studies including mixed samples of adolescents and adults needed to have their mean age and standard deviation for age ≥ 18 years to be eligible.

2.1.3 Personality: definition and measures

Personality traits were defined according to the American Psychology Association's Dictionary of Psychology, as "characteristic patterns of thinking, feeling and behaving" (31). Our primary focus was classic measures of personality such as personality disorders as described by the Diagnostic and Statistical Manual of Mental Disorders (DSM) (32) or the International Classification of Diseases (ICD) (33) as well as the five dimensions of personality described in the Five Factor Model (34, 35), namely neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness.

As not all aspects of personality can be captured by the above classifications (36), we additionally included studies investigating other personality constructs as long as they were measured by a psychometric tool that explicitly conceptualized them as trait or personality. This definition relying on the psychometric tool was introduced during full text screening to avoid sampling bias, given a large number of studies in which authors categorized constructs as personality even though they were not systematically defined as such in the literature [for an example: (37)].

2.1.4 Help-seeking for psychological distress: definitions and measures

Help-seeking was defined as either observed or self-reported readiness to seek help for psychological distress from any source, including from professional sources (henceforth referred to as 'care seeking') and from social contacts (henceforth referred to as 'social support seeking'). Help-seeking outcomes encompassed self-reported attitudes towards help-seeking, including help-seeking intentions such as in-principle willingness to seek help in a hypothetical scenario of psychological distress, as well as help-seeking behavior, which could be either self-reported or based on external observations such as medical records or national databases.

As psychological distress is commonly defined as non-specific symptoms of depression, anxiety, and stress (38, 39), we considered cases of depression or anxiety (either defined by self-report or by formal diagnosis) and other, non-specific acute negative emotional states as psychological distress. A similar scope for psychological distress has been employed in another systematic review investigating help-seeking outcomes (25).

Studies reporting on help-seeking, mental healthcare utilization, or consultations for psychosomatic symptoms were eligible as long as they were explicitly investigating these outcomes in the context of psychological distress as defined above. Suicidal ideation and behavior were considered acute negative emotional states, hence eligible. Studies reporting on help-seeking for other mental health conditions were not considered, nor were studies comparing treatment preferences, coping, or problem-solving strategies that did not report specifically on associations between personality and help-seeking for psychological distress. Broadly defined psychological distress such as 'mental health problems' remained eligible.

2.2 Information sources

The search was conducted using a database combination found to constitute an optimal coverage of the literature (40) that included PubMed, PsycINFO, Web of Science, and Embase with the same set of key words (see next section). We sought additional records through Google Scholar and reference tracking.

2.3 Search strategy

2.3.1 Record retrieval and deduplication

The search was first performed in February 2023 and updated in July 2023. Searches were performed in titles and abstracts, using key words grouped under two blocks separated by 'AND': personality and help-seeking (Supplementary Table S1). The search strategy was piloted on PubMed to refine the search terms, with several terms eliminated due to their lack of contribution to relevant hits. This was the case for the specific names of all personality disorders. The search included no filters or publication date restrictions. Syntax was adapted to each database.

Deduplication took place in EndNote 20 (41), following the procedure described by Bramer and colleagues (42). Records were then imported into Rayyan (43) for title-abstract screening where a second deduplication took place using Rayyan's built-in tool.

2.3.2 Screening process

Two independent study team members screened each record at both title/abstract and full text screening stages: AS screened all records while RL and WT screened half of the records each. All

records selected by at least one screener during title/abstract screening were carried over to full text screening. Discrepancies during full text screening were resolved through consensus meetings with ML acting as tiebreaker.

Each screening phase was preceded by a piloting session where the screening team compared and discussed their decisions on 50 articles for the title/abstract phase and six articles for the full text phase.

Title/abstract screening was carried out using the online software Rayyan whereas full text screening employed EndNote 20 to store all full text articles, with screeners recording full text screening decisions on their individual copy of a standardized Excel spreadsheet.

2.4 Data extraction

Two independent study team members extracted data from each record: AS extracted data from all records, while RL and WT extracted data from half of the records each. Discrepant fields were reconciled during meetings between AS, RL, and WT.

2.5 Risk of bias assessment

Two independent team members performed a risk of bias assessment (Supplementary Table S2) for each record of quantitative studies using the Newcastle-Ottawa Scale (44), and considering the following cutoffs (45): ≥7points, high quality evidence, 4–6 points, moderate quality evidence, and ≤3 points, low quality evidence. An adapted version of the tool for cross-sectional studies used in prior systematic reviews was employed for all cross-sectional studies (46, 47). AS appraised all records. RL and WT appraised half of the records each, after an initial piloting session to clarify the appraisal criteria. Conflicts were resolved during consensus meetings with ML acting as tiebreaker.

2.6 Data synthesis methods

Data synthesis followed a narrative summary of all results grouped by personality constructs (DSM/ICD personality disorders, Five Factor Model dimensions, and other personality constructs) and further by outcome (help-seeking attitudes vs behaviors; within behaviors: observed vs self-reported). Studies were organized into tables following the same logic, and ordered following evidence quality within each subcategory.

Suitability for meta-analysis was considered for each of the above sections. Given the scarce number of studies in most subsections, indication for a meta-analysis was only established for studies reporting on associations between Five Factor Model dimensions and help-seeking attitudes, given that most outcome measures in this subsection were adaptations of the same scale, the Attitudes Towards Seeking Professional Psychological Help Scale (48).

We employed random-effects meta-analyses using correlation coefficients between each Five Factor Model dimension and scores on the help-seeking attitudes scales. In studies where only multivariate results were reported, we estimated correlation coefficients based on adjusted beta coefficients in order to factor out variations in effect size due to the use of difference sets of covariates (49). As this method could be subject to biased estimates (50), we conducted an additional sensitivity analysis including only studies that reported correlation coefficients (Supplementary Figure S1). In case of significant heterogeneity in the main meta-analysis models, we planned on performing subgroup analyses using the following classifications: sample size, population, country, gender, and race.

3 Results

3.1 Overview and study characteristics

3.1.1 Screening overview

Figure 1 summarizes the screening process. The initial search yielded 10,671 records, of which 7,546 remained after deduplication. Of these, title/abstract screening selected 269 for full text screening. Several records met more than one criteria for exclusion during full text screening (Figure 1). Full text screening resulted in the inclusion of 42 records. Reference tracking provided four additional ones, while the search on Google Scholar provided one additional record.

3.1.2 Final set of records

In total, 47 records were included (51–97), of which nine were doctoral dissertations (53, 57, 58, 71, 76, 81–83, 96). Publication dates ranged from 1967 to 2022, with 10 records published in or after 2020, 32 records between 2010 and 2019, six records between 2000 and 2009, six records between 1990 and 1999, and three records before that.

Twenty-two records were from North America, namely the United States (n = 20) and Canada (n = 2); 15 records were from Europe, including the Netherlands (n = 4), Germany (n = 4), Ireland (n = 2), Norway (n = 2), the United Kingdom (n = 2), and Sweden (n = 1); five records were from the Middle East, including Turkey (n = 2), India (n = 1), Israel (n = 1), and Tunisia (n = 1); three records were from Oceania (n = 3; all from Australia); the remaining two records were from West Africa (n = 1; Nigeria) and East Asia (n = 1; South Korea), respectively.

One record reported on two eligible studies (74), hence the total number of studies included in the review was 48. For clarity, we refer to the number of studies instead of the number of records from this point on.

3.1.3 Study characteristics

Two studies had a qualitative design (87, 88), the rest were quantitative. Of the 46 quantitative studies, one followed a prospective design (90) and 45 were cross-sectional.

The samples used in most studies were college/university students (n = 18), followed by community-dwelling participants (n = 12), other specific populations (based on profession, ethnicity, or other sociodemographic factors; n = 11), and psychiatric

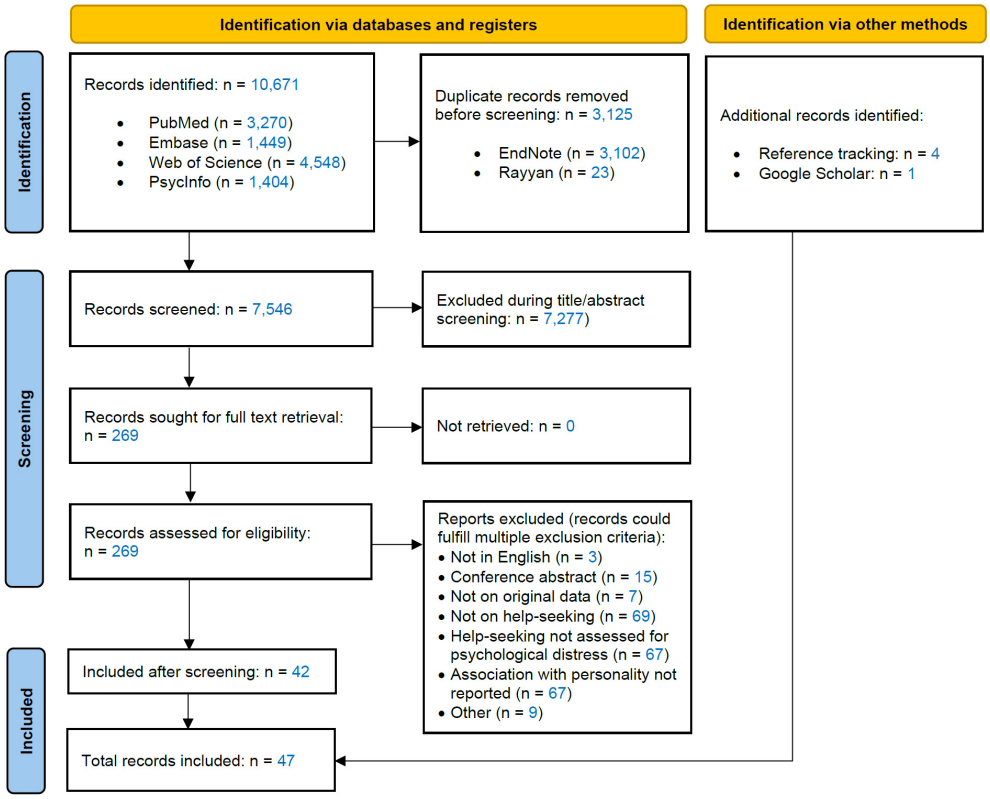

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

populations (n = 8). Two records reported on mixed samples of students and community-dwelling participants (61, 84). Notably, five out of the nine doctoral dissertations reported on student samples (57, 71, 76, 81, 82).

3.1.4 Assessment of personality

Overall, nine studies assessed personality as DSM/ICD personality disorders (Subsection 3.3.1.; Tables 1–3), 29 as Five Factor dimensions (Subsection 3.3.2.; Tables 4, 5), and 13 as other personality constructs (Subsection 3.3.3.; Tables 6, 7). Two studies (68, 84) assessed Eysenck's three personality dimensions (98), neuroticism, extroversion, and psychoticism. The two first dimensions were grouped with the Five Factor Model's neuroticism and extraversion respectively, given these constructs' considerable overlap (99), whereas psychoticism was reported with other personality traits.

Of the nine studies on DSM/ICD personality disorders, one study used medical records to assess personality (56), the others used fully structured, clinician-administered questionnaires (70, 89, 91), or self-reports (54, 63, 64, 88, 94). Assessments of the Five Factor Model dimensions and of other personality traits employed self-reports.

3.1.5 Assessment of help-seeking

About the same number of studies investigated attitudes towards help-seeking (n = 23) and past help-seeking behaviors (n = 25); one quantitative study (96) and one qualitative study (88) investigated both types of outcomes.

One study among those assessing help-seeking attitudes (63), and four studies among those assessing past help-seeking behaviors (54, 74, 75, 84) investigated social support seeking. Most other studies (n = 43) investigated care seeking, with one study reporting on both types of help-seeking (75). Information was lacking about the type of help-seeking in one study (92).

All 23 studies reporting on help-seeking attitudes used self-reports. The most commonly used self-report scales were the 29-item Attitudes Towards Seeking Professional Psychological Help (ATSPPH) questionnaire (48) used in eight studies (53, 57, 58, 61, 66, 82, 95, 96), its 10-item short form (100) used in seven studies (64, 69, 72, 76, 79, 81, 83), and the 24-item Inventory of Attitudes towards Seeking Mental Health Services (101), a modified version of the ATSPPH, used in four studies (62, 68, 73, 85).

The majority of the 25 studies investigating help-seeking behavior relied on self-reports, with only three studies measuring help-seeking through external observations such as official records (94), or collateral history from relatives and/or mental healthcare providers (56, 65). One study measured help-seeking behavior as part of a structured interview and used external data sources as confirmation where available (97). One study left unclear whether it assessed care seeking by self-reports or counseling center records (77). With respect to the past help-seeking behavior's timeframe, 15 studies set a limited timeframe, which ranged from six weeks (56) to one year (51, 60, 74, 75, 90, 91, 97), or was determined by context, e.g., years spent in medical school (87) or in jail (94). Six studies investigated lifetime help-seeking behavior (67, 70, 80, 86, 89, 97),

TABLE 1 Studies testing associations between DSM/ICD personality disorders grouped under Cluster A and outcomes measuring help-seeking attitudes and behaviors.

Help – seeking	First author, year, reference	Country	Population	Sample size	Mean age, years (SD)	Sex - % Female	Personality assessment tool	Outcome measure (tool, if applicable)	Association with outcome			RoB
Cluster A: odd or eccentric personality disorders									paranoid	schizoid	schizo-typal	
attitude	Fekih-Romdhane 2021 (64)	Tunisia	college students with high/low schizotypy scores	101	21.1 (1.7)	65.7%	SPQ	ATSPPH-SF			-	***
	Eurelings-Bontekoe 1997 (63)	Netherlands	psychiatric patients	230	36.8 (11.3)	67.8%	VKP	seeking social support as coping in hypothetical scenario (UCL scale item)	-[a]	-[a]	-[a]	**
behavior	Iza 2013 (70)	USA	community-dwelling adults	34,653	NR	NR	AUDADIS-IV	lifetime care seeking for anxiety disorders	-[bc]	-[bc]	Ø	***
	Blanch 2021 (54)	Australia	college students	800	21.0 (NR)	76.8%	SPQ	help-seeking for anxiety symptoms ≤ last 8 weeks			+	**

All studies in the table had a cross-sectional design. Studies are organized by outcome type (attitude vs behavior) and risk of bias (from high to low evidence quality). In the 'Association with outcome' column, green cells indicate positive associations, pink cells negative associations, grey cells non-significant associations, and black cells that the association was not tested. RoB, Risk of bias assessment with the Newcastle-Ottawa scale for cross-sectional studies; ***, high quality evidence (low risk of bias); **, moderate quality evidence (moderate risk of bias); NR, not reported; [a-c], association tested while controlling for [a], age and sex/gender; [b], race; [c], age of onset of psychopathology; SPQ, Schizotypal personality questionnaire; VKP, Vragenlijst voor Kenmerken van de Persoonlijkheid (Questionnaire on Personality Traits); AUDADIS-IV, Alcoholism's Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV Version; UCL, Utrecht Coping List; ATSPPH-SF, Attitudes Towards Seeking Professional Psychological Help Scale – Short Form.

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TABLE 2 Studies testing associations between DSM/ICD personality disorders grouped under Cluster B and outcomes measuring help-seeking attitudes and behaviors.

Help – seeking	First author, year, reference	Country	Population	Sample size	Mean age, years (SD)	Sex - % Female	Personality assessment tool	Outcome measure (tool, if applicable)	Association with outcome				RoB
Cluster B: emotional or erratic personality disorders									antisocial/ dissocial	borderline	histrionic	narcissistic	
attitude	Eurelings-Bontekoe 1997 (63)	Netherlands	psychiatric patients	230	36.8 (11.3)	67.8%	VKP	seeking social support as coping in hypothetical scenario (UCL scale item)	- [a]	- [a]	Ø	Ø	**
behavior	Iza 2013 (70)	USA	community-dwelling adults	34,653	NR	NR	AUDADIS-IV	lifetime care seeking for anxiety disorders	- [bc]	+ [bc]	Ø	Ø	***
	Broadbear 2020 (56)	Australia	suicide decedents	2870	NR	24.8%	medical records	care seeking ≤ 6 weeks prior to death by suicide [#]		+			***
	Yasmeen 2022 (94)	USA	jail inmates	506	32,4 (10.0)	30%	PAI-BOR	requests for jail-based treatment [#]		+ [ab]			***
	Ullrich 2009 (91)	United Kingdom	community-dwelling adolescents & adults	1051	56.3 (15.2)	68%	SCID-II	care seeking ≤ 12 months	+				***
	Tomko 2014 (89)	USA	community-dwelling adults	34,481	NR	NR	AUDADIS-IV	lifetime care seeking for low mood		+			**
both	Svanborg 2008 (88)	Sweden	patients with non-remitting depression	10	NR	60%	DIP-Q	care seeking (qualitative interview)	*qualitative findings: see main text*				NA

All studies in the table had a cross-sectional design. Studies are organized by outcome type (attitude vs behavior vs both) and risk of bias (from high to low evidence quality). In the 'Association with outcome' column, green cells indicate positive associations, pink cells negative associations, grey cells non-significant associations, and black cells that the association was not tested. RoB, Risk of bias assessment with the Newcastle-Ottawa scale for cross-sectional studies; ***, high quality evidence (low risk of bias); **, moderate quality evidence (moderate risk of bias); NA, not applicable; NR, not reported; [#], outcome data based on external observations (not self-reports); [a-c], association tested while controlling for [a], age and sex/gender; [b], race; [c], age of onset of psychopathology; VKP, Vragenlijst voor Kenmerken van de Persoonlijkheid (Questionnaire on Personality Traits); AUDADIS-IV, Alcoholism's Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV Version; PAI-BOR, Personality Assessment Inventory-Borderline Scale; SCID-II, Structured Clinical Interview for DSM-IV Axis II Personality Disorders; DIP-Q, DSM-IV and ICD-10 Personality Questionnaire; UCL, Utrecht Coping List.

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TABLE 3 Studies testing associations between DSM/ICD personality disorders grouped under Cluster C or pertaining to former DSM/ICD classifications and outcomes measuring help-seeking attitudes and behaviors.

Help – seeking	First author, year, reference	Country	Population	Sample size	Mean age, years (SD)	Sex - % Female	Personality assessment tool	Outcome measure (tool, if applicable)	Association with outcome					RoB
Cluster C: anxious or fearful personality disorders									avoidant		dependent		obsessive-compulsive	
attitude	Eurelings-Bontekoe 1997 (63)	Netherlands	psychiatric patients	230	36.8 (11.3)	68%	VKP	seeking social support as coping in hypothetical scenario (UCL scale item)	Ø		Ø		- [a]	**
behavior	Iza 2013 (70)	USA	community-dwelling adults	34,653	NR	NR	AUDADIS-IV	lifetime care seeking for anxiety disorders	- [bc]		Ø		- [bc]	***
both	Svanborg 2008 (88)	Sweden	patients with non-remitting depression	10	NR	60%	DIP-Q	care seeking (qualitative interview)	*qualitative findings: see main text*					NA
Additional personality disorders from earlier classifications (DSM-III, ICD-10)									passive-aggressive	self-defeating	sadistic	anxious	impulsive	
attitude	Eurelings-Bontekoe 1997 (63)	Netherlands	psychiatric patients	230	36.8 (11.3)	68%	VKP	seeking social support as coping in hypothetical scenario (UCL scale item)	Ø	- [a]	Ø	Ø	Ø	**

All studies in the table had a cross-sectional design. Studies are organized by outcome type (attitude vs behavior vs both) and risk of bias (from high to low evidence quality). In the 'Association with outcome' column, pink cells indicate negative associations, grey cells non-significant associations, and black cells that the association was not tested. RoB, Risk of bias assessment with the Newcastle-Ottawa scale for cross-sectional studies; ***, high quality evidence (low risk of bias); **, moderate quality evidence (moderate risk of bias); NA, not applicable; NR, not reported; [a–c], association tested while controlling for [a], age and sex/gender; [b], race; [c], age of onset of psychopathology; VKP, Vragenlijst voor Kenmerken van de Persoonlijkheid (Questionnaire on Personality Traits); AUDADIS-IV, Alcoholism's Alcohol Use Disorder and Associated Disabilities Interview Schedule–DSM-IV Version; DIP-Q, DSM-IV and ICD-10 Personality Questionnaire; UCL, Utrecht Coping List.

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TABLE 4 Studies testing associations between five factor personality dimensions and outcomes measuring help-seeking attitudes.

First author, year, reference	Country	Population	Sample size	Mean age, years (SD)	Sex - % Female	Tool measuring personality	Outcome measure	Association with outcome					RoB
								N	E	O	A	C	
Hatchett, 2019 (66)	USA	college students	458	20.3 (3.6)	80%	NEO Five Factor Inventory	ATSPPH	Ø	+ acf	+ acf	+ acf	+ acf	***
Puma, 1996 (T) (82)	USA	college students	263	18.6 (1.2)	54%	NEO Five Factor Inventory	ATSPPH	Ø	Ø	Ø	Ø	Ø	***
Kakhnovets, 2011 (72)	USA	college students	411	18.8 (2.4)	47%	NEO Personality Inventory - Revised	ATSPPH-SF	+ M	+ F	+	Ø	Ø	***
Miller, 2010 (T) (76)	USA	college students	784	19.6 (2.1)	61%	IPIP Five Factor Model	ATSPPH-SF	+ e	Ø				***
Oluyinka, 2011 (79)	Nigeria	college students	452	23.3 (2.7)	48%	Openness to Experience scale	ATSPPH-SF			+ e			***
Drapeau, 2016 (62)	worldwide; 82.3% USA	adults bereaved by suicide	418	49.5 (13.1)	90%	NEO Five Factor Inventory	IASMHS	- c	- c	+ c	+ c	Ø	***
Joyce, 2013 (T) (71)	USA	college students	494	NR	60%	IPIP Five Factor Model	ISCI	Ø	Ø	+ c	+ c	Ø	***
Billingsley, 1999 (T) (53)	USA	non-professionals & professionals at a rehabilitation hospital	132	47.9 (4.0)	63%	NEO Five Factor Inventory	ATSPPH	Ø	Ø	+ af	Ø	Ø	**
Yelpaze, 2020 (95)	Turkey	college students	1,284	NR	58%	Basic Personality Traits Inventory	ATSPPH	Ø	Ø	- ce	+ ce	+ ce	**
Ingram, 2016 (69)	USA	primary care patients	227	43.1 (12.8)	41%	Mini IPIP	ATSPPH-SF	Ø	+	Ø	+	Ø	**
Rankine, 2021 (T) (83)	USA	community-dwelling adults	200	34.2 (9.2)	41%	Mini IPIP	ATSPPH-SF	Ø	Ø				**
Samuel, 2022 (85)	Canada	college students	167	NR	78%	Big Five Inventory	IASMHS	Ø	Ø	Ø	Ø	Ø	**
Hyland, 2015 (68)	Ireland	active and retired policemen	331	28.4 (8.6)	39%	Eysenck Personality Questionnaire Revised	IASMHS	+	Ø				**
Kessler, 2015 (73)	Germany	community-dwelling older adults	156	71.5 (6.4)	57%	NEO Five Factor Inventory-30	IASMHS	- abfeg		- abfeg			**
Atik, 2011 (52)	Turkey	college students	524	20.0 (2.1)	76%	Big Five Inventory	SASPH-S	Ø	+ af	+ af	+ af	+	**
O'Connor, 2014 (78)	Australia	college students	180	NR	82%	Big Five Inventory	ISPHQ		+ efg				**

All studies in the table had a cross-sectional design. Studies are organized by risk of bias (from low to high) and outcome measure. In the 'Association with outcome' column, green cells indicate positive associations, pink cells negative associations, grey cells non-significant associations, and black cells that the association was not tested. N, neuroticism; E, extraversion; O, openness to experience; A, agreeableness; C, Conscientiousness; RoB, Risk of Bias assessment with the Newcastle-Ottawa scale adapted for cross-sectional studies; ***, high quality evidence (low risk of bias); **, moderate quality evidence (moderate risk of bias); (T), PhD thesis dissertation; NR, not reported; [a-g], association tested while controlling for [a], gender/sex, [b], other demographics, [c], the Five Factors and/or other personality traits, [d], psychiatric diagnosis/mood, [e], other psychological constructs, [f], mental health knowledge and/or experience, [g], social support; IPIP, International Personality Item Pool; ATSPPH, Attitudes Towards Seeking Professional Psychological Help Scale; ATSPPH-SF, Attitudes Towards Seeking Professional Psychological Help Scale – Short Form; IASMHS, Attitudes Toward Seeking Mental Health Services; ISCI, Intentions to Seek Counseling Inventory; ISPHQ, Intention to Seek Professional Help Questionnaire; M, in men only; F, in women only.

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TABLE 5 Studies testing associations between five factor personality dimensions and outcomes measuring help-seeking behavior.

First author, year, reference	Country	Population	Sample size	Mean age, years (SD)	Sex - % Female	Tool measuring personality	Outcome measure	Association with outcome					RoB
								N	E	O	A	C	
Delay in care seeking													
Gormley, 1998 (65)	Ireland	psychiatric patients	82	41.1 (NR)	57%	Maudsley Personality Inventory	time to initial medical consult for depression [#]	+					***
Valipay, 2019 (92)	India	psychiatric patients with depression	100	NR	54%	Big Five Inventory-10	early vs late help-seeking for depression	Ø	Ø	Ø	Ø	Ø	**
Presence vs absence of care seeking													
Cuijpers, 2007 (59)	Netherlands	nursing home residents	350	84.7 (6.2)	72%	NEO Five Factor Inventory	care seeking for depression ≤ 3 months (ATCWD item)	+ abcde	Ø	Ø	Ø	+ d	***
Schomerus, 2013 (86)	Germany	adults with depression	354	NR	NR	NEO Five Factor Inventory-30	lifetime care seeking for depressive symptoms	Ø	Ø	Ø	Ø	+ abcd ef	***
Boerema, 2016 (55)	Netherlands	adults with depression	102	52 (NR)	54%	NEO Five Factor Inventory	care seeking for major depression ≤ 6 months	Ø					***
van Zoonen, 2015 (93)	Netherlands	adults with subclinical depression	162	57.2 (17.8)	56%	NEO-Five Factor Inventory	care seeking for psychological problems ≤ 6 months	+					***
Park, 2017 (80)	South Korea	community-dwelling adults	1544	NR	54%	Big Five Inventory-10	lifetime care seeking for mental health difficulties	+ abd	Ø	+ abd	- abd	Ø	***
Maier, 1992 (97)	Germany	community-dwelling adults with depression	447	41. (NR)	54%	Munich Personality Test	lifetime and one-year care seeking for depression	Ø	- d				**
Hayslip, 2010 (67)	USA	community-dwelling older adults	233	73.1 (7.7)	66%	NEO Personality Inventory-S	lifetime care seeking for emotional/ mental problems	+ R	Ø	+ U			*
Shahaf-Oren, 2021 (87)	United Kingdom	medical students with health issues	11	23.1 (NR)	46%	qualitative interviews	seeking mental health care as medical students	*qualitative findings: see main text*					NA
Social support seeking													
McCrae, 1986 (74)	USA	community-dwelling adults	151	NR	47%	NEO Inventory	seeking social support as coping ≤ 1 year… from checklist (Study 1) freely reported (Study 2) (Ways of Coping Checklist – modified by authors)	Ø	+ g S2	Ø			**
Rim, 1986 (84)	Israel	college students & community-dwelling adults	174	NR	46%	Eysenck Personality Questionnaire	seeking social support as coping (Ways of Coping Checklist Revised)	+ M	+ F				*

All studies in the table had a cross-sectional design. In the 'Association with outcome' column, green cells indicate positive associations, pink cells negative associations, grey cells non-significant associations, and black cells that the association was not tested. N, neuroticism; E, extraversion; O, openness to experience; A, agreeableness; C, Conscientiousness; RoB, Risk of Bias assessment with the Newcastle-Ottawa scale adapted for cross-sectional studies; ***, high quality evidence (low risk of bias); **, moderate quality evidence (moderate risk of bias); *, low quality of evidence (high risk of bias) (T), PhD thesis dissertation; NA, not applicable; NR, not reported; [#], outcome data based on external observations (not self-reports); [a-g], association tested while controlling for [a], gender/sex, [b], other demographics, [c], chronic illness/comorbidities, [d], psychiatric diagnosis/mood, [e], other psychological constructs, [f], social support, [g], mental health knowledge and/or experience; R, only in rural subsample; U, only in urban subsample; M, in men only; F, in women only; S2, in Study 2 only; ATCWD, Actions To Cope With Depression questionnaire.

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TABLE 6 Studies testing associations of other personality traits with outcomes measuring help-seeking attitudes.

First author, year	Country	Population	Sample size	Mean age, years (SD)	Sex - % Female	Personality trait: definition (measuring tool)	Outcome measure	Association with outcome	RoB
Cortese, 2004 (58) (T)	USA	male university employees	308	44.3 (12.2)	0%	maladaptive psychological traits (Personality Adjective Check List)	ATSPPH	Ø [a]	***
Yi, 1998 (96) (T)	USA	Korean Americans	157	31.9 (9.9)	55%	psychological maladjustment: *social alienation, emotional disturbance* (OPI-PI)	ATSPPH	Ø	**
Yelpaze, 2020 (95)	Turkey	college students	1,284	NR	58%	negative valence: *negative self-view* (Basic Personality Traits Inventory)	ATSPPH	- [ab]	**
Dang, 2020 (61)	Canada	college students & community-dwelling adults	376	23.3 (4.6)	61%	perfectionism traits: *tendency to seek perfection in all tasks/actions* (Multidimensional Perfectionism Scale)	ATSPPH	- S	**
Cole, 2014 (57) (T)	USA	male college students	366	20.2 (2.8)	0%	trait hope: *tendency to be hopeful* (Trait Hope Scale – Revised)	ATSPPH	+ M	**
Pugh, 2002 (81) (T)	USA	college students	281	18.4 (1.9)	50%	interpersonal affect: *emotional, tender* (Jackson Personality Inventory)	ATSPPH-SF	+	**
						tolerance: *broadminded, impartial* (Jackson Personality Inventory)		+	
						other traits of the same inventory (Jackson Personality Inventory)		Ø	
Hyland, 2015 (68)	Ireland	active and retired policemen	331	28.4 (8.6)	39%	psychoticism: *risk-taking, impulsivity, antisocial behavior, non-conformity* (Eysenck Personality Questionnaire Revised)	IASMHS	Ø	**

Studies in the table had a cross-sectional design except for Tyssen, 2004, which was prospective. In the 'Association with outcome' column, green cells indicate positive associations, pink cells negative associations, grey cells non-significant associations, and black cells that the association was not tested. Legend: RoB, Risk of Bias assessment with the Newcastle-Ottawa scale adapted for cross-sectional studies; ***, high quality evidence (low risk of bias); **, moderate quality evidence (moderate risk of bias); (T), PhD thesis dissertation; NR, not reported; [a-b], association tested while controlling for [a], other psychological constructs, [b], other personality traits; M, in men only; S, in student subsample; OPI-PI, Omnibus Personality Inventory – Personal Integration subscale; ATSPPH, Attitudes Towards Seeking Professional Psychological Help Scale; ATSPPH-SF, Attitudes Towards Seeking Professional Psychological Help Scale – Short Form; IASMHS, Attitudes Toward Seeking Mental Health Services.

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TABLE 7 Studies testing associations of other personality traits with past help-seeking behavior.

First author, year	Country	Population	Sample size	Mean age, years (SD)	Sex - % Female	Personality trait: *definition* (measuring tool)	Outcome measure	Association with outcome	RoB
Dalum, 2022 (60)	Norway	veterinarians	3,464	NR	70%	reality weakness personality trait: *proneness to thoughts/perceptions in-between reality and fantasy* (Torgersen's Basic Character Inventory)	care seeking for mental health problems ≤ 1 year	-	***
Tyssen, 2004 (90)	Norway	physicians during last year of medical school and at their first and fourth year post medical school	631	28.0 (2.8)	57%	reality weakness personality trait: *proneness to thoughts/perceptions in-between reality and fantasy* (Torgersen's Basic Character Inventory)	care seeking for mental health problems ≤ 1 year	- abcd	***
						vulnerability: *similar to neuroticism* intensity: *similar to extraversion* control: *compulsiveness, orderliness* (Torgersen's Basic Character Inventory)		Ø	
Arbisi, 2022 (51)	USA	national guard soldiers	40	31.2 (8.7)	NR	cynicism: *tendency to view others as motivated by self interest* (MMPI2-RC3)	one-year post-deployment mental health service utilization	- def	***
Michal, 2011 (75)	Germany	community-dwelling adolescents & adults	2,495	48.7 (17.4)	55%	Type D Personality: *tendency towards negative affectivity and social inhibition* (Type D Scale-14)	help-seeking and care seeking from various sources ≤ 1 year	+	***
Maier, 1992 (97)	Germany	community-dwelling adults with depression	447	41.1 (NR)	54%	rigidity: *obsessionality* (Munich Personality Test)	lifetime and one-year care seeking for depression	+ d	**
						schizoidia: *isolation & esoteric tendencies* (Munich Personality Test)		Ø	
Minge, 1967 (77)	USA	college students	125	NR	NR	abasement: *tendency to accept blame for problems and confess errors* (Edwards Personal Preference schedule)	counseling clients vs non-clients	+	**
						dominance: *need to lead/influence others* (Edwards Personal Preference schedule)		-	
						order: *need to plan and be organized* (Edwards Personal Preference schedule)		-	
						other traits of the same inventory (Edwards Personal Preference schedule)		Ø	
Yi, 1998 (96) (T)	USA	Korean Americans	157	31.9 (9.9)	55%	psychological maladjustment: *social alienation, emotional disturbance* (OPI-PI)	Help Seeking Behavior Scale	Ø	**
Rim, 1986 (84)	Israel	students & community-dwelling adults	174	NR	46%	psychoticism: *risk-taking, impulsivity, antisocial behavior, non-conformity* (Eysenck Personality Questionnaire)	seeking social support as coping	- F	*

Studies in the table had a cross-sectional design except for Tyssen, 2004, which was prospective. In the 'Association with outcome' column, green cells indicate positive associations, pink cells negative associations, grey cells non-significant associations, and black cells that the association was not tested. RoB, Risk of Bias assessment with the Newcastle-Ottawa scale adapted for cross-sectional studies; ***, high quality evidence (low risk of bias); **, moderate quality evidence (moderate risk of bias); (T), PhD thesis dissertation; NR, not reported; [a-f], association tested while controlling for [a], gender/sex, [b], other demographics, [c], social support, [d], psychiatric diagnosis/mood, [e], other psychological constructs, [f], mental health knowledge and/or experience; F, in women only; MMPI2-RC3, Minnesota Multiphasic Personality Inventory 2 – Restructured Clinical Scale 3; OPI-PI, Omnibus Personality Inventory – Personal Integration subscale.

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whereas the timeframe was not specified in one study (84) and one study assessed both one year and lifetime help-seeking (97). Two studies assessed delays in care seeking (65, 92).

3.2 Assessment of risk of bias

About half of the quantitative studies (23 out of 46) were rated as high evidence quality (low risk of bias). Most other studies were rated as moderate evidence quality (n = 21), whereas two studies were rated as low evidence quality (67, 84).

Appraisal categories where a majority of studies showed concern included outcome reliability (n = 42), as the outcome was measured as self-report in most studies; comparability of findings, as many studies did not adjust their analysis to mental health status or other potential confounders (n = 32), and reporting on non-respondents (n = 28). Detailed scores for the risk of bias assessment can be found in Supplementary Table S2. Risk of bias ratings have also been added to Tables 1–7 for ease of reference.

3.3 Synthesized findings by personality construct

3.3.1 DSM/ICD personality disorders

Tables 1–3 provide a summary of studies reporting on the association between DSM/ICD Personality Disorders and help-seeking attitudes (n = 2), help-seeking behavior (n = 6), or both (n = 1).

3.3.1.1 Cluster A personality disorders

As indicated in Table 1, four studies reported on the association between Cluster A personality disorders, namely paranoid, schizoid, and schizotypal personality disorders, and help-seeking (54, 63, 64, 70), with two of them investigating schizotypal personality alone (54, 64).

All three personality disorders were associated with more negative attitudes towards social support seeking (63) and schizotypal traits were also associated with more negative attitudes towards seeking professional psychological help (64).

However, whereas paranoid and schizoid personality disorders were also associated with a lower likelihood of having sought care for anxiety disorders in a community sample, this association was not found with schizotypal personality disorder (70), which was linked to an increased likelihood of recent (≤ 8 weeks) help-seeking for anxiety symptoms in college students (54).

3.3.1.2 Cluster B personality disorders

As indicated in Table 2, one qualitative (88) and six quantitative studies (56, 63, 70, 89, 91, 94) reported on associations between help-seeking and Cluster B personality disorders, namely antisocial [labeled 'dissocial' in ICD-10 (102)], borderline, histrionic, and narcissistic personality disorders: two studies investigated all four Cluster B traits (63, 70), whereas other studies reported associations with antisocial (91) or borderline traits (56, 88, 89, 94).

In the only study investigating attitudes towards help-seeking for psychological distress, antisocial and borderline personality disorders were associated with more negative attitudes (63). Patients with non-remitting depression and borderline traits suggested that the tendency to conceal their feelings contributed to their negative attitudes and delayed help-seeking (88).

However, all associations between borderline personality disorder/traits and past help-seeking behaviors were positive, indicating that individuals with more borderline traits were more likely to seek professional help for anxiety or low mood during their life (70, 89), but also in more acutely stressful situations, such as a suicidal crisis (56) or during time spent in jail (94).

Findings were more inconsistent for antisocial personality disorder, with studies reporting a lower likelihood of lifetime care seeking for anxiety disorders (70) but a higher likelihood of one-year care seeking for more generally defined psychological distress (91).

Limited evidence found no associations between histrionic and narcissistic personality disorders and attitudes towards help-seeking (63) or past help-seeking behavior (70).

3.3.1.3 Cluster C personality disorders

As indicated in Table 3 (upper), one qualitative (88) and two quantitative studies (63, 70) reported on associations between help-seeking and Cluster C personality disorders, namely avoidant, dependent, and obsessive-compulsive personality disorders.

Of the three personality disorders, only obsessive-compulsive had a negative association with attitudes towards help-seeking (63).

Both avoidant and obsessive-compulsive personality disorders had negative associations with lifetime care seeking for anxiety disorders (70). In a qualitative study, patients with non-remitting depression and avoidant personality traits further indicated that their difficulties with handling conflict could hinder their engagement in therapy (88).

3.3.1.4 Personality disorders from former classifications (DSM-III/ICD-10)

As also indicated in Table 3 (lower), one study investigated former personality disorder diagnoses, namely passive-aggressive, self-defeating, sadistic, anxious, and impulsive personality disorders (63). It found that self-defeating personality was associated with more negative attitudes towards help-seeking, yet no associations were found for the other personality disorders.

3.3.2 Five factor personality dimensions

A total of 16 studies investigated associations between Five Factor dimensions and help-seeking attitudes (Table 4), all of which investigated attitudes towards care seeking (52, 53, 62, 66, 68, 69, 71–73, 76, 78, 79, 82, 83, 85, 95), whereas 13 studies contained in 12 records tested associations with help-seeking behaviors [Table 5 (55, 59, 65, 67, 74, 80, 84, 86, 87, 92, 93)]. Of these, ten studies focused on care seeking and three studies from two records investigated social support seeking (74, 84).

3.3.2.1 Neuroticism

With respect to help-seeking attitudes, three studies out of the 14 investigating neuroticism found significant positive associations

(68, 72, 76), with one of them only finding this association in men (72). Two other studies, which adjusted their analysis to confounders such as the four other Five Factor dimensions or sociodemographic characteristics and mental health experience found negative associations (62, 73). Of note, the negative associations were found in studies with older study samples (mean age ≥ 49.5 years) compared to studies reporting positive associations (mean age ≤ 28.6 years).

Neuroticism was positively associated with help-seeking behavior in six out of eleven studies. Care seeking was associated with neuroticism in community-dwelling adults (80), rural older adults (67), nursing home residents (59), and subclinically depressed adults (93), whereas social support seeking was positively associated with neuroticism in a male subsample of college students and community-dwelling adults (84). However, one study out of two also linked neuroticism to a longer delay before seeking care in psychiatric patients (65).

3.3.2.2 Extraversion

Of the 14 studies investigating associations between extraversion and help-seeking attitudes, five found positive associations, namely in primary care patients (69), college students (52, 66, 78), and female college students only (72). One study on adults bereaved following suicide found a negative association between extraversion and help-seeking attitudes (62).

One out of five studies found a negative association between extraversion and care seeking (97), whereas two out of three studies found positive associations between extraversion and social support seeking (74, 84), with one study only finding this association in women (84).

3.3.2.3 Openness to experience

Seven out of twelve studies investigating the relationship between help-seeking attitudes and openness to experience found positive associations (52, 53, 62, 66, 71, 72, 79), whereas two found negative associations (73, 95). Positive as well as negative associations were reported in both student samples and older populations. However, studies reporting positive associations had overall higher evidence quality.

Openness to experience had a positive association with lifetime care seeking for mental health difficulties in community dwelling adults (80) and in urban (but not rural) older adults (67). In a qualitative study, medical students with physical and/or mental health issues also named openness as an important personality trait to be able to disclose mental suffering to healthcare professionals (87). There were no associations reported with other types of help-seeking behaviors.

3.3.2.4 Agreeableness

Of the ten studies investigating agreeableness and attitudes towards help-seeking, positive associations were found in six studies with diverse populations, namely college students (52, 66, 71, 95), adults bereaved by suicide (62), and primary care patients (69), whereas none reported negative associations.

With respect to help-seeking behaviors, a negative association between agreeableness and lifetime care seeking for mental health difficulties was found in a Korean population study with a large sample (N = 1,544) and high evidence quality (80), but in none of the other three studies investigating this relationship (59, 86, 92).

3.3.2.5 Conscientiousness

Three out of ten studies found a positive relationship between conscientiousness and attitudes towards help-seeking, all of which were conducted in college students (52, 66, 95) and two of which were carried out in Turkey (52, 95). No study found negative associations.

With respect to help-seeking behaviors, two studies found positive associations with care seeking for depression, within three months in nursing home residents (59) and at any point in life in depressed adults (86).

3.3.2.6 Confirmation of main trends by meta-analysis for help-seeking attitudes

Random-effects meta-analyses for the Five Factor dimensions (Figure 2) did not show significant heterogeneity, hence we did not conduct any subgroup analysis. The main analysis supported the presence of modest associations between neuroticism and more negative attitudes towards seeking professional psychological help as well as between agreeableness and more positive attitudes towards seeking professional psychological help.

Of these two associations, only the one with neuroticism remained in a sensitivity analysis excluding studies for which correlation coefficients were estimated based on beta coefficients (Supplementary Figure S1).

3.3.3 Other personality traits not belonging to DSM/ICD personality disorders or to the Five Factor Model

Of the 14 studies assessing personality constructs not included in DSM/ICD personality disorders or in the Five Factor Model, seven investigated attitudes towards help-seeking [Table 6 (57, 58, 61, 68, 81, 95, 96)] and eight investigated help-seeking behavior [Table 7 (51, 60, 75, 77, 84, 90, 96, 97)]. One study investigated both types of outcomes (96).

With respect to attitudes towards help-seeking, negative associations were present in college students who had higher levels of negative valence (negative self-view) (95) and more perfectionistic traits (61). By contrast, traits related to a positive mindset such as trait hope, interpersonal affect (the tendency to be emotional and tender, close to the Five Factor Model's agreeableness), and tolerance (the tendency to be broadminded and impartial, close to the Five Factor Model's openness to experience) had positive associations with help-seeking attitudes (57, 81), although the association with trait hope was only present in men (57).

With respect to help-seeking behavior, care seeking for mental health difficulties was negatively associated with reality weakness (the tendency to experience thoughts/perceptions in-between reality and fantasy, especially when feeling overwhelmed by situations) in Norwegian samples of veterinarians (60) and early-

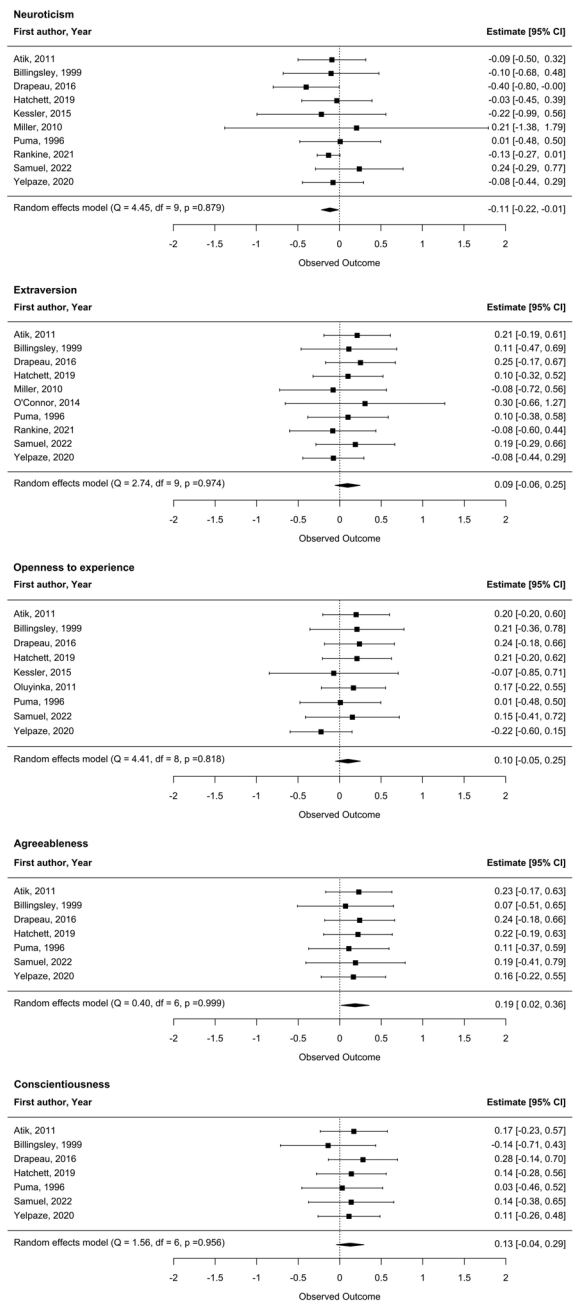

FIGURE 2
Meta-analysis results (Forest plots) of associations between the Five Factor dimensions of personality and attitudes towards professional help seeking. Estimates indicate correlation coefficients (reported by studies or estimated based on standardized beta coefficients).

career physicians over a four-year follow up period (90). By contrast, abasement, the tendency to accept blame and confess errors was positively associated with care seeking in college students (77).

Traits related to interpersonal functioning, namely cynicism, the tendency to view others as motivated by their own interest (51), and dominance, the need to lead/influence others (77) were also related to less care seeking, whereas psychoticism, defined by risk-taking, impulsivity, and non-conformity, was related to less social support seeking (84).

Order, which is seen by some authors as a dimension of perfectionism (103) and conscientiousness (104) and is defined by the need to be organized and to plan ahead, was also negatively associated with care seeking in college students (77). However, rigidity, a trait characterizing obsessionality and linked to order, perfectionism (105), and obsessive-compulsive personality disorder (106, 107), was positively associated with lifetime and one-year treatment-seeking for depression (97).

Finally, Type D personality, which encompasses negative affectivity and social inhibition, was positively associated with both help- and care seeking in a community sample (75).

4 Discussion

4.1 Summary of main findings

This work reviewed the evidence on associations between personality and help-seeking for psychological distress. Of the 48 studies reporting on this association, about half investigated help-seeking behaviors as opposed to attitudes towards help-seeking. Most studies used self-reports to assess help-seeking and less than half provided high quality evidence.

With respect to DSM/ICD personality disorders, limited cross-sectional evidence indicated opposite associations of attitudes and behaviors with schizotypal and borderline personality disorders, which were related to increased help-seeking behavior despite more negative attitudes towards help-seeking. In contrast, avoidant, obsessive-compulsive, paranoid, and schizoid personality disorders were associated with less help-seeking behavior, and with more negative attitudes towards help-seeking in the case of the latter three. Surprisingly, neither histrionic nor narcissistic personality disorders were associated with help-seeking attitudes or behaviors, despite their established associations with emotional liability and with increased general health care utilization in the case of histrionic personality disorder (108, 109). However, as only two studies reported on each disorder, this lack of associations may primarily reflect a scarcity of research, which should be addressed.

Of the Five Factor personality dimensions, neuroticism was the only one that was associated with negative attitudes towards professional care seeking. This association was confirmed by meta-analysis and is generally consistent with findings from other studies linking neuroticism to poorer disease self-management (110), and to the use of more maladaptive coping strategies in response to depression and anxiety (111). At the same time, neuroticism was associated with more help-seeking behavior (care seeking in particular) across most studies, suggesting a similar dissociation between attitudes and behavior as observed for some DSM/ICD personality disorders. The four 'adaptive' Five Factor dimensions manifested trends of positive attitudes towards professional care seeking, although they only reached significance for agreeableness in the meta-analysis, and did not hold after removing estimated correlation coefficients. Extraversion was positively associated with social support seeking, but had a negative association with care seeking. By contrast, conscientiousness was positively associated with care seeking and had no association with social support seeking.

Associations reported for other personality constructs corroborated several above-mentioned relationships with help-seeking attitudes. Negative attitudes towards help-seeking were linked to negative valence, which is close to the self-consciousness facet of neuroticism (104), and to perfectionism, a dimension of obsessive-compulsive personality disorder (32). Associations with help-seeking behavior supported findings of DSM/ICD personality disorders and the Five Factor Model, e.g., the negative relationship between help-seeking behavior and cynicism, which is included in paranoid personality (32, 33), or the positive associations with Type D personality, closely related to neuroticism (112).

Yet, findings with other personality constructs and help-seeking behavior sometimes nuanced results obtained with DSM/ICD personality disorders or the Five Factor Model. Reality weakness, commonly associated with paranoid, schizotypal, and borderline personality disorders (113, 114), had negative associations with help-seeking behavior, suggesting that escaping into fantasy when feeling overwhelmed may contribute to an avoidance of seeking help in the two Cluster A disorders, but not necessarily in borderline personality disorder, where other symptoms may play a larger part in getting into mental health care.

Similarly, rigidity's positive association with help-seeking behavior suggests that the negative relationship between help-seeking behavior and obsessive-compulsive personality disorder may arise from different underlying dimensions. Even though rigidity has been defined as a form of perfectionism (105), these two constructs have been identified as distinct factors of obsessive-compulsive personality disorder (106, 107), with perfectionism corresponding to orderliness, and rigidity mapping more clearly on stubbornness (107). As rigidity has been associated with depression above and beyond other personality traits such as neuroticism (105), it may be the case that it reflects a particularly maladaptive side of obsessive-compulsive personality disorder, which is independent, or only partially overlapping with perfectionism.

4.2 Integration of findings regarding help-seeking attitudes and behavior

The integrated evidence highlights a dissociation between certain individuals' reservations towards seeking help for psychological distress and their actual help-seeking behavior. This appears to be the case for adults with high neuroticism, a strong predictor of prospective risk of depression and anxiety (115), as well as schizotypal and borderline personality disorders, identified as the most robust independent predictors of persisting major depression among all DSM personality disorders (116). It seems likely that these personality traits/disorders tie in with dysfunctional behavioral patterns, which reduce emotional expressivity on the one hand (117–119), while increasing emotional instability and subsequent mental healthcare use on the other.

By contrast, some of the personality constructs that displayed a consistent pattern of negative attitudes towards help-seeking and less past help-seeking behavior may delineate groups that remain undertreated for acute psychological distress. Based on scarce evidence, such patterns may be present for paranoid and schizoid personality disorders, and possibly for obsessive-compulsive personality disorder, although a contrasting positive relationship between rigidity and help-seeking behavior weakens this last supposition.

Consistent with the notion of under-treatment, paranoid and schizoid personality disorders are scarce in mental healthcare settings. Adding to the challenge, their prognosis remains poorer than for other personality disorders when admitted for inpatient treatment (120). Obsessive-compulsive personality disorder has been linked to death by suicide in old age (121), which most often arises in the context of depression (122), and may signal failure at seeking help (123).

Associations with personality traits facilitating the help-seeking process remained inconsistent, possibly due to a lack of adjustment for mental illness presence and/or severity. Moreover, it remains likely that personality traits may compensate for each other (124), and studying their combinations would yield more consistent results.

Finally, it appears necessary to test personality in relation to objective measures of help-seeking, namely externally observed, longitudinal help-seeking outcomes. Only one third of individuals who report positive attitudes towards help-seeking for serious emotional problems will seek professional psychological help over the following 10 years (125). Moreover, intervention studies promoting help-seeking for psychological distress tend to impact help-seeking attitudes but fail to obtain results on help-seeking behavior (25). Looking at help-seeking through the lens of personality can help understand broader behavioral patterns underlying help-seeking behavior and personalize motivational approaches to a greater extent. Personality measures have already been integrated into machine learning algorithms for risk/outcome prediction (126), suggesting their relevance for precision mental health.

4.3 Strengths and limitations

Strengths of the present systematic review and meta-analysis include its robust methodology and comprehensive synthesis of a broad range of personality constructs and outcomes that enabled a more nuanced understanding of the dynamics between personality and attitudinal vs behavioral assessments of help-seeking for psychological distress.

With respect to limitations, it is worth noting that the definitions of personality and psychological distress were limited to a relatively narrow scope. Further, as only three studies assessing help-seeking behavior consistently relied on external observations and only one used longitudinal data, most reported relationships retain non-negligible subjectivity, even though observed and prospective outcomes aligned with most self-reported, cross-sectional associations. Prior research has found considerable recall bias for self-reported ambulatory physician visits over the past year (127). The heterogeneity of findings in most subsections did not make it possible to conduct meta-analyses. Finally, the limited number of studies with similar characteristics made it challenging to draw conclusions about differences between sampled populations on age, sex, culture, psychopathology, and other factors.

5 Conclusions

Many pathological and maladaptive personality disorders and traits have been linked to negative attitudes towards seeking psychological help, in particular from professionals. Personality profiles characterized by high neuroticism, schizotypal, and borderline traits may be more likely to engage in mental healthcare despite negative general attitudes towards care seeking, whereas others, such as schizoid, paranoid, or obsessive-compulsive personality disorders will more likely remain concealed from potential sources of help despite unfavorable long-term prognostics. Future research should confirm prominent findings with more longitudinal evidence and objectively measured outcomes, while clinical interventions should consider focusing efforts on hard-to-reach populations, such as individuals with paranoid, schizoid, or obsessive-compulsive traits. Traits that can be leveraged in interventions aimed at improving help-seeking may include extraversion for social support seeking, conscientiousness for care seeking, and agreeableness for more positive attitudes towards help-seeking.

Author contributions

AS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. RL: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. WT: Data curation, Investigation, Methodology, Writing – review & editing. LZ: Formal analysis, Methodology, Writing – review & editing. ML: Investigation, Methodology, Writing – review & editing. AM: Conceptualization, Methodology, Supervision, Writing – review & editing. JV: Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing.

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Conflict of interest

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

The authors AM and JV declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1405167/full#supplementary-material

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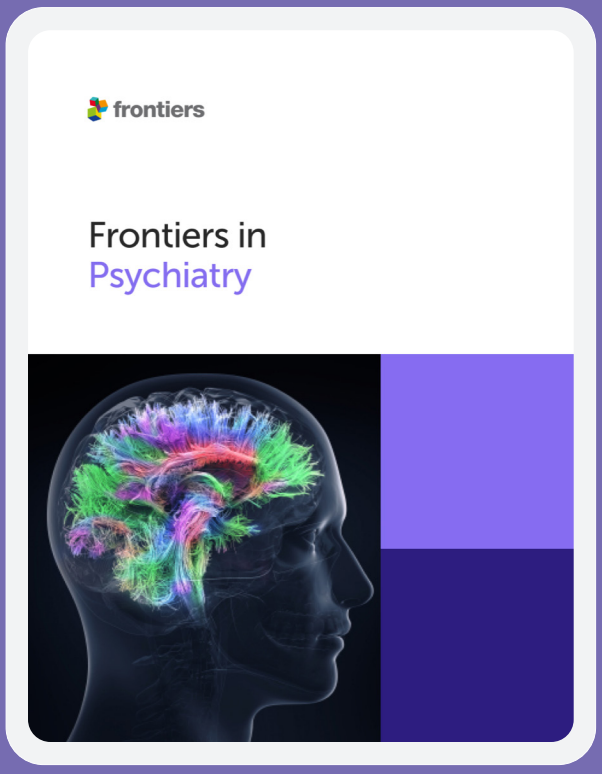

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