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# Journal of PSYCHO PATHO LOGY

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# Alterations in body image, self-esteem and quality of life in a sample of Italian transgender individuals before gender-affirming surgery

Giuseppe Maniaci<sup>1\*</sup>, Caterina La Cascia<sup>1</sup>, Crocettarachele Sartorio<sup>1</sup>, Laura Ferraro<sup>1</sup>, Alessandra Giammanco<sup>1</sup>, Rosalia Anselmo<sup>1</sup>, Giuseppe Oddo<sup>1</sup>, Elisa Parrinello<sup>1</sup>, Francesca Toia<sup>2</sup>, Giovanni Zabbia<sup>2</sup>, Adriana Cordova<sup>2\*</sup>, Daniele La Barbera<sup>1\*</sup>

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\*Adriana Cordova and Daniele La Barbera equally supervised the manuscript. They both are last authors.

## SUMMARY

### Objectives

*Mental health, alterations in body image, self-esteem, general and sexual quality of life among transgender individuals waiting for gender-affirming surgery versus cisgender individuals were investigated.*

### Methods

*47 Italian transgender participants and 47 cisgender participants completed self-report measures.*

### Results

*Compared to cisgender ones, trans participants showed higher alterations in self-esteem, body image, and psychological, social, and sexual quality of life, together with a comparable level of mental health conditions (Tab. I). No significant differences emerged between trans men and trans women in terms of the variables taken into account (Tab. II). Moreover, trans individuals receiving hormone therapy are more likely to report both better quality of life and body image than those who are not receiving it yet (Tab. III).*

### Conclusions

*The main psychological distress of individuals diagnosed with gender dysphoria seems related to the symptoms directly associated with their gender incongruence, such as body image, self-esteem, and quality of life. Healthcare professionals should consider providing surgery and hormonal therapy together with psychotherapy as best practices for such patients.*

**Key words:** body image, gender-affirming care, gender dysphoria, gender incongruence, quality of life

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## Introduction

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* defines gender dysphoria (GD) as a form of clinically significant distress resulting from incongruence between one's experienced gender and one's assigned gender, along with a persistent, strong desire to be rid of one's primary and/or secondary sex characteristics, typically due to a marked incongruence with experienced and/or expressed gender and a strong desire for the primary and/or secondary sex characteristics of the other gender. Beyond those defined characteristics, GD is associated

with clinically significant impairment in important areas of functioning<sup>1</sup>. Recently, in the World Health Organization's eleventh revision of the International Classification of Diseases and Related Health Problems (ICD-11), the diagnostic category of "transsexualism" has been replaced with the term "gender incongruence", and it has been moved into the "Conditions related to sexual health" chapter<sup>2</sup>.

The Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, version 7 (SOC-7), developed by the World Professional Association for Transgender Health (WPATH), offer clinical guidance for health professionals assisting transsexual, transgender, and gender-nonconforming people. Such assistance includes providing primary, gynecological and urological care, voice and communication therapy, mental health services, and hormonal and surgical treatments<sup>3</sup>.

Data on the association of GD and mental health are not homogeneous<sup>4</sup>. Indeed, studies conducted on transgender individuals with GD recruited before<sup>5</sup>, during<sup>5,6</sup> and after gender-affirming treatment<sup>7</sup> highlighted higher rates of coexisting mental health conditions in trans people than the general population<sup>5</sup> and a control-matched group<sup>6,7</sup>. In contrast, other research with trans people recruited before<sup>8</sup>, during<sup>8,9</sup> and after<sup>8</sup> gender-affirming treatment have not found any significant differences.

Despite the possible presence of any mental health problem, commencing hormonal treatment is associated with reduced levels of depression, better self-esteem<sup>10</sup> and improved psychological functioning<sup>11</sup>, sexual function, and overall quality of life<sup>12</sup>.

Alteration of body image is another pathological pattern characterizing patients who have received a GD diagnosis<sup>13</sup>, together with a dissatisfying sexual<sup>14</sup>, physical, and mental quality of life<sup>15</sup>.

Although studies focusing on Italian transgender people are on the rise<sup>16-18</sup>, more research is needed. Indeed, as far as we know, only one of them investigated both mental health and body image<sup>17</sup> on this population, and none of these studies compared transgender adults with a cisgender group.

Starting from this lack of consensus regarding the psychological well-being of individuals with GD, the aim of this study was to make a psychological assessment of trans people with GD waiting for gender-affirming surgery (GAS) compared to a group of cisgender individuals matched in terms of birth-assigned sex, age, and years of education. For the purpose of this paper, "transgender" is used as an inclusive term for individuals with GD who desire to undergo GAS, whereas "cisgender" is used for individuals whose gender identity and gender expression align with their birth-assigned sex.

Specifically, we assessed coexisting mental health conditions, alterations in body image, self-esteem, general and sexual quality of life in a sample of Italian trans men and trans women compared to a control group of cisgender ones. Possible differences in those psychological characteristics between trans men and trans women and between transgender participants receiving hormone therapy and those not receiving hormone therapy yet were also investigated.

## Methods

### Participants and procedure

Recruited from February 2019 to August 2020, all participants had been examined in the Plastic Surgery Unit of the AOUP "P. Giaccone" in Palermo, Italy, in order to be wait-listed for GAS and were consecutively invited to participate in this study. None of the individuals refused to participate in the study. Each participant was also assessed in a psychiatric interview as well as a psychological interview and asked to answer self-report questionnaires anonymously. A group of cisgender individuals homogenous in terms of birth-assigned sex, age, and years of education was recruited. Cisgender individuals could volunteer to enroll in the study by responding to an advertisement posted in the outpatient clinic and on social media.

Eligibility criteria to participate in the study included: aged at least 18 years old; self-identifying as transgender; meeting the DSM-5 diagnostic criteria for GD; being able to provide their written informed consent. Individuals who self-identified as non-binary were excluded because they typically receive hormone treatment that differs from that of other transgender people.

Specifically, forty-nine consecutive trans patients were screened; among them, two were excluded since they self-identified as non-binary.

Forty-seven individuals with a GD diagnosis (trans women = 42.6%, mean age 28.15, *SD* = 9.20) and forty-seven cisgender adults (42.6% males, mean age 31.57, *SD* = 9.89) participated in this study. Among them, two transgender individuals were excluded from the analysis since during medical history taking it was not possible to clarify if they received hormone treatment under the supervision of health care professionals. In terms of hormone therapy, transgender men took exogenous testosterone, whereas transgender women took exogenous estrogen and anti-androgens. All trans patients asked for psychotherapy, and also received endocrinology and surgical consultations.

This study was approved by the ethical review board of the AOUP "P. Giaccone" in Palermo, Italy ("Comitato Etico Palermo 1", Verb N° 02/2019). Informed consent was obtained from each participant, and all measures were administered with respect for the participants' privacy.

## Measures

### *Millon Clinical Multiaxial Inventory – III*

In order to investigate the presence of coexisting mental health conditions, the Millon Clinical Multiaxial Inventory – III (MCMI-III) was used. The MCMI-III is a 175-item, true-false, self-report questionnaire that measures 14 personality disorders and 10 clinical syndromes according to DSM-IV criteria. The Italian version of the MCMI-III was found to have good psychometric properties: Cronbach's alpha values ranged from 0.66 to 0.90; test-retest reliability was between 0.82 and 0.96<sup>19</sup>.

### *Body Uneasiness Test*

The Body Uneasiness Test (BUT) is a self-report questionnaire that consists of two parts: BUT-A, which measures weight phobia, body image concerns, avoidance, compulsive self-monitoring and depersonalization; and BUT-B, which measures specific worries about particular body parts. The questionnaire consists of 71 items on a 6-point Likert scale (from 0 "never" to 5 "always"). Cronbach's alpha of the Italian-validated version ranges between 0.69 (only BUT-B VII factor "hair, skin") and 0.90; the questionnaire showed a good test-retest reliability<sup>20</sup>.

### *World Health Organization Quality of Life-BREF (WHOQOL-BREF)*

The WHOQOL-BREF was derived from the WHOQOL-100. This self-administered questionnaire is composed of 26 items and it produces scores for 4 domains related to quality of life: physical health, psychological health, social relationships and environment. The Italian version of the WHOQOL-BREF domains has shown good internal consistency, ranging from 0.65 for the social relationships domain to 0.80 for the physical domain; test-retest reliability values range from 0.76 for the environment domain to 0.93 for the psychological domain<sup>21</sup>.

### *Sexual Quality of Life-Female (SQOL-F)*

This self-report questionnaire is composed of 18 items on a 6-point Likert scale, ranging from "completely agree" to "completely disagree". The items were developed through interviews with 82 women and it reflects three specific areas: self-esteem, emotional issues, and relationship issues. A higher total score reflects a better sexual quality of life. The instrument was found to have good internal consistency (Cronbach's alpha = 0.95) and good test-retest reliability<sup>22</sup>.

### *Sexual Quality of Life-Male (SQOL-M)*

The SQOL-M is a 11-item self-administered instrument derived from the SQOL-F questionnaire. Each item is graded on a 6-point Likert-type response scale, ranging from "completely agree" to "completely disagree". High-

er scores imply better sexual quality of life. The questionnaire showed good psychometric properties (Cronbach's alpha = 0.92; test-retest reliability = 0.82)<sup>23</sup>.

### *Basic Self-Esteem Scale*

This self-report test measures that particular type of self-esteem which is independent of personal skills, achievement or outside validation. The questionnaire is composed of 22 items rated along a 5-point Likert scale (from 1 "totally disagree" to 5 "totally agree"). The Italian-validated version showed good psychometric properties: Cronbach's alpha was 0.85, test-retest reliability was between 0.81 and 0.83<sup>24</sup>.

## Statistical analysis

Group-based differences in terms of mental health were analyzed with  $\chi^2$  tests. Normality assumption was tested using the Kolmogorov-Smirnov test. Group-based differences in terms of body image, general and sexual quality of life, and self-esteem levels were analyzed with independent samples *t* tests or Mann-Whitney *U* tests. All analyses assumed an alpha risk of 5%. All statistical analyses were performed in the Statistical Package for the Social Sciences for Windows 22.0.

## Results

The two groups did not differ significantly in age, level of education, birth-assigned sex, or marital status (all  $p > .05$ ).

The Kolmogorov-Smirnov test for normality was significant for body image concerns, avoidance, compulsive self-monitoring, depersonalization, and sexual quality of life ( $p < .05$ ), violating assumption of normality. Moreover, the test was not significant for weight phobia, global severity index, total positive symptoms, positive symptom distress index, overall quality of life, and levels of self-esteem, reflecting normal distribution.

Compared to cisgender ones, transgender participants showed significant higher alterations in several dimensions of body image, including weight phobia, body image concerns, avoidance, compulsive self-monitoring, depersonalization, global severity index, total positive symptoms, and positive symptom distress index. Differences in levels of self-esteem were also significant between the groups, showing that transgender people reported lower levels of self-esteem than cisgender people. Moreover, transgender individuals reported a significant worse sexual, psychological and social relationships quality of life than cisgender ones. No significant differences emerged in terms of physical and environmental quality of life, and mental health problems (Tab. I).

Furthermore, no significant differences emerged between the trans men and trans women in terms of body

**TABLE I.** Comparisons between transgender and cisgender groups.

Factor	Transgender group (n = 47) M (SD)	Cisgender group (n = 47) M (SD)	Independent t test (p value)
Weight phobia	2.55 (1.02)	1.01 (.91)	.000
Global severity index	2.39 (.90)	.91 (1.13)	.000
Positive symptom total	22.69 (8.32)	12.10 (7.93)	.000
Positive symptom distress index	3.29 (.92)	1.74 (.53)	.000
Physical health QoL	66.42 (17.69)	71.25 (17.02)	.199
Psychological QoL	57.48 (20.43)	68.08 (16.23)	.008
Social relationships QoL	62.08 (20.58)	72.01 (17.18)	.016
Environment QoL	61.01 (14.66)	65.11 (16.02)	.220
Self-esteem	39.13 (32.96)	57.59 (33.07)	.010
Factor	Transgender group (n = 47) M Rank	Cisgender group (n = 47) M Rank	Mann-Whitney U test (p value)
Body image concerns	67.61	27.39	.000
Avoidance	66.67	28.33	.000
Compulsive self-monitoring	58.37	36.63	.000
Depersonalization	67.64	27.36	.000
Sexual QoL	24.23	60.83	.000
Factor	Transgender group (n = 47) Frequency (%)	Cisgender group (n = 47) Frequency (%)	Chi Square of Pearson (p value)
Schizoid	2 (4.3%)	-	.153
Avoidant	5 (10.6%)	2 (4.3%)	.239
Depressive	10 (21.3%)	5 (10.6%)	.159
Dependent	5 (10.6%)	1 (2.1%)	.091
Histrionic	3 (6.4%)	1 (2.1%)	.307
Narcissistic	5 (10.6%)	9 (19.1%)	.247
Antisocial	-	-	-
Aggressive	1 (2.1%)	-	.315
Compulsive	2 (4.3%)	1 (2.1%)	.557
Passive-aggressive	3 (6.4%)	4 (8.5%)	.694
Self-defeating	4 (8.5%)	2 (4.3%)	.399
Schizotypal	1 (2.1%)	-	.315
Borderline	-	1 (2.1%)	.315
Paranoid	-	2 (4.3%)	.153
Anxiety	8 (17.0%)	3 (6.4%)	.109
Somatic symptom	1 (2.1%)	-	.315
Bipolar disorder	-	-	-
Persistent depression	-	-	-
Alcohol use	-	-	-
Drug use	1 (2.1%)	-	.315
Post-traumatic stress	-	-	-
Thought disorder	-	-	-
Major depression	1 (2.1%)	-	.315
Delusional disorder	-	-	-

M: mean; SD: standard deviation; M rank: mean rank; QoL: quality of life; NS: non-significant; \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .005$ ; \*\*\*\* $p < .001$ .

image, self-esteem, sexual quality of life, or physical, psychological, social relationships, or environmental quality of life (Tab. II).

Last, comparing transgender participants receiving hormone therapy and those not receiving hormone therapy

yet, those receiving it showed significant higher rates of self-esteem, several domains of quality of life, such as physical and psychological ones, and in several dimensions of body image, including body image concerns, avoidance, and global severity index. No significant

**TABLE II.** Comparisons between trans women and trans men.

Factor	Trans women (n = 20) M (SD)	Trans men (n = 27) M (SD)	Independent t test (p value)
Body image – Global Severity index	2.22 (1.01)	2.53 (.81)	.255
Physical health QoL	67.85 (15.71)	65.36 (19.30)	.667
Psychological QoL	61.48 (18.58)	54.52 (21.61)	.293
Social relationships QoL	59.80 (21.29)	65.906 (23.99)	.554
Environment QoL	59.24 (15.06)	62.31 (14.55)	.520
Self-esteem	48.05 (34.29)	33.30 (31.35)	.154
Factor	Trans women (n = 20) M Rank	Trans men (n = 27) M Rank	Mann-Whitney U test (p value)
Sexual QoL	22.85	18.76	.274

M: mean; SD: standard deviation; QoL: quality of life; M rank = mean rank; NS = non-significant; \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .005$ ; \*\*\*\* $p < .001$ .

**TABLE III.** Comparison between transgender participants receiving hormone therapy and those not receiving hormone therapy yet.

Factor	Hormone therapy group (n = 21) M (SD)	Hormone-naive group (n = 24) M (SD)	Independent t test (p value)
Weight phobia	2.33 (1.05)	2.86 (.89)	.076
Global severity index	2.10 (1.00)	2.76 (.59)	.009
Positive symptom total	20.57 (8.73)	25.26 (7.05)	.056
Positive symptom distress index	3.37 (.95)	3.31 (.87)	.822
Physical health QoL	73.21 (13.92)	60.35 (19.45)	.026
Psychological QoL	63.62 (19.68)	50.20 (19.23)	.041
Social relationships QoL	65.73 (19.78)	57.91 (20.85)	.244
Environment QoL	62.26 (12.49)	60.04 (17.02)	.654
Self-esteem	52.05 (34.26)	26.78 (28.10)	.013
Factor	Hormone therapy group (n = 21) M Rank	Hormone-naive group (n = 24) M Rank	Mann-Whitney U test (p value)
Body image concerns	17.74	27.60	.012
Avoidance	16.64	28.56	.002
Compulsive self-monitoring	22.86	23.13	.945
Depersonalization	19.12	26.40	.062
Sexual QoL	20.71	18.52	.547

M: mean; SD: standard deviation; QoL: quality of life; M rank: mean rank; NS: non-significant; \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .005$ ; \*\*\*\* $p < .001$ .

differences emerged between the groups in terms of weight phobia, compulsive self-monitoring, depersonalization, positive symptom total, and positive symptom distress index, sexual quality of life, social relationships and environmental quality of life (Tab. III).

## Discussion

To our knowledge, this study marks the first aimed at investigating the coexisting mental health conditions in GD diagnosis, alterations in body image, self-esteem, general and sexual quality of life in a sample of Italian

transgender individuals waiting for GAS compared to a homogeneous group of cisgender ones in terms of birth-assigned sex, age, and years of education. Indeed, only a very few studies have been conducted recruiting an Italian sample of people with GD, and none of them compared transgender people versus a homogeneous group of cisgender individuals taking into account all the variables we considered.

This study revealed that the main psychological problems among transgender individuals compared to cisgender ones were a strong alteration of body image, an

unsatisfying sexual and overall quality of life, and low levels of self-esteem.

According to our data, transgender people who received a GD diagnosis experienced more concerns with their body image and appearance, weight phobia, compulsive self-monitoring, and symptoms of depersonalization than cisgender participants. Moreover, transgender patients receiving hormone therapy were more likely to report positive feelings towards their body image and physical appearance than those who were not receiving hormone therapy yet. Furthermore, transgender people can adopt avoidance behaviors and experience feelings of detachment and estrangement toward their bodies. Those results are congruent with Jones et al.<sup>13</sup>, who have underscored the alteration of body image as an important factor that contributes to psychological suffering in patients diagnosed with GD. Indeed, the distress and unhappiness experienced by transgender individuals are focused on the areas of their body related to the birth-assigned sex<sup>25</sup>. In this regard, hormone therapy and GAS are considered as a way for relieving body dissatisfaction in transgender individuals<sup>26</sup>. According to our data, transgender participants who received a GD diagnosis reported lower levels of self-esteem than cisgender ones, and individuals receiving hormonal therapy are more likely to report higher self-esteem than those who are not receiving hormone therapy yet. Previous studies underlined that self-esteem can be negatively impacted by internalized transphobia and positively impacted by social connectedness<sup>27</sup>; in this regard the assessment of self-esteem in subjects with GD is relevant, since low self-esteem is a predictor of depression<sup>28</sup>, and low quality of life<sup>29</sup>. Furthermore, our data showed an unsatisfying sexual quality of life among transgender individuals versus cisgender ones, including a lack of pleasure and confidence, feelings of guilt, embarrassment, anger, and anxiety, and a tendency to avoid sexual activity. That result is congruent with previous findings indicating dissatisfying sexual quality of life in transgender individuals<sup>15</sup>.

Surprisingly, in contrast with Bartolucci and colleagues<sup>14</sup>, no differences between transgender participants treated with hormone therapy and transgender hormone-naive ones were found on sexual quality of life. This result suggests that hormone treatment alone could be insufficient for improving this dimension of quality of life, at least in transgender individuals who are seeking for gender-affirming surgery. Indeed, a better quality of life and a satisfactory sexual function were found in transgender individuals who received GAS<sup>30</sup>. Moreover, in our sample, transgender people reported a worse psychological and social relationships quality of life than cisgender individuals, whereas transgender

participants receiving hormone therapy are more likely to report a better quality of life than those who are not receiving it yet. Recently, a systematic review and meta-analysis suggested that transgender people have lower quality of life than the general population, however some evidence suggests that it improves after the onset of the hormonal treatment or GAS, which could be explained by being able to live as the experienced gender<sup>31</sup>.

Finally, our data showed comparable rates of coexisting mental health conditions between the two groups, indicating that transgender people compared to cisgender people are not characterized by higher levels of psychological distress. Such results are consistent with reported findings indicating no evidence of elevated levels of depression, anxiety, psychosis-related symptoms, or signs of serious personality disorders in people diagnosed with GD<sup>9</sup>.

Last, no significant differences emerged between trans men and trans women in terms of body image, self-esteem, sexual or general quality of life. Those findings indicate that in our sample those variables were not influenced by birth-assigned sex.

To our knowledge, the present study was the first to investigate mental health conditions, alterations in body image, levels of self-esteem, sexual quality of life, and the physical, psychological, social, and environmental dimension of quality of life in general in an Italian sample of transgender adults compared to a control group of cisgender ones matched in terms of birth-assigned sex, age, and years of education.

The chief limitation of the study was its small sample. However, considering the peculiarity of the condition investigated, it continues to be difficult to recruit transgender individuals in large numbers. Furthermore, it was not considered whether the participants in either group were taking psychopharmacological drugs, which could have affected some variables taken into account.

## Conclusions

The results of the study show that the chief psychological problems of individuals diagnosed with GD seem to relate to significant alterations of body image, low self-esteem, and poor sexual and overall quality of life and it is not characterized by significantly higher levels of psychological distress.

In turn, such results provide support for reducing the social stigma of transgender individuals, which is a widespread issue in Italy<sup>32</sup>: trans people experience rejection since their childhood because of their gender nonconformity<sup>33</sup>, and, to date, there are no Italian laws that criminalize violence and hate speech against LG-BT+ people. By highlighting not significant higher rates of mental health conditions in transgender participants compared to cisgender ones, our findings potentially

contribute to deconstructing and reducing false beliefs and prejudices about trans people.

### Implications for research and practice

These findings suggest that patients with a GD diagnosis could benefit from an integrated therapeutic approach until they have completed their gender transition, especially in terms of their body image, self-esteem, and quality of life. Furthermore, it would be useful for Italian mental health professionals to receive a specific training on gender identity and gender-affirming care, in order to adequately assist patients during their transition.

By extension, healthcare professionals who treat transgender individuals should consider providing surgery and hormonal therapy together with psychotherapy as best practices for such patients. Indeed, according to the WPATH's Standards of Care, health professionals should help patients to evaluate the full range of possibilities for care in accordance with their needs and goals<sup>3</sup>. According to Selvaggi and Giordano<sup>34</sup>, offering psychological assistance is not a form of discrimination but can improve transgender patients' care by alleviating their internalized transphobia, improving their body image, promoting their resilience, and assisting the surgeons with preparing for GAS and with delivering follow-up care. The aim of such psychotherapy is to help people diagnosed with GD to overcome their distress by enabling them to achieve a greater sense of stability, acceptance, and satisfaction with their chosen gender. Currently, however, the sole psychotherapeutic approach aimed at treating GD directly is dialectical behavior therapy, which indicates that additional studies addressing psychotherapy are needed.

In the future, given the continued lack of consensus on mental health, researchers could benefit from the results reported herein, especially if able to investigate the variables assessed in a larger sample. In any case, studies are also needed that involve examining self-esteem,

sexual quality of life, and overall quality of life among transgender individuals who have received GAS.

### Conflict of interest statement

The Authors declare no conflict of interest.

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### Author Contributions

GM: conceptualization, investigation, methodology, writing-original draft, writing-review & editing, formal analysis, resources; CLC: conceptualization, methodology, writing-review & editing, resources; CRS: Methodology, writing-review & editing, resources; LF: methodology, writing-review & editing, resources; AG: investigation, writing-original draft, writing-review & editing, resources; RA: investigation, resources; GO: investigation, writing-original draft, resources; EP: investigation, writing-original draft, resources. FT: Writing-review & editing, Resources; GZ: writing-review & editing, resources; AC: conceptualization, project administration, supervision, writing-review & editing; DLB: conceptualization, project administration, supervision, writing-review & editing.

### Ethical consideration

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

### Data availability statement

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

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# Clinical staging and PID-5: a dimensional approach to diagnosis in the early stages of psychopathology

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## SUMMARY

### Objective

The study presents the data on the use of a dimensional model complementary to the traditional categorical diagnosis, specifically applied to the mental health of young people and to the early clinical stages of emerging psychiatric disorders and psychosis.

### Methods

For this goal, the data obtained from the assessment of young users were collected; subjects recruited were the first 100 attending at the Child and Adolescent Neuropsychiatry and Psychiatry Services of the ASST Melegnano and Martesana in the period 2018-2020, and enrolled in the Regional Innovative Projects dedicated to psychic disorders at a young age. The traditional diagnosis and the assessment of the mental state at risk were compared with the PID-5 Personality Inventory indexes (version extended to 220 items), based on the alternative model for personality disorders of Section III of DSM-5; we considered Domains, Traits and the specific psychopathological indices relating to Psychoticism domain.

### Results

our data show that the more one advances in the progression stage of the disease (identified by the mental state at risk), the more there is a concordance with the traditional diagnosis. The diagnostic dispersion is higher in less vulnerable group. Our findings also suggest that PID-5 facets are more articulated in less compromised subjects and more coherent in the pre- and psychotic groups.

### Conclusions

The finding of transversal, polymorphic and fluid pathological traits between the different diagnostic categories, especially in subjects in which a vulnerability in the level of risk of the mental state is recognized, suggest the usefulness of a dimensional approach complementary to traditional diagnosis, at least in the early stages of psychopathology.

**Key words:** early interventions, PID-5, personality disorders, dimensional psychopathological models, early onset psychopathology

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## Introduction

This study is based on the model of Clinical Staging in psychiatry, a relatively new proposal for an alternative heuristic approach to diagnosis, especially in the early clinical stages of emerging mental disorders<sup>1,2</sup>.

The model, derived from other medical branches<sup>3,4</sup>, in particular oncology, was initially proposed by Fava and Kellner<sup>5</sup> as a “neglected dimension of the psychiatric classification”, limited to mood disorders, and systematized more extensively by McGorry’s Australian research group on Early Intervention in Psychosis<sup>1</sup>.

This area of research started from the consideration that “the diagnosis is essentially a classification with utility”<sup>6</sup>; clinical researchers have oriented towards the search for alternative and / or complementary heuristic models

to categorical diagnostic systems, considering that, in the latter, the first clinical forms are not differentiated from those which apparently become persistent disorders. The traditional diagnostic approach of DSM 5 and ICD 10 had an absolute merit: they created a common language in the diagnostic field for clinicians and researchers and they gave an operational description of psychiatric diagnoses; the same models have, nevertheless, a main limitation: they are derived from samples of patients with overt and chronic pathologies, in tertiary care contexts. Therefore, this type of diagnosis can be reliably used only in contexts in which such pathologies represent a stable outcome. They are less useful tools to guide early intervention<sup>7</sup> or the treatment of people with disorders less severe or in an initial phase<sup>8</sup>. In the field of youth mental health this problem is significantly more evident. In this specific population, evolving syndromic patterns are the norm, early clinical phenotypes are fluid, dynamic and pluripotential. The urgent need for management long before a traditional diagnosis can be defined is essential to reduce the risk of developing more elaborate, persistent, recurrent and disabling syndromes.

The McGorry's group model attributes the young subjects to one of the stages of psychopathological progression: Stage 0 - asymptomatic subjects and population at risk, Stage 1a - Non-specific anxiety and depressive syndromes, Stage 1b - Attenuated psychiatric syndromes, Stage 2 - First psychotic episode, Stage 3 - Recurrence or Persistence, Stage 4 - Chronicity<sup>8,9</sup>. This model therefore proposes a diagnostic classification organized along a continuum, recognizing that in the general population exists a wide range of illness / mental health expressions, widespread, below the diagnostic threshold and relatively non-specific. Emphasis is placed on a wider and transdiagnostic level of preclinical manifestations or early or prodromal clinical states. These states are recognized as having a potential for suffering, dysfunctionality and need for care, which must be intercepted long before the achievement of traditional diagnostic clarity, since in this condition the recovery potential appears significantly lower (Early Intervention, EI). According to the available experimental data, the same "categorical" DSM 5, in its Section III, proposes both alternative diagnostic approaches and a more dimensional perspective<sup>10,11</sup>. Of particular interest for the present work are the diagnostic models of the attenuated psychosis syndrome and the alternative model for describing personality disorders, the practical utility of which will be verified in this work using the operative tool of investigation proposed by DSM 5 for personality disorders, the Personality Inventory for DSM-5, PID-5<sup>12,13</sup>.

Starting from this theoretical frame of reference, of great relevance in the EI panorama<sup>14</sup>, we wanted to verify how this approach can prove to be clinically useful, in a

complementary way and alongside the traditional psychiatric diagnosis. In particular, we compared and put in correlation the categorical and dimensional / stage diagnosis. The stages used in this study are not exactly superimposable to the more refined and even broader spectrum ones described by McGorry and listed above, however we describe the risk level of actual mental state according to a progressive stage model represented by Groups as below described. Furthermore, we assessed the coexistence of transversal psychopathological traits using the Personality Inventory for DSM-5, PID-5<sup>12,13</sup>. It is a self-administered questionnaire, proposed in the Italian validated 220-item version<sup>15,16</sup>. Finally, we wanted to investigate specifically the Psychoticism Domain of the Scala and its predictivity, according to the patient's self-assessment, in the sample of CHR (Clinical High Risk) and ARMS (At Risk Mental State) subjects. In fact, these are the categories historically taken over by EI projects, before they extended to prevention in a transdiagnostic perspective.

Assuming that (a) psychotic disorders in the early stages have a multifaceted clinical presentation and (b) different mental disorders in comorbidities or co-occurrence are very often recognized, classical diagnostic stability is poor making difficult to set up an effective and early treatment plan. It therefore becomes fundamental to evaluate how much these nonspecific and fluctuating symptoms may reflect more stable psychopathological dimensions that extend beyond the traditional boundaries of the classical diagnostic classification<sup>8</sup>. The goal is to bring diagnostic fluidity back to a more stable dimensional system that allows a more effective diagnosis and possible interventions in the young clinical population.

## Materials and methods

This research recruited the first 100 patients enrolled in the Departmental Project of the ASST Melegnano and Martesana, North Area, dedicated to Mental Health in the young age (14-24 yrs. age), over the period June 2018 - December 2020. This project integrates two Regional funded projects relating respectively to Psychiatry (Prevention and Early Intervention of psychiatric disorders in youths) and to Neuropsychiatry of Childhood and Adolescence (Adolescents with Psychiatric Disorders).

The articulated assessment, shared between the participating Services, included different Scales and Inventories:

1. PID-5 (Personality Inventory for DSM-5), in the extended form to 220 items, in its Adult (> 18 years) and Adolescents (11-17 years) versions;
2. PQ 16 (Questionnaire for prodromal symptoms);
3. SOFAS (Social and Occupational Functioning Assessment Scale);

4. GAF (Global Assessment of Functioning Scale);
5. CAARMS (Comprehensive Assessment of at-risk Mental States) in selected cases worthy of further study.

In the present study, the evaluation will be focused only on the data of the PID-5 Inventory, self-assessment form. The results were analyzed according to Krueger et al. scoring for the Adult version<sup>15</sup> and to the adolescent normative sample described in Fossati et al.<sup>16</sup> PID-5 offers a trait assessment on a multiple psychopathological spectrum, providing a multidimensional assessment relating to both personality disorders and psychotic phenomena. The inventory is made up of 5 Domains (Negative Affectivity, Detachment, Antagonism, Disinhibition, Psychoticism) and 25 traits or facets (Anxiety, Emotional Liability, Hostility, Perseveration, Reduced Affection, Separation Anguish, Submission, Anhedonia, Depressivity, Avoidance of intimacy, Suspiciousness, Withdrawal, Attention seeking, Insensitivity, Deception, Grandiosity, Manipolarity, Distractibility, Impulsiveness, Rigid perfectionism, Tendency to take risks, Irresponsibility, Eccentricity, Perceptual dysregulation, Unusual beliefs and experiences).

The inventory is present, in its extended form used here, both as a self-assessment and as a hetero-assessment by a family member or even a clinician. Each case was also evaluated by a clinician according to traditional diagnosis (ICD-10) and attributable mental state risk, according to one of the following risk levels: Group 0 = no psychotic vulnerability, Group 1 = vulnerable subjects, Group 2 = attenuated psychosis, Group 3 = Brief Limited Intermittent Psychotic Symptoms (BLIPS), Group 4 = psychosis / antipsychotic treatment threshold.

### Statistical analysis

Statistical analysis was conducted using IBM® SPSS® Statistics rel. 27. Descriptive statistics (frequencies and ranks) were used to summarize data as in tables I to VI. Due to the small number of cases and the not normal distribution of ordinal variables the authors chose to adopt a non-parametric statistical approach. Subjects were aggregated according to different criteria (see after) and the derived groups were compared using non-parametric statistics ( $\chi^2$  statistics for frequencies distribution among groups and rank analysis with Kruskal-Wallis test for multiple independent samples for ranks distribution in the different groups).

The aggregation criteria used to constitute the comparison groups are as follows:

- mental state at risk (Group 0 = no psychotic vulnerability, Group 1 = vulnerable subjects, Group 2 = attenuated psychosis, Group 3 = BLIPS, Brief Limited Intermittent Psychotic Symptoms, Group 4 = threshold psychosis / antipsychotic treatment);
- traditional diagnostic categories according to ICD-10;

- number of pathological Domains of the PID-5 (higher than the 90th percentile);
- number of pathological Facets (above 90th percentile) of the PID-5, grouped by range (< 5, between 5 and 10, > 10);
- value in the Psychoticism domain of PID-5 according to the following operational classification: Normal (< 75<sup>th</sup> percentile), Sensitive (between 75<sup>th</sup> and 90<sup>th</sup> percentile), Pathological (above 90<sup>th</sup> percentile).

### Results

The sample is composed of 100 subjects, of which 52 females and 48 males; the average age is 19.2 years (sd 2.5), in the female sample the age was slightly lower than in the male sample (18.6 sd 2.6 vs 19.8 sd 2.2), the difference was not statistically sound.

Table I lists the diagnoses according to the ICD-10 diagnostic macro-aggregations. The sample sees a significant prevalence of subjects belonging to the psychotic and affective spectrum and to the area of personality disorders.

Based on the at-risk mental state categorization, almost half of the sample fell within the category of vulnerable people. The most interesting finding, however, is that 39% of the sample already had clinically significant conditions (Tab. II). For subsequent analyses, due to the minimal number of Group 3 (BLIPS N = 1), the only patient in this group was aggregated to Group 4 (Threshold/Antipsychotic treatment) as the clinical picture was similar.

Furthermore, we wanted to highlight the distribution of diagnoses by diagnostic classes and of mental state at risk, grouped by sex.

Diagnoses F0, F1, F7, F8, and F9 were then grouped in a "mixed category" in order to give greater prominence to the more specific categories with respect to the project (psychotic disorders, affective disorders, personality disorders, disorders afferent to the neurotic spectrum). According to the literature data, a different distribution emerges with respect to sex: in the male sample symptoms of the psychotic spectrum occur more frequently than in the female sample, where diagnosis of neurosis and personality disorder are more represented ( $\chi^2 = 18.68$ , df 4,  $p = 0.0009$ ) (Tab. I).

Compared to the mental state at risk, the distribution by sex shows significant differences, males being more represented in the psychosis threshold group (31.3%, compared to 3.8% of females), and vice versa females are more represented in the no psychotic vulnerability group (38.5%, compared to 12.5% of males) ( $\chi^2 = 15.69$ , df 3,  $p = 0.0013$ ) (Tab. II).

Subsequently, the analysis took into consideration the data relating to PID-5, according to the following aggregation variables:

**TABLE I.** Sample distribution ( $n = 100$ ) according to diagnostic classes and by sex.

ICD-10 diagnosis		Total	Female	Male
F0	Mental disorders due to known physiological conditions	1	0	1
F1	Mental and behavioral disorders due to psychoactive substance use	2	0	2
F2	Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	21	3	18
F3	Mood [affective] disorders	10	8	2
F4	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	23	14	9
F6	Disorders of adult personality and behavior	32	21	11
F7	Intellectual disabilities	1	0	1
F8	Pervasive and specific developmental disorders	3	1	2
F9	Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	6	5	1
X	Unspecified mental disorder	1	0	1

**TABLE II.** Sample distribution ( $n = 100$ ) according to at-risk mental state and by sex.

At-risk mental state		Total sample	F (% column)	M (% column)
Group 0	No psychotic vulnerability	26	20 (38.5)	6 (12.5)
Group 1	Vulnerable subjects	45	24 (46.2)	21 (43.8)
Group 2	Attenuated psychosis	11	5 (9.6)	6 (12.5)
Group 3	BLIPS	1		
Group 4	Threshold/antipsychotic treatment	17	3 (5.8)	15 (31.3)

Group 0: no psychotic vulnerability; Group 1: vulnerable subjects; Group 2: attenuated psychosis; Group 3: BLIPS; Group 4: psychosis threshold.

- the number of domains found to be psychopathological: 37% of the sample presented 2 or more psychopathological domains above the risk threshold (Tab. III);
- the number of traits found to be psychopathological, broken down by range; 63% of the sample presented an overall number of psychopathological traits greater than 5 (Tab. IV);
- the score of the Psychoticism Domain; in this case the sample shows a trend of the indicator towards pathological values (28% can be classified in the "Sensitive" category and 17% in the "Pathological one) (Tab. V).

Subsequent analyses focused on a possible concordance between traditional clinical diagnoses and attribution of a mental state at risk (Tab. VI). Even with the interpretative limit deriving from the high number of cells with an expected value  $< 5$ , it emerges that the more one advances in the progression stage of the disease (identified by the mental state at risk), the more there is a concordance with the traditional diagnosis. In subjects with no psychotic vulnerability there are, in fact, mainly neurotic disorders and a range of residual

diagnoses (which includes "non-psychiatric diagnosis" or "childhood onset disorders"), while the dispersion of traditional diagnoses is maximum in group 1 (vulnerable subjects) where at 46.7% we find personality disorders and the range of diagnostic categories is very wide. This dispersion is reduced in group 2 (attenuated psychosis), and at minimum in group 4, in which the agreement with the traditional diagnosis of psychotic disorder is 82.2% ( $\chi^2 = 69.965$ ,  $df = 12$ ,  $p < 0.0001$ ).

PID-5 was subsequently correlated (based on the number of pathological domains) with the categorization of mental states at risk (Tab. III). The simple observation of Table III allows us to highlight how the progress in the stage of progression of the disease (identified by the mental state at risk) does not uniquely correlate with the "severity" of PID-5 (according to the total number of pathological domains identified). Indeed, paradoxically, it seems that the more severe subjects have a relatively fewer pathological domains at PID-5. The sample does not show statistically significant differences nor for analysing frequencies or analysing for ranks ( $\chi^2 = 9.96$ ,  $df = 15$ ,  $p = 0.822$ ; Kruskal-Wallis  $H = 3.622$ ,  $df = 3$ ,  $p = 0.305$ ).

**TABLE III.** Psychopathological domains (PID-5) total and by at-risk mental state.

Number of psychopathological domains over the threshold	Total sample	Group 0 (% column)	Group 1 (% column)	Group 2 (% column)	Group 3 and 4 (% column)
0	41	14 ( 53 . 8 )	14 (31.1)	5 (45.5)	8 (44.4)
1	22	3 (11.5)	12 (26.7)	2 ( 18 . 2 )	5 ( 27.8 )
2	15	4 (15.4)	6 (13.3)	1 ( 9.1 )	4 ( 22 . 2 )
3	15	4 (15.4)	8 (17.8)	2 ( 18.2 )	1 ( 5.6 )
4	6	1 (3.8)	4 (8.9)	1 ( 9.1 )	/
5	1	/	1 (2.2)	/	/
Tot.	100	26	45	11	18

Group 0: no psychotic vulnerability; Group 1: vulnerable subjects; Group 2: attenuated psychosis; Group 3: BLIPS; Group 4: psychosis threshold.

**TABLE IV.** Psychopathological traits (PID-5) total and by at-risk mental state.

Number of psychopathological traits	%	Group 0 (% column)	Group 1 (% column)	Group 2 (% column)	Group 3 and 4 (% column)
< 5	37	No.	No.	No.	No.
Between 5 and 10	38	13 ( 50 )	13 (28.9)	2 (18.2)	9 (50)
> 10	25	6 (23.1)	16 (35.6)	7 (63.6)	9 (50)
Tot.	100	7 (26.9)	16 (35.6)	2 (18.2)	/
		26	45	11	18

Group 0: no psychotic vulnerability; Group 1: vulnerable subjects; Group 2: attenuated psychosis; Group 3: BLIPS; Group 4: psychosis threshold.

The number of pathological traits of PID-5 were then analysed according to the at-risk mental state. In this case, the differences are more evident: the psychopathologically more structured conditions (groups 2 and 3-4) are associated to a "normalization" of the pathological traits of PID-5. In addition, in this case there is a paradoxical reduction of psychopathological indices in the group of subjects at higher risk. Conditions more "fluid" with respect to the risk (groups 0 and 1) present instead a more complex facets of psychopathological manifestations ( $\chi^2 = 14.79$ , df 6,  $p = 0.022$ ) (Tab. IV).

We analysed the concordance between the scores of the "Psychoticism" Domain (PID-5) and at-risk mental

state. Also in this case we are witnessing a paradoxical "normalization" of the pathological values in the most severe group (Group 3-4) with respect to the less serious groups, where the correlation between the normal value and the absence of vulnerability is maximum (73%) and distribution of the different pathological values is large in groups 1 and 2. This trend of results, only apparently paradoxical, will be discussed in the conclusions. ( $\chi^2 = 15.769$ , df 6,  $p = 0.015$ ) (Tab. V).

## Discussion

The analysis of the data by categorizing the sample ac-

**TABLE V.** Psychoticism summary score (PID-5) total and by at-risk mental state.

Psychoticism domain	%	Group 0 (% column)	Group 1 (% column)	Group 2 (% column)	Group 3 and 4 (% column)
Normal	55	19 (73.1)	23 (51.1)	5 (45.5)	8 (44.4)
Sensitive	28	3 (11.5)	13 (28.9)	2 (18.2)	10 (55.6)
Pathological	17	4 (15.4)	9 (20)	4 (36.4)	/
Tot.	100	26	45	11	18

Group 0: no psychotic vulnerability; Group 1: vulnerable subjects; Group 2: attenuated psychosis; Group 3: BLIPS; Group 4: psychosis threshold.

**TABLE VI.** Agreement between traditional diagnostic categories and at-risk mental state.

Main diagnosis (ICD-10)	Group 0	Group 1	Group 2	Group 3 and 4
F2 Psychotic dis.	0	1	5	15
F3 Affective dis.	2	5	2	1
F4 Neurotic dis.	11	11	1	0
F6 Personality dis.	9	21	2	0
Other diagnoses	4	7	1	2

Group 0: no psychotic vulnerability; Group 1: vulnerable subjects; Group 2: attenuated psychosis; Group 3: BLIPS; Group 4: psychosis threshold.

According to the subgroups defined by the level of at-risk mental state showed that the largest subgroup was that of vulnerable subjects, in line with expectations, considering the age group and the mission of the Projects to which the recruited subjects belong. In fact, 45% of the sample belongs to this group; subjects with no psychotic vulnerability represent the second largest group (26%), while the other categories are represented by preclinical conditions (psychosis threshold, 17%, and attenuated psychosis, 11%).

The analysis of concordance between “classic” diagnoses and at-risk mental state confirmed the importance of assessing this state of risk in a sample of young people with so-called early onset manifestations. In fact, beyond the obvious high concordance value between the diagnosis of psychotic spectrum and the mental state of psychosis (attenuated or manifest), what we want to underline is how in other diagnostic spectra (in particular the affective ones and, above all, of the personality) the dispersion of mental states at risk is maximum. Our data emphasize once again the importance of a functional more than a categorical evaluation to favour an early interception of the disorder.

However, the most interesting data, in our opinion, comes from the evaluation by the PID-5. The results at PID-5 on the general sample reveal the importance of conducting a more in-depth evaluation at the level of the traits, compared to that of the domains alone, which the 220-item scale allows us to grasp. In fact, if the results are analysed only at the broader level of the domains, 41% of the sample reports non-psychopathological levels. This data however appears to be overrepresented, both when compared with the diagnoses, traditional and of at-risk mental state, and with respect to traits level, in which however 37% turn out to have less than 5 and another 38% between 5 and 10. Reading the level of traits therefore allows us to identify more subtle psychopathological nuances, which are often more significant and of greater interest in clinical settings, especially

in the case of emerging pathologies in young people and again, as seen, in the area of vulnerability rather than frank psychopathology. The careful evaluation of the psychopathological traits allows in fact a more complete representation of the individual subject evaluated, favouring both an earlier treatment and a more individualized treatment path.

The potential of use of a multidimensional tool such as the PID-5 shows all power especially when the results are analysed not in a general sense (i.e. considering the tested subject as belonging to a generic “general sample”) but correlating them to the at-risk mental state evaluation. Moreover, it also emerges that the evaluation of results at the Facets level (traits) is more useful than at the Domain level. According to our results, at the level of the Domains psychopathology is under-dimensioned in the patient’s self-assessment compared with the diagnosis made by the clinician. On the contrary, the traits level of description accounts for a diversification of much broader psychopathological nuances, which allow us to intercept multiple and transversal facets pertaining to different diagnostic categories, in particular for the group where such fluidity is maximum, once again the vulnerable subjects we need to treat as soon as possible.

This observation underlines the importance of combining the staging diagnostic assessment with a multidimensional psychopathological assessment, especially in the early stages of psychopathology, the ones in which the diagnostic fluidity is maxima and the symptomatic polymorphism suggests multiple and diversified subsequent psychopathological outcomes. This polymorphism in the early stages, particularly evident in vulnerable subjects, is also supported by what emerges from PID 5, especially with an analysis that goes down to the level of traits, as presented by our data.

The evaluation of the PID-5 Psychoticism Domain deserves a particular consideration. This domain, in fact, apparently seems not very specific in identifying the manifest psychotic conditions. In fact, in our opinion, it represents a particularly sensitive and therefore important indicator to be analysed especially in conditions of medium risk (Groups 1 and 2). As expected by its construct, the score of the Psychoticism Domain is “normal” in 73.1% of subjects in Group 0 (without psychotic vulnerability), but it progressively worsens in vulnerable subjects and then in attenuated psychosis subjects. In fact, the percentages of “sensitive” and “pathological” scores increase in Groups 1 and 2, on the contrary subjects belonging to the psychosis threshold group show a prevalent “sensitive” level in the Psychoticism domain, none of them reporting “pathological” scores. The same phenomenon is however evident analysing the number of pathological traits, or the number of pathological do-

mains, as mentioned before. We can therefore hypothesize that this result is subverted in this subgroup of patients with a more advanced stage of psychopathology due to a more marked difficulty in recognize illness at this stage (fall of critic functions). An alternative explanation may be that the traits investigated are felt more egodistonic in the early stages, in which they are less integrated in the initial phases of illness and, for this reason, are well recognized and described. Worsening the clinical state, patients undergo to a sort of adaptation whereby problems are no longer critically detected. Some limitations have to be underlined. Our results need to be replicated in a more robust sample, in order to have the possibility to have a more significant stratification of variables and have a number of alternative explicative hypothesis. Another limitation of this study is the non-availability of data regarding the ability of critic of psychotic subjects, in order to explain the “paradoxes” we found, but the results we found were somewhat unexpected. The issue needs to be better studied in a future work.

## Conclusions

Despite these limitations, we can draw some concluding remarks. In line with what was expected with respect to the mission of the two Projects “Prevention and Early Intervention of Psychiatric Disorders in Youth” and “Adolescents with Psychiatric Disorders”, the group of vulnerable subjects was the most numerous. The same group appears to be a fluid one, in which there are polymorphic psychopathological facets, transversal to the various traditional diagnostic categories, potentially leading to different psychopathological outcomes, stabilize or regress. According to that, we have highlighted how a trait-level analysis can be useful in setting up a specific treatment path. In a more specific way, the presented data confirm the great utility of a tool such as PID-5 in highlighting transdiagnostic psychopathological traits, especially in the earliest stages of the disease and especially in the vulnerable group. In particular, the

clinical utility is evident if these symptomatic manifestations are sought at a more specific and profound level, that is, that of the Traits, or Facets.

Therefore, with respect to the usefulness of different models and approaches to diagnosis, it seems appropriate to refer to the observations that the most useful approach depends on the context in which the question is posed and each clinical decision, to treat or not, is ultimately a categorical one, even when based on a dimensional assessment of severity and impact<sup>17</sup>.

As a final remark, we are aware that our data will not close the debate regarding the question of whether a dimensional approach can really improve our diagnostic approach, even if the latest version of the DSM-5 recognize the dimensionality of psychopathology. But at the same time, we are aware that, in particular in the field of the early clinical stages of mental disorders emerging in youth and psychosis, a dimensional approach is suggested as a complementary value in diagnostic terms<sup>18</sup>, and our data seem to point in that direction.

## Conflict of interest statement

The Authors declare no conflict of interest.

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## Author contributions

SC: recruited subjects and collected data; RM, CM: contributed to recruitment; FD: reviewed and analysed data. All the Authors contributed to literature analysis and discussion of results.

## Ethical consideration

This study was previously authorized by ASST Direction, according to local office of Ethical Committee, because it was an observational study, with aggregated data, and there was not any clinical experimentation necessitating a specific authorization.

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## Depressed mood in first episode psychosis: findings from the “Parma-Early Psychosis” program

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### SUMMARY

#### Objective

Depressed mood (DM) is relatively frequent in psychosis and significantly associated with suicidal behavior and poorer prognosis. However, it is often under-recognized and under-treated, especially at the illness onset. The aims of this research were: (1) to longitudinally assess DM levels in young subjects with First Episode Psychosis (FEP) over a 2-year follow-up period, and (2) to explore any relevant association of DM with clinical features and the specialized intervention components of an Italian “Early Intervention in Psychosis” (EIP) program, both at baseline and along the follow-up.

#### Methods

The Positive And Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF) were completed by 266 FEP individuals (aged 12-53 years). Regression analyses with DM as the dependent measure and sociodemographic, psychopathological and treatment characteristics as independent parameters were also performed (both at baseline and along the follow-up).

#### Results

Relevant DM (i.e. PANSS “Depression” item subscore of  $\geq 5$ ) decreased over time and showed longitudinally stable associations with PANSS “Negative Symptoms” and “Positive Symptoms” scores. Along the follow-up, reduction in DM levels was also related to higher antidepressant dose at entry and lower antipsychotic dose prescribed at the end of our research (i.e. after 24 months of follow-up).

#### Conclusions

Relevant DM is experienced in FEP and in the first specialist contact within specialized EIP programs. However, DM severity levels tends to decrease overtime, together with general improvements in psychosis psychopathology and with antidepressant prescription at entry.

**Key words:** depression, early intervention in psychosis, first episode psychosis, treatment response, follow-up

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### Introduction

Depressed Mood (DM) is relatively common in First Episode Psychosis (FEP). It occurs in its prodromal stage, during the acute phase or may follow the course of positive symptoms in the post-acute period<sup>1,2</sup>. About this, a 35-45% baseline prevalence of clinical depression was reported in FEP populations<sup>3</sup>, where it significantly contributes to increase the risk for psychotic relapse and to induce poor real-world performance and bad quality of life<sup>4</sup>. Furthermore, it has been reported that DM is one of the

major predictors for suicidal ideation in FEP, even more than command hallucinations<sup>5</sup>. Early identification and timely intervention on DM in FEP should therefore be considered as a crucial clinical strategy for suicide prevention and for prognosis improvement<sup>6</sup>.

Although quite common, DM in FEP is overall *neglected*, especially in its treatment correlates, mainly due to the clinical emphasis on treating positive and negative symptoms of psychosis<sup>7</sup>. Specifically, knowledge is particularly limited on the role of DM on treatment response<sup>8</sup> and discharge outcomes of FEP people enrolled into “Early Intervention in Psychosis” (EIP) protocols<sup>9</sup>.

Starting from this background, the *aims* of this research were:

1. to investigate the baseline prevalence rate of FEP patients with relevant DM and to compare their sociodemographic and clinical features with FEP subjects without relevant DM;
2. to longitudinally monitor the course of DM in the FEP total group along a 2-year follow-up period within a specialized EIP protocol;
3. to explore the associations of DM with sociodemographic characteristics, clinical data and the specific EIP treatment components both at baseline and across 24 months of follow-up.

No Italian investigation specifically examining the longitudinal course of DM in FEP and its treatment response to specialized EIP intervention components has been published in the literature to date.

## Materials and methods

### Setting and sample

Participants were recruited between January 2013 and June 2019 within the “Parma-Early Psychosis” (*Pr-EP*) program, a specialized EIP program specifically implemented in all adult and adolescent mental health services of the Parma Department of Mental Health<sup>10</sup>.

*Inclusion criteria* were: (1) mental health help-seeking request; (2) age 12-35 years; (3) FEP within one of the following DSM-IV-TR diagnoses<sup>11</sup>: schizophrenia, schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, delusional disorder, affective (bipolar or major depressive) psychosis or psychotic disorder not otherwise specified; and (4) a DUP (“Duration of Untreated Psychosis”) of < 2 years. This DUP length was specifically selected because it is the usual limit to provide specialized interventions within the EIP paradigm<sup>12</sup>.

*Exclusion criteria* were: (1) past antipsychotic intake or current antipsychotic intake for more than 2 months; (2) past full-blown psychotic episode within a DSM-IV-TR diagnosis of both affective and non-affective psychosis; (3) current substance dependence as defined in

the DSM-IV-TR criteria<sup>11</sup>; (4) neurological disorder or any other medical condition associated with psychiatric symptoms; and (5) known intelligence quotient < 70. Specifically, we considered past antipsychotic intake (i.e. in previous illness episodes and prior to the Pr-EP enrollment) as a functional equivalent of a past psychotic episode, in line with the definition of psychosis threshold proposed by Yung and co-workers<sup>13</sup> within their EIP paradigm (i.e. “essentially that at which antipsychotic medication would probably be started in the common clinical practice”).

All participants (and their parents, if minors) gave their written informed consent prior to their inclusion in this study. Local ethical approvals were obtained for the research (AVEN protocol n. 36102/09.09.2019). This research was also conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

### Measures

The clinical evaluation of this investigation included the Positive And Negative Syndrome Scale (PANSS)<sup>14</sup> and the Global Assessment of Functioning (GAF) scale<sup>11</sup>. Trained Pr-EP team members completed such instruments at entry and every year during the follow-up. Regular supervision sessions assured their inter-rater reliability<sup>15</sup>.

The PANSS is commonly used to evaluate psychopathology in psychosis. In the present research, we considered a PANSS “Depression” (G6) item subscore of  $\geq 5$  (i.e. at least “a distinctly depressed mood associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation and interference in sleep and appetite”) <sup>14</sup> as a clinical index of relevant DM. Moreover, as proposed by Shafer and Dazzi<sup>16</sup>, we also considered the following 4 main dimensions in the “core” psychopathology of psychosis: “Positive Symptoms”, “Negative Symptoms”, “Disorganization” and “Resistance/Activation”. The Italian version of the PANSS has been widely used also in young subjects with FEP<sup>17</sup>.

The GAF is commonly used to evaluate socio-occupational functioning in psychosis. The Italian version of the GAF has been frequently administered also in young individuals with FEP<sup>18</sup>.

### Procedures

The axis-I diagnosis was formulated by trained Pr-EP team members using the Structured Clinical Interview for DSM-IV-TR axis I Disorders (*SCID-I*)<sup>19</sup>. According to their symptom severity, FEP individuals were then provided with a 2-year comprehensive intervention protocol including psychopharmacological therapy and a multicomponent psychosocial treatment (combining an intensive recovery-oriented case management, psy-

choeducational sessions for family members and an individual psychotherapy mainly based on cognitive-behavioral modules)<sup>20</sup>, as suggested by the current guidelines on the topic<sup>21</sup>.

Low-dose atypical *antipsychotic* medication was used as first-line pharmacological therapy<sup>22</sup>. According to the “Defined Daily Doses” method<sup>23</sup>, the daily dose of different antipsychotics was reported and standardized as equivalent dose of chlorpromazine (mg/die). As for *antidepressants*, we used a method suggested in a recent meta-analysis on dose equivalence of antidepressant medications, which were standardized and reported as equivalent dose of fluoxetine [mg/day]<sup>24</sup>.

In accordance with the modules proposed by Fowler and colleagues<sup>25</sup>, *individual psychotherapy* sessions were also addressed on treating clinical depression, suicide risk, anxiety and distress. Ten meetings (each lasting 1 hour) were offered in the first year of treatment. Booster sessions were also provided in case of specific symptoms of psychotic relapse<sup>26</sup>.

In line with the model developed by Kuipers and co-workers<sup>27</sup>, *psychoeducational* sessions for family members included problem-solving, communication and support techniques. Eight meetings were offered to each family in the first 6 months of treatment. Booster sessions were provided in case of functioning decline and/or critical family relationships<sup>28</sup>.

*Case management* was aimed at promoting early recovery and at preventing long-term disability<sup>29</sup>. Two sessions per month (each lasting 1 hour) were provided in the first year of treatment. Monthly booster sessions were also offered in case of specific functioning needs<sup>30</sup>.

Individuals having a baseline PANSS “Depression” item subscore of  $\geq 5$  were classified as FEP patients with relevant DM (FES/DM+). The remaining participants were considered as not having a relevant DM at entry and were included in the FES/DM- subgroup.

### Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) for Windows, version 15.0<sup>31</sup>. All tests were two-tailed with a significance level set at 0.05. In inter-group comparisons, the Mann-Whitney U test was used to examine quantitative parameters, while the Chi-square ( $\chi^2$ ) test was performed to assess qualitative variables. The Wilcoxon test for repeated measures was used in the FEP total sample to investigate the longitudinal stability of DM severity levels during the 2-year follow-up period.

A binary logistic regression analysis with the dichotomized PANSS “Depression” item score (cut-off score of  $\geq 5$ ) as the dependent parameter and clinical and sociodemographic features as independent parameters was performed at entry in the FEP total group. Moreover, a

**TABLE I.** Sociodemographic data and clinical features of the FEP total sample ( $n = 266$ ).

Variable	
Age at entry (in years)	24.00 (20.00-30.00)
Gender (males)	165 (62.0%)
Education (in years)	13.00 (10.00-13.00)
Ethnic group (white Caucasians)	225 (84.6%)
DUP (in months)	6.00 (2.00-13.00)
T0 PANSS “Depression” item subscore	4.00 (2.00-5.00)
T1 PANSS “Depression” item subscore	2.00 (1.00-3.00)
T2 PANSS “Depression” item subscore	2.00 (1.00-2.00)

FEP: first episode psychosis; DUP: duration of untreated psychosis; PANSS: Positive And Negative Syndrome Scale. Frequencies (and percentages) and median (and inter-quartile range) are reported.

linear regression analysis with PANSS “Depression” item score as the dependent measure and Pr-EP treatment components, clinical and sociodemographic characteristics as independent parameters was also conducted in the FEP total sample across the 2-year follow-up period. In our longitudinal analyses, we specifically considered the differences (deltas [ $\Delta$ ]) between PANSS scores at baseline (T0) and at the 2-year assessment time (T2) as primary clinical parameters to examine over time. Indeed, in line with what was suggested by Ver Hoef<sup>32</sup>, the delta scores better describe the temporal dynamics and longitudinal changes of psychosis psychopathology in comparison with T0 and T2 single measures.

## Results

Two hundred and sixty-six FEP patients were recruited for this research. Their sociodemographic and clinical features are shown in the Table I. The baseline DSM-IV-TR axis I diagnoses were: schizophrenia ( $n = 117$ ; 44.0%), affective psychosis ( $n = 74$ ; 27.8%), psychotic disorder not otherwise specified ( $n = 25$ ; 9.4%), brief psychotic disorder ( $n = 17$ ; 6.4%), schizophreniform disorder ( $n = 15$ ; 5.6%), schizoaffective disorder ( $n = 10$ ; 3.7%) and delusional disorder ( $n = 8$ ; 3.1%). Antidepressant prescription rate at entry was 20.3% ( $n = 54$ ).

### Baseline evaluation

At baseline (T0), 82 (30.8%) FEP participants had a baseline PANSS “Depression” item subscore of  $\geq 5$  and were included in the FEP/DM+ subgroup (Tab. II). Only 21 (25.6%) of them were taking an antidepressant drug at entry. Compared to FEP/DM-, FEP/DM+ participants showed a younger age, higher PANSS “Positive Symptoms” and “Negative Symptoms” factor subscores and a lower GAF score.

Moreover, a baseline PANSS “Depression” item cut-off score of  $\geq 5$  (i.e. the presence of a relevant DM at entry)

**TABLE II.** Sociodemographic data and clinical features of the FEP total group and the two subgroups.

Variable	FEP total group (n = 266)	FEP/DM+ (n = 82)	FEP/DM- (n = 184)	$\chi^2/z$
Gender (females)	165 (62.0%)	50 (61.0%)	115 (62.5%)	0.056
Ethnic group (white Caucasians)	225 (84.6%)	69 (84.1%)	156 (84.8%)	0.018
Age at entry (in years)	25.72 ± 7.69	24.07 ± 6.92	26.45 ± 7.92	<b>-2.286**</b>
Education (in years)	15.68 ± 6.04	12.06 ± 2.72	17.33 ± 6.63	-0.216
DUP (in months)	9.01 ± 7.74	10.08 ± 8.49	8.53 ± 7.36	-0.947
<i>DSM-IV-TR diagnosis</i>				
Schizophrenia spectrum disorder	150 (56.4%)	43 (52.4%)	107 (58.2%)	0.753
Affective psychosis	74 (27.8%)	22 (26.8%)	52 (28.3%)	0.058
Brief psychotic disorder	8 (3.0%)	3 (3.7%)	5 (2.7%)	0.172
Psychotic disorder not otherwise specified	34 (12.8%)	14 (17.1%)	20 (10.9%)	1.958
T0 PANSS "Positive Symptoms" factor score	17.33 ± 6.06	19.57 ± 5.68	16.33 ± 5.97	<b>-4.174*</b>
T0 PANSS "Negative Symptoms" factor score	25.12 ± 9.44	26.98 ± 8.46	24.29 ± 9.75	<b>-2.007**</b>
T0 PANSS "Disorganization" factor score	22.22 ± 8.47	22.21 ± 7.62	22.23 ± 8.84	-0.096
T0 PANSS "Activation/Resistance" factor score	8.71 ± 4.20	8.10 ± 3.49	8.98 ± 4.47	-1.248
T0 GAF score	44.61 ± 11.24	39.66 ± 11.13	46.86 ± 10.58	<b>-4.737*</b>
T0 equivalent dose of chlorpromazine (mg/day)	198.00 ± 167.64	222.00 ± 214.38	187.80 ± 141.37	-0.612
T0 equivalent dose of fluoxetine (mg/day)	13.68 ± 39.72	23.53 ± 55.74	9.29 ± 29.09	-1.681
T0 antipsychotic prescription rate	237 (89.1%)	71 (86.6%)	166 (90.2%)	0.770
T0 antidepressant prescription rate	54 (20.3%)	21 (25.6%)	33 (17.9%)	2.065

FEP: first episode psychosis; FEP/DM+: FEP patients with relevant Depressed Mood ([DM] = PANSS "Depression" item cut-off score  $\geq 5$ ); FEP/DM-: FEP patients without relevant DM; DUP: duration of untreated psychosis; DSM-IV-TR: Diagnostic and statistical manual for mental disorders, IV Edition, text revised; PANSS: Positive And Negative Syndrome Scale; GAF: global assessment of functioning; T0: baseline assessment. Frequencies (and percentages), mean  $\pm$  standard deviation, Chi-square test ( $\chi^2$ ) and Mann-Whitney test (z) values are reported. \* $p < 0.001$ ; \*\* $p < 0.5$ . Statistically significant results are in bold.

was significantly predicted by higher T0 PANSS "Positive Symptoms" and "Negative Symptoms" factor subscores, as well as lower T0 GAF score (Tab. III). The overall percentage of dichotomized ascription using this model for predicting relevant baseline DM levels in our FEP patients was 75.2%. No association with sociodemographic data was found.

### Follow-up evaluation

All FEP subjects ended the 2-year follow-up period. At the T1 assessment, antidepressant medication was still prescribed to 49 (18.4%) FEP individuals, with a median equivalent dose of fluoxetine equal to 30.00 mg/day (Interquartile Range [IR] = 20.00-80.00 mg/die). Only 7 (2.6%) FEP participants had a T1 PANSS "Depression" item cut-off score of  $\geq 5$ , with a T1 incidence rate of new cases with relevant DM of 1.5% (n = 4).

At the end of our follow-up (T2 assessment), the median of case management sessions was 30 (IR = 16-50), the median of individual psychotherapy sessions was 21 (IR = 12-30) and the median of psychoeducational sessions for family members was 8 (IR = 3-13). Antidepressants were still prescribed to 64 (24.1%) FEP subjects, with a median equivalent dose of fluoxetine of 20.00

mg/day (IR = 20.00-50.00 mg/die). Only 5 (1.9%) FEP individuals had a T2 PANSS "Depression" item cut-off score of  $\geq 5$ , with a T2 incidence rate of new cases with relevant DM of 0.75% (n = 2). Over the 2-years of follow-up, we therefore observed 6 new FEP/DM+ cases for an overall incidence rate equal to 2.25%.

Along the follow-up, a significant decrease in PANSS "Depression" item subscores was found (Tab. IV). Our linear regression analysis results showed that the delta reduction between T0 and T2 PANSS "Depression" item subscores was significantly predicted by higher T0 equivalent dose of fluoxetine, lower T2 equivalent dose of chlorpromazine and delta reductions between T0 and T2 PANSS "Positive Symptoms" and "Negative Symptoms" factor scores.

### Discussion

In the current study, 1/3 of FEP patients had a relevant DM at entry (i.e. an at least "moderate severe" PANSS "Depression" item subscore = "a distinctly depressed mood associated with pessimism, obvious sadness, loss of social interest, psychomotor retardation and interference in appetite and sleep")<sup>14</sup>. This result is substantially in line with what (35-45%) was reported in the current

**TABLE III.** Binary logistic regression results of the dichotomized PANSS “Depression” item score (cut-off ≥ 5) by sociodemographic data and clinical features within the FEP total sample (n = 266) at baseline.

Variable	B	SE	Wald	df	p	OR	95% CI for OR(B) Lower upper	
Gender (males)	-0.109	0.313	0.120	1	0.729	1.115	-2.060	-0.603
Age at entry (in years)	-0.031	0.022	2.068	1	0.150	1.032	-1.076	-0.989
Education (in years)	-0.001	0.008	0.034	1	0.855	1.001	-1.016	-0.987
Ethnic group (white Caucasians)	0.028	0.418	0.004	1	0.947	0.973	0.429	2.205
DUP (in months)	0.023	0.019	1.449	1	0.229	0.977	0.941	1.015
T0 PANSS “Positive Symptoms” factor score	0.103	0.030	11.566	1	<b>0.001</b>	0.902	0.850	0.957
T0 PANSS “Negative Symptoms” factor score	0.049	0.023	4.740	1	<b>0.029</b>	0.952	0.910	0.995
T0 PANSS “Disorganization” factor score	-0.045	0.026	3.084	1	0.079	1.046	-1.100	-0.995
T0 PANSS “Activation/Resistance” factor score	-0.119	0.043	7.682	1	0.076	1.126	-1.225	-1.035
T0 GAF score	-0.044	0.015	8.215	1	<b>0.004</b>	1.044	-1.076	-1.014
Constant	0.658	1.234	0.284	1	0.594	0.518	-	-
Overall model fit test → X <sup>2</sup> = 49.923; p = 0.0001								
Associated strength → Cox–Snell R <sup>2</sup> = 0.172, Nagelkerke R <sup>2</sup> = 0.247								

FEP: first episode psychosis; DUP: duration of untreated psychosis; PANSS: Positive And Negative Syndrome Scale; GAF: global assessment of functioning; T0: baseline assessment; B: regression coefficient; SE: standard error; Wald: Wald statistic value; df: degrees of freedom; OR: odd ratio; 95% CI: 95% confidence intervals for odd ratio; X<sup>2</sup>: Chi-square value; R<sup>2</sup>: R-square or coefficient of determination; p: statistical significance; p-value lower than 0.05 are reported as bold values.

**TABLE IV.** PANSS “Depression” item scores and their associations with sociodemographic data, relevant clinical features and the specialized intervention components of the Pr-EP program across the 2-year follow-up period in the FEP total sample (n = 266).

Variable	T0	T1	T2	z (T0-T1)	z (T0-T2)	z (T1-T2)	
PANSS “Depression” item score	4 (2-5)	2 (1-3)	2 (1-2)	<b>-9.736*</b>	<b>-8.657*</b>	<b>-3.578*</b>	
T0-T2 Delta PANSS “Depression” item scores		B	SE	95% CI for B Lower Upper		β	p
Constant							R <sup>2</sup> = 0.341 F <sub>[df=20]</sub> = 2.901 p = <b>0.0001</b>
Gender (females)	0.260	0.871	-1.462	1.983	-	0.765	
Age at entry (in years)	0.205	0.255	-0.299	0.709	0.630	0.423	
Education (in years)	-0.014	0.017	-0.047	0.019	-0.065	0.406	
Ethnic group (non-white Caucasians)	-0.003	0.002	-0.006	0.000	-0.124	0.100	
DUP (in months)	0.162	0.315	-0.461	0.785	0.039	0.608	
T0 equivalent dose of Chlorpromazine (mg/day)	0.031	0.017	-0.003	0.064	0.141	0.070	
T1 equivalent dose of Chlorpromazine (mg/day)	0.003	0.044	-0.083	0.090	0.006	0.939	
T2 equivalent dose of Chlorpromazine (mg/day)	0.002	0.004	-0.005	0.010	0.042	0.581	
T0 equivalent dose of Fluoxetine (mg/day)	-0.030	0.014	-0.059	-0.002	-0.159	<b>0.039</b>	
T1 equivalent dose of Fluoxetine (mg/day)	0.011	0.005	0.001	0.022	0.186	<b>0.035</b>	
T2 equivalent dose of Fluoxetine (mg/day)	0.000	0.004	-0.008	0.009	0.011	0.905	
T2 number of individual psychotherapy sessions	0.006	0.004	-0.001	0.013	0.139	0.097	
T2 number of psychoeducational sessions for family members	-0.008	0.010	-0.028	0.012	-0.067	0.418	
T2 number of case management sessions	0.024	0.017	-0.010	0.059	0.123	0.158	
T0-T2 Delta “Positive Symptoms” factor scores	-0.002	0.004	-0.009	0.006	-0.035	0.678	
T0-T2 Delta “Negative Symptoms” factor scores	0.055	0.027	0.002	0.108	0.188	<b>0.040</b>	
T0-T2 Delta “Disorganization” factor scores	0.053	0.020	0.012	0.093	0.288	<b>0.011</b>	
T0-T2 Delta “Excitement/Resistance” factor scores	-0.009	0.025	-0.059	0.040	-0.044	0.709	
T0-T2 Delta GAF scores	-0.039	0.034	-0.106	0.029	-0.104	0.258	
T0-T2 Delta GAF scores	-0.003	0.010	-0.024	0.017	-0.028	0.734	

PANSS: Positive And Negative Syndrome Scale; Pr-EP: Parma-Early Psychosis; FEP: first episode psychosis; T0: baseline; T1: 1-year assessment time; T2: 2-year assessment time; DUP: duration of untreated psychosis; GAF: global assessment of functioning; B: regression coefficient; SE: standard error; 95% CI: 95% Confident Intervals for B; β: standardized regression coefficient; p: statistical significance; R<sup>2</sup>: R-square or coefficient of determination; F: statistic test value for linear regression; df: degrees of freedom. Median (and interquartile range) and Wilcoxon test (z) values are also reported. Statistically significant p values are in bold.

literature<sup>3,33,34</sup>, supporting that a quite relevant proportion of FEP patients may show a clinically significant DM already at the enrollment within EIP services<sup>35</sup>. DM in FEP is therefore sometimes relevant enough to justify early identification and a timely targeted intervention<sup>36</sup>. About this, Griffiths and colleagues<sup>37</sup> considered depression in FEP as an *early clinical feature* in the developmental trajectory of psychosis psychopathology and as a central psychopathological characteristic in the clinical network maps of psychotic symptoms, both at baseline and over time. According to these authors, effective treatments on DM could have the potential to lead to a better recovery and to global symptom improvements.

However, we observed a baseline *antidepressant prescription* rate of only 20% (25% in the FEP/DM+ subgroup). These findings further support that DM may be often under-recognized and under-treated in FEP individuals<sup>38</sup>, probably due to the clinical emphasis given at treating positive and negative symptoms of psychosis. These results are also in line with what was observed by Herniman and co-workers<sup>34</sup> in a recent meta-analysis on comorbid depressive features in subjects with first-episode schizophrenia spectrum disorders, reporting no significant link between antidepressant therapy and prevalence of clinically relevant depressive symptoms. Additionally, in a longitudinal study on concomitants of depression in first episode schizophrenia, Phahladira and co-workers<sup>39</sup> found only a 5% prescription rate of antidepressant drugs at baseline.

### Clinical suggestions

The results of this investigation showed a significant association of DM in FEP and *positive symptom* severity levels, both at baseline and as longitudinal changes in scores along the 2 years of follow-up. According to Phahladira and co-workers<sup>39</sup>, the psychopathological link between depressive and positive dimensions at the psychosis onset could be particularly important at a “symptom-level”, reflecting state-related fluctuations in positive symptoms. This is also in line with the intrinsic hypothesis of depression in psychosis, hypothesizing that DM could partly follow the development of positive symptoms<sup>34</sup>.

Furthermore, DM in FEP patients was significantly associated also with *negative symptom* severity levels, both at entry and as longitudinal changes in scores across the follow-up. As depressive and negative symptoms are often hard to differentiate from one another in FEP, we can't ascribe a clear causality to these simple quantitative relationships, which could be partly related to their phenomenological overlap<sup>40</sup> and/or to secondary negative symptoms as consequences of clinically relevant depressed mood<sup>20</sup>.

Given the longitudinal stability of associations of DM with positive and negative dimensions of early psycho-

sis, mood depression in FEP could also be potentially considered as a *stable index of psychopathological severity* overtime. In this respect, Birchwood and colleagues<sup>41</sup> suggested that DM could develop in early psychosis due to the intrinsic illness process and/or negative cognitive appraisals of the experience and meaning of psychotic disorder. Indeed, the disruption that FEP can have on patients' interpersonal relationships, on their vocational goals and their identity construction could be particularly unfavorable during the critical developmental phase of adolescence and/or young adulthood<sup>42</sup>.

The findings of this research also showed a relevant association between *functioning decline* and DM at baseline. Previous results on this topic was substantially mixed, with some investigations suggesting poor daily functioning in FEP patients with clinically relevant depression<sup>43</sup>, and others observing no relationship<sup>44,45</sup>. Such inconsistent findings could be due to third parameters that may mediate this association (e.g. personality traits, neurocognitive factors, developmental trajectory). Finally, we found a significant association between DM and *younger age* at entry. This seems to further support that the negative impact of FEP onset during adolescence or young adulthood could have a “pathoplastic” role for the development of relevant DM at the psychosis onset, which may also subsequently contribute to induce poorer real-world performance and to increase suicidal risk<sup>5</sup>.

### Treatment response

The findings of this study showed a significant *decrease in DM* during the 2 years of our follow-up. This supports the results reported by Phahladira and co-workers<sup>39</sup>, who observed that depressive symptoms in patients with first episode schizophrenia were greatest at baseline, with the most significant reduction during the first 3 months of intervention and improvement maintenance along the 2 years of their follow-up period. Furthermore, considering all the duration of our follow-up, we found exclusively 6 new FEP/DM+ cases [4 (66.7%) of them in the first 12 months], with a cumulative incidence rate of “de novo” DM in FEP equal to only 2.25%. Overall considered, our findings support a relevant decrement of DM severity levels in FEP patients treated within specialized EIP programs. In the current research, this decrease was positively associated with the equivalent dose of antidepressant medication prescribed at baseline and with longitudinal reductions in positive and negative symptom severity observed over the follow-up, as well as negatively related with the equivalent dose of antipsychotic drug still prescribed at the end of the investigation (T2 assessment).

Our evidence on negative association between longitudinal decrease in DM and T2 *antipsychotic* dosage

could suggest a potential, direct “depressogenic effect” of antipsychotic medications<sup>39</sup>. About this, a lack of improvement in positive symptoms overtime could induce clinicians in increasing the prescribed dose of antipsychotics, resulting in a vicious circle potentially worsening comorbid DM in FEP patients.

Finally, we observed that the baseline prescription of an *antidepressant* drug was related to significant improvements in DM severity levels at the end of our study. This is not concordant with what was reported in the current literature<sup>46,47</sup>, overall suggesting no association between longitudinal severity in clinical depression and prescription of antidepressants in early psychosis. However, in a recent meta-analysis on antidepressants in individuals at Clinical High Risk (CHR) for psychosis, Raballo and colleagues<sup>48</sup> suggested that ongoing antidepressant exposure at inception in CHR subjects was associated to a reduced risk of transition to psychotic disorder at follow-up. Thus, future research in larger FEP populations to confirm our promising results is needed.

### Limitations

A first weakness of this research is associated to sample characteristics. Indeed, we investigated FEP patients in a “real-world” care setting, primarily aimed at offering specialized EIP interventions within community mental health services. Our findings therefore may be exclusively compared to similar clinical populations. Moreover, even if a strength of this study was the recruitment of patients at the onset of psychosis, our findings cannot be generalized to patients at different illness phases (such as those with a prolonged psychotic disorder).

Furthermore, the current research was designed within an EIP program not specifically focused on DM in FEP. Specifically, psychopathology was assessed with the PANSS, an instrument widely administered in FEP populations, but poorly articulated for measuring depression. Therefore, future studies exploring DM with more specific instruments for psychosis [e.g. the Calgary Depression Scale for Schizophrenia (CDSS)]<sup>49</sup> are needed. However, given the common application of the PANSS in FEP patients, our research has the potential to be replicated in similar samples. This is of primary importance since investigations exploring treatment response of EIP protocols on DM at the psychosis onset are still poor and depression is commonly associated with negative long-term outcomes and suicide risk.

Finally, our treatment parameters were not randomly attributed. This restricts our ability to derive causal conclusion on the reported longitudinal associations with changes in DM severity levels. Indeed, these correlations could also depend on other plausible explanations (e.g. FEP patients with more severe psychopathology could get more intensive treatments and improve the most, partially because they had the most to improve).

### Conclusions

DM is quite relevant in FEP, where it could be considered not exclusively as a superimposed comorbidity, but also as an inextricable clinical dimension of the disorder<sup>50</sup>. An in-depth assessment of comorbid depression is therefore crucial at the first presentation of FEP individuals within EIP services, especially in order to prevent suicide and to improve long-term outcomes. The findings of this study showed a longitudinal improvement in DM severity levels, which was significantly associated with higher antidepressant dose at baseline, lower antipsychotic dosage still taken at T2 assessment and longitudinal reductions in positive and negative symptoms across the 2 years of follow-up. An antidepressant therapy in FEP subjects with clinically relevant DM is thus recommended.

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The Authors declare no conflict of interest.

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### Author contributions

LP, E: study conceptualization and design; SP: literature search; LP, EL, EQ, SA: data collection and curation; LP: formal analyses; LP: wrote the first draft of the manuscript; all Authors: reviewed and approved the final version of the manuscript.

### Ethical consideration

This study was approved by AVEN Institutional Ethics Committee (n. 36102/09.09.2019).

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association’s Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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## Post-traumatic stress disorder in nurses during COVID-19: a narrative review

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### SUMMARY

#### Background

Since December 2019, the new coronavirus disease (COVID-19) or severe acute respiratory syndrome SARS-CoV-2 has spread rapidly around the world and has reached pandemic proportions that have affected all continents.

#### Methods

Thanks to the PICO research strategy (population, intervention, comparison, results), a specific search string was used. To include relevant literature on the topic, several search terms belonging to each PICO section were combined. 339 studies published in English in the last 3 years (2020-2022) were identified, available on: EMBASE and MEDLINE.

#### Results

The studies included in this narrative review included 14 observational studies. Summarize the article's main findings.

#### Conclusions

Cultural, social and economic differences significantly influenced the mental health condition of all healthcare workers involved.

**Key words:** COVID-19, nurse, post traumatic stress disorder

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### Introduction

Since December 2019, the new coronavirus disease (COVID-19) or severe acute respiratory syndrome (SARS) CoV-2 has spread rapidly around the world and has reached pandemic proportions that have affected all continents<sup>1-4</sup>. The World Health Organization (WHO) declared the outbreak as an international public health emergency, in fact, from 11<sup>th</sup> March 2020 it was declared as a global pandemic<sup>5</sup>. Until April 8, 2022, around 494 million COVID-19 confirmed cases and over 6 million deaths have been globally reported (WHO Coronavirus - COVID-19). Previous respiratory infections from this century, such as SARS (Middle East Respiratory Syndrome, MERS), and Ebola infectious diseases have been shown to cause psychological damages to nurses, affecting their coping skills and, in some cases, their long lasting effects manifesting themselves, such as: stress, anxiety, depression and post-traumatic stress disorder (PTSD)<sup>6-8</sup>. According to the Diagnostic and Statistical Manual<sup>9</sup>, Post Traumatic Stress Disorder (PTSD) is a psychiatric illness caused by traumatic incidents outside the context of common human encounters, such as physical assault, violence, illness, disaster natural and healing from some diseases. People

with PTSD experience disturbing thoughts or emotions related to a traumatic accident long after the event has occurred. A traumatic accident can be personally encountered or observed, or it can also result from knowledge of a traumatic event suffered by a close individual. PTSD is diagnosed after a person has experienced symptoms for at least 1 month after a traumatic accident. Symptoms most commonly appear within 3 months of the event, but they can take years to develop. A wide range of signs is associated with PTSD, such as reliving painful memories, recurring memories, flashbacks, nightmares, mental numbness and avoiding trauma-related individuals, environments and accidents, as well as heightened arousal such as difficulty sleeping and processing, becoming nervous and feeling anxious and annoyed. The severity of this disease lies in the fact that these symptoms can occur at any age and that if not treated promptly can lead to symptoms up to 10 years after the traumatic event<sup>10,11</sup>, causing high turnover of nurses, endanger patient safety and affect the quality of life of affected nurses<sup>11</sup>. A recent American study<sup>12</sup> has addressed the financial issue of PTSD costs, calculating that the major studies have been done for the military, it has been determined that the overall expenditure is very onerous; it was estimated at \$ 232.2 billion for 2018 (\$ 19,630 per individual with PTSD). Total excess costs were \$ 189.5 billion (81.6%) in the civilian population and \$ 42.7 billion (18.4%) in the military population, corresponding to \$ 18,640 and \$ 25,684 per individual with PTSD in the civilian and military populations, respectively. In the civilian population, the excess burden was from direct health care (\$ 66.0 billion) and the costs of unemployment (\$ 42.7 billion). In the military population, the burden was from disability (\$ 17.8 billion) and the direct costs of health care (\$ 10.1 billion).

The COVID-19 pandemic also impacted the psychological health in nurses<sup>13-17</sup> and healthcare professionals<sup>18,19</sup>, as evidenced by several studies conducted in different parts of the world. It also appeared that all healthcare professionals experienced psychological distress but, it has been recognized, that nurses reported higher risks of burnout and PTSD<sup>20</sup>.

Although a recent systematic review summarized the evidence regarding mental health outcomes in healthcare workers during the COVID-19 pandemic, highlighting increased levels in burnout (ranging from 3.1 to 43.0%) and PTSD (ranging from 7.4 to 37.4%)<sup>21</sup>. Few studies evaluated PTSD occurring as a secondary outcome of stress<sup>17,22-24</sup>.

The specificity in the literature on mental health in nurses was still poorly summarized. It could contribute to limit the updated understanding estimates regarding burnout and PTSD levels among nurses<sup>25</sup>. Considering that nurses represent more than half of all healthcare

professionals globally<sup>26</sup>, a review of the literature concerning to their burnout and PTSD levels will help frame an updated assessment of the current global scenario. This assessment could be useful in informing decision makers about planning supportive and preventative strategies to support mental health in nurses in a medium- and long-term perspective.

### Objective

This review aimed to systematically synthesize evidence related to PTSD among nurses working in the front lines of COVID-19 patients.

### Materials and methods

Thanks to the PICO research strategy (population, intervention, comparison, results), a specific search string was used<sup>27</sup> (Tab. I).

To include relevant literature on the topic, several search terms belonging to each PICO section were combined (Tab. II). Articles written in English were only considered. The search strategy envisaged the use of the following terms indicated in the Table II, both for free search and using the MeSH database, individually and in combination with the Boolean operators AND and OR. The same terms were used for the search on the Embase and Medline databases (Tab. II).

339 studies published in English in the last 3 years (2020-2022) were identified, available on: EMBASE (148) and MEDLINE (191)<sup>28</sup> (Fig. 1).

Through an initial bibliographic search on electronic databases, all the articles deemed relevant for the purposes of this review were identified.

Repeated articles were removed several times in the databases consulted and those suitable for review were identified. Subsequently, two authors evaluated potentially relevant studies with respect to the initial research objective and the possibility of access to full-text (Fig. 1)<sup>28</sup>.

All studies that met the following criteria were included in the review:

- studies that aimed to investigate, as a primary objective, the impact of the COVID-19 pandemic on the nurses suffering from PTSD;

**TABLE I.** *The PICO instrument to literature review conduction.*

<b>P = patients/population</b>	Studies on nurses during the covid pandemic
<b>I = Interventions</b>	Onset of mental disorders post traumatic stress disorder
<b>O =Outcome</b>	Incidence of new cases

**TABLE II.** Search queries.

No.	Query	Results	Date
#4	((('wuhan coronavirus':ti,ab,kw OR 'wuhan seafood market pneumonia virus':ti,ab,kw OR 'covid19*':ti,ab,kw OR 'covid-19*':ti,ab,kw OR 'covid-2019*':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR sars2:ti,ab,kw OR '2019-ncov':ti,ab,kw OR '2019 novel coronavirus':ti,ab,kw OR 'severe acute respiratory syndrome coronavirus 2':ti,ab,kw OR '2019 novel coronavirus infection':ti,ab,kw OR 'coronavirus disease 2019':ti,ab,kw OR 'coronavirus disease-19':ti,ab,kw OR 'novel coronavirus':ti,ab,kw OR coronavirus:ti,ab,kw OR 'sars-cov-2019' OR 'sars-cov-19':ti,ab,kw OR 'sars-cov-2019' OR 'sars-cov-19':ti,ab,kw OR 'sars-cov-2019':ti,ab,kw) AND (('nurse'/mj OR 'anaesthetist nurse assistant':ti OR 'anesthetist nurse assistant':ti OR 'community health nurse':ti OR 'community health nurses':ti OR 'nurse':ti OR 'nurse, community health':ti OR 'nurses':ti OR 'nurses, community health':ti OR 'nurses, public health':ti OR 'nursing assistance':ti OR 'public health nurse':ti OR 'public health nurses':ti OR 'staff nurse'/mj OR 'staff nurse':ti OR 'psychiatric nursing'/mj OR 'mental health nursing':ti OR 'psychiatric nursing':ti OR 'nurse attitude'/mj OR 'nurse attitude':ti,ab,kw OR 'nurse's attitude':ti,ab,kw OR 'nurse's role':ti,ab,kw OR 'nurses attitude':ti,ab,kw OR 'nurses role':ti,ab,kw) AND ('depression'/mj OR 'central depression':ti OR 'clinical depression':ti OR 'depression':ti OR 'depressive disease':ti OR 'depressive disorder':ti OR 'depressive episode':ti OR 'depressive illness':ti OR 'depressive personality disorder':ti OR 'depressive state':ti OR 'depressive symptom':ti OR 'depressive syndrome':ti OR 'mental depression':ti OR 'parental depression':ti OR 'anxiety'/mj OR 'anxiety':ti OR 'mood disorder'/mj OR 'affective disorder':ti OR 'affective disorders':ti OR 'affective disturbance':ti OR 'affective illness':ti OR 'mood disorder':ti OR 'mood disorders':ti OR 'mood disturbance':ti OR 'mood disturbances':ti OR 'mental health'/mj OR 'condition, mental':ti OR 'health, mental':ti OR 'mental care':ti OR 'mental condition':ti OR 'mental factor':ti OR 'mental health':ti OR 'mental help':ti OR 'mental service':ti OR 'mental state':ti OR 'mental status':ti OR 'mental status schedule':ti OR 'psychic health':ti OR 'physiological stress'/mj OR 'physiologic stress':ti OR 'physiological stress':ti OR 'physiological stresses':ti OR 'stress':ti OR 'stress capacity':ti OR 'stress reaction':ti OR 'stress resistance':ti OR 'stress response':ti OR 'stress situation':ti OR 'stress tolerance':ti OR 'stress, physiological':ti OR 'alarm reaction':ti OR 'acute stress disorder'/mj OR 'acute stress disorder':ti OR 'acute traumatic stress disorders':ti OR 'stress disorder, acute':ti OR 'stress disorders, traumatic, acute':ti OR 'mental stress'/mj OR 'mental stress':ti OR 'mental stresses':ti OR 'mental tension':ti OR 'nervous stress':ti OR 'psychic stress':ti OR 'psychic tension':ti OR 'psycho-social stress':ti OR 'psycho-social stresses':ti OR 'psychologic stress':ti OR 'psychological stress':ti OR 'psychosocial stress':ti OR 'psychosocial stresses':ti OR 'stress, mental':ti OR 'stress, psychological':ti OR 'stress, psychological':ti OR 'tension, mental':ti OR 'tension, psychic':ti OR 'distress syndrome'/mj OR 'distress':ti OR 'distress syndrome':ti OR 'dystress syndrome':ti OR 'psychological distress':ti OR 'professional burnout'/mj OR 'burnout, professional':ti OR 'career burn-out':ti OR 'career burnout':ti OR 'occupational burn-out':ti OR 'occupational burnout':ti OR 'professional burn-out':ti OR 'professional burnout':ti))) AND (2020:py OR 2021:py OR 2022:py)	339	March 31, 2022

- research articles, such as observational, interventional studies;
- full text available in English.

Studies were excluded:

- editorials, literature review;
- studies which explored other mental health disorders, such as: anxiety, depression or insomnia;
- studies dealt with other healthcare professionals, without including nurses.

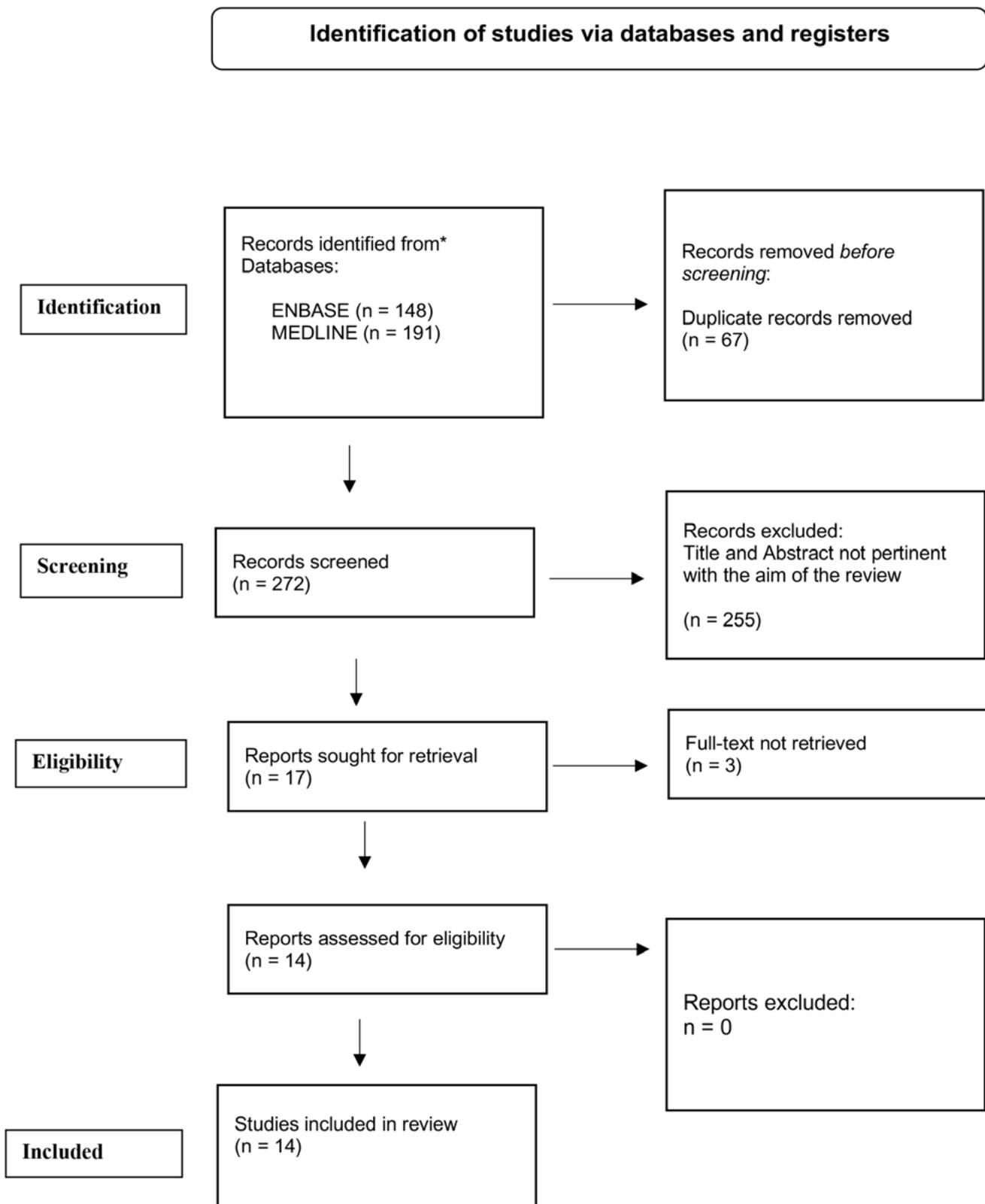
## Results

The studies included in this narrative review included 14 observational studies of which (Tab. III):

- 13 cross-sectional studies<sup>17,29-40</sup>;
- 1 study performed through a qualitative analysis<sup>41</sup>.

The selected studies were performed heterogeneously in all parts of the world:

- 3 in the USA<sup>32,40,41</sup>;
- 1 in Italy<sup>36</sup>;



**FIGURE 1.** PRISMA 2020 flow diagram for “Post-Traumatic Stress Disorder in Nurses during the covid-19 pandemic”.

TABLE III. *Studies included.*

Author(s) Publication year Country	Objective	Sampling	Study design PTSD tool assessment	Results
Zeiber W. et al., 2022 <sup>40</sup> USA	To explore any associations between: NPE PTSD the intention to leave	56 nurses	Cross-sectional study PES-NWI, PCL-S, TIS	PTSD scores were higher in nurses with an unfavorable environment than (M [SD], 27.91 [7.01]) than nurses who lived a favorable practice environment
King M. et al., 2022 <sup>34</sup> Irlanda	To evaluate psychological effects in mental health nurses	161 nurses	Cross-sectional study IES-R, SAS	PTSD diagnosis was experienced in nurses during the COVID-19 pandemic
Levi P. et al., 2022 <sup>41</sup> USA	To investigate the lived experiences in ICU nurses during the COVID-19 pandemic which impacted their mental health and attitudes towards their careers	10 nurses	Qualitative study Semi-structured interviews PTSD checklist job	7 out of 10 nurses met the diagnostic criteria for PTSD. 5 out of 10 nurses considered to leave their professions
Bani Issa et al., 2021 <sup>30</sup> Emirati Arabi	To assess the extent of PTSD development among frontline nurses, exploring motivational factors for continuation of work and investigating factors associated with PTSD	370 nurses	Transversal Study PDS	36.2% of participants had a probable diagnosis of PTSD (PDS score $\geq 28$ ). Nurses reported from moderate to severe PTSD, with avoidance and hyper arousal as the most frequent reported symptoms
Engelbrecht et al., 2021 <sup>31</sup> Sud Africa	To investigate PTSD and coping strategies in nurses during the second wave of the COVID-19 pandemic	286 nurses	Cross-sectional study IES-R, COPE, PPE	Nurses had an M score of 31.5 (SD 20,586) on IES-R. One more look careful revealed that 44.4% of nurses scored above 32 on the IES-R, which is indicative of higher levels of PTSD, with 38.8% of nurses suffering from severe PTSD
Hill R., 2021 <sup>32</sup> USA	To explore the impact of COVID-19 and the prevalence of PTSD among careers in COVID-19 patients	31 nurses 18 (58.0%) with high exposure 7 (22.6%) with low exposure 6 (19.4%) with no exposure		18 high exposure participants experienced symptoms of PTSD
Kabungu A. et al., 2021 <sup>33</sup> Africa	To analyze PTSD and associated predictors during the second wave of COVID-19.	601 nurses	cross-sectional descriptive study PDS-5 PCL-C	61.7% of nurses reported PTSD. Healthcare professionals working in COVID-19 environment were nearly 3 times more likely to report symptoms of PTSD versus those not exposed

- 2 in Africa (South Africa, Uganda) <sup>31,33</sup>;
- 2 in China <sup>17,35</sup>;
- 1 in the United Arab Emirates <sup>30</sup>;
- 1 Korea <sup>37</sup>;
- 1 Jordan <sup>39</sup>;
- 1 in Poland <sup>38</sup>.

In particular, Table III showed a summary of the main characteristics and results of the included studies. Among the selected studies, PTSD was assessed by using different tools. Although, the most assessment tools adopted were: the 7 PCLs (1 PCL-S, 3 PCL-C, 3 PCL-5), 5 used IES-R, for a total of 2967 nurses.

## Discussion

The current review suggests that healthcare professionals have reported a substantial degree of PTSD incidence during the COVID-19 pandemic.

The studies included in the review covered a total of 2947 nurses worldwide employed in the USA, Italy, Africa, China, Korea, United Arab Emirates, Jordan and Poland <sup>17,29-41</sup>. Different PTSD measurement tools were adopted, such as: PCL and IES-R. A significant incidence of PTSD in nurses was highlighted, showing prevalence differences related to different variants, including geographic location, gender, the marital status and the Department of belonging.

In particular, the highest incidence of PTSD was found in female nurses, in the wards at the front line of the COVID-19 emergency, including Emergency Department, Intensive Care and Infectious Diseases. Data were in agreement to previous literature <sup>37,38</sup>. In this regard, Marcomini et al. <sup>36</sup> found that nurses who experienced themselves in the front lines of COVID-19 patients care registered higher levels of PTSD, presumably linked to lack of experience before the pandemic in infectious disease. Just literature showed that age and work experience did not appear as predictive factors in infectious disease management <sup>41-43</sup>. A greater incidence was found among married nurses and nurses with children, although <sup>44</sup> positively highlighted the existence in family and social support as a protection strategy. Compared to the different parts of the world, there was a substantial increase in PTSD in the Eastern Mediterranean regions, the Western Pacific and South-East Asia compared to Europe.

These geographical discrepancies might be, presumably, attributable to the degree of responsibility and seniority in their workplaces and in their families, their social support networks <sup>45,46</sup>. Greater importance, in the PTSD developing risk, was given to factors, such as: isolated working environmental and lack working conditions and the forced usage of the personal protective equipment (PPE) <sup>35</sup>, the lack of rest and protracted shifts <sup>47</sup> and the discomfort in carrying out the work shift wearing all the required PPE <sup>32</sup>.

The association between the onset of the PTSD and the personal predisposition referable to the perception of one's health emerged, since an incorrect lifestyle and / or the presence of pre-existing diseases could lead to greater psychological fragility <sup>48,49</sup>.

From the work carried out it emerged that all the studies examined reported, a significant lowering of the sense of personal and work safety and a growing desire to abandon the nursing profession, a worrying fact already found in scientific reading, with exception of 2 studies which concluded by stating that the health crisis experienced during the pandemic peaks have strengthened the ability of nurses to respond and successfully adapted care practices.

To better understand the experiential experience that professionals are facing, it is important to mention some statements made by them during the data collection of the Hill study <sup>32</sup>, which are emblematic of the situation that workers faced and face:

- “a patient death is difficult as it is. But some days we just had to switch from one code to another. And a few moments before all this, these patients had to say goodbye to the family who cannot even cry at their bedside”;
- “people [were] dying without seeing their families or without being kept alive with machines with a very poor prognosis”;
- “we have run repeated codes on patients who medically and ethically should be DNR”;
- “with this virus, patients deteriorate rapidly. You can do anything that comes to your mind and the patient continues to deteriorate. It's hard to be a caregiver and not be able to help your patient no matter how hard you try”;
- “[I have] feelings of inadequacy and failure due to our COVID [patients] not receiving the care they deserve (mainly due to the need to pool care). Even feeling like we are doing things to them rather than to them because we don't really know how to cure this disease”.

In our systematic review we have identified both strengths as:

- the included studies photographed the problem of PTSD on nurses in different parts of the world, increasing the overall view of the problem;
- the data and the eligibility of the studies was performed by two independent researchers, increasing the solidity of the results;
- the general vision of the PTSD problem only two years after the pandemic gives a general picture of the problem and the programmatic direction that one wants to take;
- the psychological status of nurses in the included studies was not assessed prior to the pandemic.

This has limited our ability to explore the additional psychological burden on the nurse due to the COVID-19 pandemic as we have no data on their psychological state prior to it;

- failure to find 3 items;
- due to the worldwide blocking policy, most of the included studies were web-based cross-sectional surveys, so that there could be the possibility of sampling errors;
- substantial heterogeneity between studies was identified, which could be increased due to the difference in rating scales (variation in cut-off scores) used in the studies to explore outcomes;
- furthermore, the estimates of the aggregate analyses were based on cross-sectional data, undermining the possibility of describing the trajectory of PTSD over time (before COVID-during).

Only research papers published in English were included, contributing to the lack of some studies.

## Conclusions

The COVID-19 pandemic was a traumatic event of unprecedented magnitude that pushed normal beyond normal and human and professional endurance threshold of nurses, causing serious mental health disorders. The current narrative revision aimed to give an update regarding the mental health status, in particular on PTSD among nurses who were at the front line during the COVID-19 pandemic. From the selected literature, it could state that cultural, social and economic differences significantly influenced the mental health condition of all healthcare workers involved. Consequently, health care organizations should be more sensitized to the needs of nurses by providing various arrangements, such as: short service hours and adequate rest hours,

sufficient protective supplies, support services. National disaster preparedness plans should also have included a plan to safeguard mental health in nurses and health workers in general. For example: regular screening for mental health disorders, physical symptoms, promoting coping and resilience strategies, targeted interventions to prevent PTSD, turnover, providing more flexible working hours and encouraging nurses to use psychological support services. Furthermore, greater investment in addressing the global shortage of nurses should take priority in national health policies, especially in low- and middle-income countries, where rates of PTSD have been shown to be higher. These actions will be helpful to prevent the PTSD effects, such as: personal distress, also in the own workplaces, with the risk of reducing professional skills, the empathic involvement level, the relational skills in individual operators and then, in the whole teams, respectively.

It will be also desirable to implement all existing services to support mental health in nurses, in prevention, treatment and rehabilitation areas.

## Conflict of interest statement

The Authors declare no conflict of interest.

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## Author contributions

The Authors equally contributed.

## Ethical consideration

Not applicable.

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## Coexisting gender dysphoria, cross-dress and bipolar schizoaffective disorder: a psychopathological conundrum

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### SUMMARY

*The co-occurrence of Schizophrenic psychoses (with sex changes delusional experiences or themes) and gender dysphoria has been debated since the end of 19<sup>th</sup> century with different accents: as an association of sexual psychopathy and paranoia, for the possible etiopathogenic role of bi-sexuality and gender dysphoria in different psychic disorders, as psychopathologies that needed to be accurately differentiated, and, at last, as co-occurring conditions that can interfere each to the other.*

*The Authors describe in detail the clinical case of a 54 years old man who in relation with the periodic sharpening of his schizo-affective maniform psychosis, showed temporary shameless, grotesque and even bizarre cross-dressing behavior and sex re-assignment request. In euthymic or depressive phase, his transexual behavior was much less evident or even repressed. The psychopathological implications of this rare but impressive co-occurrence are discussed.*

**Key words:** schizophrenia, gender dysphoria, cross-dressing, bisexuality, non-binary, sexual reassignment

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According to earlier epidemiological estimates about 1/37000 (0,0027%) males and 1/103.000 (0,00097%) females seek reassignment surgery <sup>1</sup>. The prevalence is getting higher and, in 2007, a Belgian study <sup>2</sup> found out values of about 1/12900 (0,0077%) in males and 1/33800 (0,0029%) in females. The percentage of people seeking sex surgery reassignment is nowadays increasing because of the progress in technical surgery, safe and successful today more than ever <sup>3,4</sup>. Clearly, the wider ethical acceptance and political support of gender-fluid patterns of sexuality makes their affirmation easier. Recent evidence shows ever higher rates of gender dysphoria in females (from 1/3000 to 1/15000), overcoming the percentage in males <sup>5</sup>. However, the surgical sex reassignment and gender affirmation practices are ever more requested both from males to females than from females to males without any deep prior psychological and psychopathological assessments <sup>4,6</sup>.

The prevalence of schizophrenic psychoses is about 1-2% in adults' people, and the prevalence of sex change delusions of sexual transformations in schizophrenia are not so rare as Krafft-Ebing <sup>7</sup> believed. According to Borrás et al. <sup>8</sup>, 20% of delusional experiences in schizophrenia have gender change or other genital modification's themes. The co-occurrence of schizophrenia and gender dysphoria, and even more of schizophrenia and other psychotic disorders with sex change delusions and sex gender reassignment should be considered very rare, but possible <sup>9</sup>. Hence, the literature on the co-occurrence is sparse and anecdotic <sup>5,10</sup>. However, from a psychiatric standpoint, the relations between the two conditions

are difficult to disentangle <sup>8,11,12</sup> and represent a true psychopathological conundrum.

### A brief recall to myths and literature

The transformation of a sex gender in another is a myth found in universal mythologies <sup>13</sup>. In Greek mythology, the most quoted sex change is that of Tyresias (Τυρσηϊας) that, in the most common tale, lived seven years as woman and seven years as a man (after having killed alternately the male and the female exemplary of a couple of snakes during their coupling). So, Zeus and Era called him as a judge to establish which sex would have felt more pleasure during sexual activities (Tyresias answered that women felt it nine times more than man).

Among the many literary example, we may quote Orlando, the character of Virginia Woolf <sup>14</sup>, who changes sex in the centuries to meet different heroes of English literature, but the more pertinent for psychopathologic reflection is the main character of Roman Polansky's movie "The tenants" <sup>15</sup>, drawn from Roland Topor's homonymous novel <sup>16</sup>. Trelkowski, the name of the character of a polish immigrant, played by Director Polansky himself, develops a delusional belief that people living in the same palace compel him to transform himself into the previous female tenant of his accommodation, who at last committed suicide jumping out of the window. In a growing dramatic climax of delusional and hallucinatory experiences, Trelkowski acts a complete cross-dress: he begins to wear female dress and uses the cosmetics of the earlier female tenant, then buys and wears female wig and heeled shoes before committing suicide dressed as his predecessor.

An experience of gender transformation is described also in Pier Paolo Pasolini's last, unaccomplished novel, "Petrolio" <sup>17</sup>: the great Italian writer was homosexual, but was deeply concerned with sexual paraphilias during his last year of life (see also his last film "Salò e le 120 giornate di Sodoma" – <sup>18</sup>). In the novel Pasolini tells two times the experiences of sex change of his main character "Carlo" who, in front of a glass, sees "the little sore that was his new sex".

### Psychiatric literature

The psychiatric literature about psychopathological aspects co-occurring with gender dysphoria is not conclusive. Anyway a lot of delusional experiences of changing sex has been referred in the course of history of psychiatry.

Krafft-Ebing <sup>7</sup> described some cases in which the gender dysphoria and cross-dressing (*antipathic sexual instinct*) progresses in a psychotic conditions and called them *Metamorphosis sexualis paranoica*. In such circumstances the subject feels the sensation of *transmutatio sexus*.

The most famous self-report of delusional sex-change (or gender transformations) experience is the one described by the remarkable Daniel Paul Schreber autobiography <sup>19</sup> "Memories of a nervous ill" (the case of the "President Schreber" analyzed by Freud directly on the basis of the writing – <sup>20</sup>): in his long hallucinatory paranoid experience, which needed two successive years long admissions in the Clinical Psychiatry in Lipsia ad in Sonnenstein Psychiatric Hospital between 1884 and 1895, Schreber, in the context of a wider well-systematized mystic experience felt two times his male genitalia transformed in female genitalia, thanks to "divine miracles". His description evokes up to date surgical procedures of sex reassignment: "The emasculation happened in this way: external male organs (scrotum and penis) were retracted inside the body and transformed in the corresponding female sexual organs, at the same time internal sexual organs transformed themselves...". Until the end of the 20<sup>th</sup> century, most of psychiatrists believed that gender dysphoria was a delusional disorder (delusion of sex change): they were subtyped as delusion of no longer being a male or female, delusion of being a neuter or both sexes simultaneously, delusion of being of the opposite sex <sup>21</sup>; the last type was the most pertinent to discuss the relationships between trans-sexualism (gender dysphoria) and schizophrenia. In the last decades, some reports described isolated cases of co-occurrence of gender dysphoria and Paranoid schizophrenia <sup>11,12,21-26</sup>. They try to suggest that psychotic disorders should be excluded in people who ask for endocrine and surgical interventions of sex change, since sex change delusions are not so rare in clinical practice and self-reports of psychotic patients and can represent a subtype of somatic delusion and hallucinations <sup>27</sup>; these case of "pseudo-trans-sexualism" should be carefully differentiated from simple gender dysphoria beliefs <sup>11,12</sup>. These delusional beliefs can sometimes remit spontaneously or with antipsychotic medication <sup>24,25</sup>. Psychiatric diagnoses comorbidity with gender dysphoria has been studied in last years with opposite aims; Dhejne et al. <sup>3</sup> found no evidence of higher prevalence with respect to the general population, while the prevalence of substances and alcohol abuse, anxiety, social anxiety, alexithymia and mood disorders is much more relevant <sup>3,9,28-31</sup>. The suicidal risk is higher than in the general population <sup>3,28</sup> and suicidal risk and the occurrence non-suicidal self-injuring behavior are more common than in the general population as well as in gay, lesbian, and bisexual people <sup>29-32</sup>. Nonetheless, the updated prevalent paradigm is to consider change sex (sex change) ideas or drives as normal, if not associated with other psychotic symptoms or experiences <sup>9</sup>. Updated reviews reverse traditional models supporting that gender dysphoria conditions may be traumatic and contribute to the presentations of psychotic symptoms;

both hormone therapy and culturally-sensitive and gender-affirming approaches may help in their prevention and treatment<sup>5,10</sup>.

Our interest in this topic rises up in our work (teamwork discussions) about the case of a fifty-four-years old bipolar schizoaffective male patient, who periodically present showy and even grotesque and manneristic cross-dressing that partially remits in course of antipsychotic treatments (haloperidol and clozapine), even if auditory verbal hallucinations persist. Remarkably, when the cross-dress behavior is at its acme, he gets in contact with specialized centers for endocrine and surgical sex reassignment. We tried to better understand his feelings reconstructing in detail his illness history in search of mutual interactions between gender dysphoria and psychotic disorders.

### The clinical sketch

B. M. is a fifty-four-years old male that has been treated in our service discontinuously since fifteen years up to now, though more regularly during the last three years, due to the worsening of his psychopathology and behavior.

The early clinical disturbances referred by the patient are correlated to alcohol abuse in his late twentieth. He was treated in a public service until his recovery and alcohol abstinence. The onset of clearer psychiatric disorders is not well described by the patient, but was likely characterized by opposite mood oscillations. In the earlier stages of his illness, he consulted academic services and private psychiatrists, even though we could not find any trace of those treatments. The severe acoustic hallucinatory psychotic disorders have risen probably after his forties and have become chronic and neuroleptic resistant. In recent years, the course of the illness is characterized by alternation of maniform and depressive-like phases associated with reference delusions and auditory verbal hallucinations, especially malevolent comments of his acts, suggestions, and orders, so that a DSM-5<sup>1</sup> diagnosis of Schizoaffective psychosis, bipolar type, continuous, has been consensually formulated.

The patient refers that doubts about his own sex gender arose in early childhood, but were repressed by his mother to protect him from his domineering father ("early-onset gender dysphoria"<sup>1</sup>). He doesn't refer sexual abuse but a single homosexual intercourse with an older boy at about ten years old.

His parents were merchants and the family was wealthy. Indeed, some unsuccessful attempts were made to push him to continue parental activities or to undertake any job whatsoever.

He has never lived with his family and, after his father's death when he was thirty-five, he has been living with his mother, which nowadays is eighty-years old upon writing. His sister lives autonomously and struggles to support and protect him.

He refers (in the phases of mood stabilization) to be shy and privacy-protective about his sexual life.

At about thirty-five, he has had a relationship with a woman, but he refers that, during sexual intercourses, sometimes, he was compelled to imagine that she was a little child. Therefore, he used to interrupt the intercourse, realizing his pedophile tendencies. Anyway, from this relationship, a male child is born, in virtue of the female's will, and is adolescent upon writing. The patient has not looked after his child for many years, due to the obsessive phobia of being a pedophile. However, he has maintained distant relations with him and his mother, and currently meets him at his mother's house.

He doesn't refer about any other relationship, neither heterosexual nor homosexual. During the phases of mood stabilization, he is not involved in sexual activities, and even he pretends to be asexual or non-binary. The clinical picture changes drastically during maniform phases. He speaks continuously about his homosexuality and argues that his main source of sexual pleasure is a point of the rectus five centimeters inside his anus, looks for sexual activities with professional transsexuals and he's obsessed by cross-dressing activities.

In the last years he has been admitted sometimes in our psychiatric ward, even mandatorily, due to the sharpening of auditory hallucinations and aggressive behavior against his mother, this time following her refuse to give him money to buy very expensive female dresses. His insight is very low, both regarding his psychotic conditions, both his inappropriate, grotesque cross-dressing during maniform phases. He has developed the somatic delusion that the voices come from a device installed in his neck and he consulted a surgeon to remove it. Other paranoid ideas concern other persecutory themes. The response of these symptoms to drug treatments (haloperidol, clozapine, lithium) is quite low, and the course of the different phases follows spontaneous remissions.

Concerning his cross-dressing, during manic-like phases, his look is very impressive and astonishing: he dresses as a provoking prostitute, but the result is quite grotesque and obscene. For example, under the very short skirt he shows with evidence the remainders of his male genitals under the slip, and the hair of his breast stick out the pink top, matched with very expensive twelve-centimeters heeled pink shoes. Dressed as such, he is used to walk in his little town's streets and pubs completely untouched by judgments of the many people that know him. In these phases, he completely loses the sense of glamour that he would like to flaunt; moreover, he looks for homosexual passive intercourses with transsexuals. At last, he took an appointment to begin the long process of surgical sex reassignment, starting with expensive private mastoplasty and buttocks rounding for which he gave a consistent advance

payment to the surgeon. In this last phase, he racked up debts for over than twenty thousand euros, so that his parents prompted for a juridical protection. The surgeon was mandated to give back the account.

Despite his cross-dressing, during manic phases he is sometimes uninhibited with young women and, at the end of the maniform phase, the cross-dress behavior remits and the patient tries to flaunt a more masculine behavior; in the past, he used to mimic more masculine behavior like driving expensive cars, looking for androgenic treatments and trying to have sexual intercourses with escorts.

In the stabilization or slightly depressive phases, he, as we have already written (as already mentioned), presents himself as a shy person, and defines himself as asexual, angelic, non-binary. He becomes critic about his transsexual behavior, especially for the moral damage he causes to his parents and his son.

## Discussion and conclusions

The question of the relations between psychotic experiences, gender dysphoria and gender fluid disposition has a long tradition in psychoanalytical literature, beginning with Freud's repeated reflections and papers about the role of bisexuality in the genesis of "Hysteria" and paranoid delusions<sup>33,34</sup>. Due to their speculative nature, these kinds of observations have been increasingly outdated in the scientific literature and psychopathological reflections. However, the question is up to date not irrelevant since both the high rates of psychopathology, especially major depressive, phobias and adjustment disorders<sup>30</sup> in addition of the anticonservative behavior associated with gender dysphoria<sup>28,31</sup>, as well the not so rare rates of sexual change themes in paranoid schizophrenics, still continue to rise it in clinical practice. Are there some psychopathological links between the two different conditions, psychosis and gender dysphoria? And, if yes, which?

The case we have described is quite interesting, for the intertwining of different psychopathological dimensions such as psychosis, obsessive phobias and abnormal personality traits, whose combinations with gender dysphoria and changes in sexual orientation during different phases of the patient's illness supported different, unstable, intriguing but also misleading clinical pictures. Our case study, that has astonishing similarities with that reported by Subbash Bhargava and Sujata Sethi<sup>26</sup>, supports with clear evidence that schizophrenia and gender dysphoria with cross-dressing are independent conditions that can co-exist. In the patients history, schizophrenic paranoid symptomatology refers to non-sexual persecutory themes and, as well as the functional social impairment, has become chronic over the course of the years. However the mood oscillations influence pervasively the expression of gender dysphoria. Outside the manic phases, the patient still complaints of delusional

themes but does not mention his gender-conflict. On the contrary, during the manic phases the gender conflict and the exorbitant cross-dressing tendencies are at their acme and represent the largest part of his psychopathology. The independence between psychosis, changes in sexual orientation and gender has been shown in the pioneering study by Hyde and Mckenna<sup>29</sup> on a pair of twins, which however did not exclude that the two conditions are two poles of a spectrum of disorders. Other explanations are: delusional and hallucinatory experiences can drag cross-dressing or desires to change sex, or, as in our case, can make the outing easier and their gestaltic and behavioral expression more pronounced. In our case, the cross-dressing during acute manic-like relapses of the illness was grotesque and shameless in its expression, quite different in its phenomenology from "normal" cross-dressing. Its theatrical expression might be considered a symptom of mania, though unrelated to hallucinatory experiences or verbal auditory hallucinatory orders that talk about other topics or simply comment patients' actions. Psychosis, then, could only modify the expression of gender identity disorders, as already suggested<sup>5,22</sup>, making it more pronounced, completely void of glamour in its expression and sometimes bizarre in its subjective motivations. We can attribute these effects to a deep disinhibition of inner-locked dispositions.

The coexistence of psychotic disorders should always be investigated in people looking for sex reassignment surgery (as well as it should be in dysmorphophobic disorders in people looking for aesthetical or bariatric surgery). Apart from the cases in which transient delusional experiences supports them, the sex reassignment request can rise up but also be given up with the remission of expansive phases of bipolar or schizoaffective disorders, so that ethical and legal ("normative") questions can easily be put forward.

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The Authors declare no conflict of interest.

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## Author contributions

Both Authors contributed to the clinical observation, the writing of the paper and the bibliographic research.

## Ethical consideration

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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## Adjustment disorders with and without embitterment

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### SUMMARY

#### Objective

Adjustment disorders have been greatly revised in the 11<sup>th</sup> version of the ICD. The definition of adjustment disorders as stress-related disorders is in accordance with many years of research on embitterment and posttraumatic embitterment disorder. The question is how often adjustment disorders are accompanied by embitterment and/or PTED and what the differences are between pure adjustment disorders (A), embittered adjustment disorders (E) and PTED (PTED).

#### Methods

A total of 186 rehabilitation patients with adjustment disorder symptomatology were classified according to their embitterment symptomatology and examined for differences in terms of sociodemographic data, depressiveness, life stresses, embitterment, wisdom, and general symptomatology.

#### Results

PTED was found in 8.1% and feelings of embitterment in 35.5% of patients with adjustment disorder.

Pure adjustment disorder patients reported lower levels of depression (BDI-II: A:10.13 vs E:19.93; PTED:20.58), adjustment disorder symptomatology (ADNM-8: A:24.7 vs E:32.2; PTED:32.7), and higher levels of wisdom (MDW-30: A:81.0 vs E:69.4; PTED:72.6). Patients with embittered adjustment disorders and PTED did not differ significantly in terms of impairment.

#### Conclusions

The data show that adjustment disorder with embitterment and adjustment disorder without embitterment and PTED can and should be distinguished as they come along with different impairment severity and symptomatology profiles. Diagnostic criteria for PTED are rather strict, which helps to avoid overdiagnosis.

**Key words:** embitterment, posttraumatic embitterment disorder, psychosomatics, psychotherapy, trauma

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### Clinical impact statement

It is relevant to differentiate between adjustment disorder with and without the emotion embitterment. Both share the same disorder. However, it is important whether the patient also developed embitterment as both come with different impairment levels and symptoms. To search for embitterment is highly relevant as it occurs in almost every second patient with adjustment disorder. These patients need proper attention. The current diagnostic criteria for Posttraumatic Embitterment Disorder (PTED) are strict to avoid overdiagnosis in daily practice.

## Introduction

The definition of adjustment disorders has been substantially changed in the ICD-11<sup>1</sup>. Core characteristics are “preoccupation with the stressors” and “failure to adapt”. These symptoms have to manifest itself in less than 3 months after the patient was exposed to the stressor. Further symptoms are recurring distressing thoughts, constant worrying or rumination about the stressor, general stress-response symptoms, depressive or anxiety symptoms, social, interpersonal, occupational, educational problems, or impulsive ‘externalizing’ symptoms, particularly increased tobacco, alcohol, or other substance use<sup>2-6</sup>. The “*Adjustment Disorder - New Module 8; ADN-8*”<sup>5</sup> is a scale specifically designed to assess the adjustment disorders according to the ICD-11.

The description of adjustment disorders (6B43) in the ICD-11 gives examples for typical psychosocial stressors such as “divorce, illness or disability, socio-economic problems, conflicts at home or work”. These are social stressors, which often entail injustice, humiliation, and breach of trust. A typical reaction to these psychological processes is embitterment, which is also listed in association with adjustment disorders in the online version of the ICD-11<sup>1</sup>.

Most people know embitterment from themselves and others<sup>7,8</sup>. Embitterment is seen in reaction to injustice, humiliation, and breach of trust, associated with helplessness<sup>9-12</sup>. Similar to anxiety, embitterment can be observed in several forms<sup>13</sup>. Normal embitterment may occur in the context of an acute dispute which is accompanied by derogative comments, but subsides a short while afterwards. Embitterment can also prevail stimulus bound for years, re-emerging whenever the critical event is mentioned, while these people are otherwise calm and unimpaired. There may also be “embitterment prone personalities”, individuals which tend to easily respond with embitterment whenever they are criticized or questioned. Additionally, there are other personality disorders like narcissistic or paranoid personalities which can be accompanied by embitterment. Comparable to anxiety and post-traumatic stress disorder, embitterment can, with greater intensity and duration, also become a disabling disorder of itself. This has been described under the term “Posttraumatic Embitterment Disorder, PTED”<sup>7,14,15</sup>. Triggering is a single negative life event which is experienced as derogative, insulting, and downgrading. Apart from embitterment, additional symptoms are a dysphoric-aggressive-depressive mood, phobic avoidance of persons and places related to the event, an impairment in daily activities, feelings of aggression and revenge, and even suicidal tendencies and sometimes extended suicide.

This raises the question how often adjustment disorders are accompanied by feelings of embitterment or even

PTED. The objective of the present study was to investigate the association between adjustment disorders and embitterment and the differences between pure adjustment disorders, embittered adjustment disorders, and PTED.

## Methods

### Patients and setting

Participants were inpatients from a psychosomatic hospital and were suffering from various mental disorders. Routine treatment included medical and pharmaceutical treatment, single and group psychotherapy, occupational therapy, sport therapy, and social work care. Length of stay was about five weeks, as predetermined by health insurance, but could be changed according to individual needs.

### Assessments

All patients were seen for clinical reasons by a senior psychosomatic specialist. He also made a judgement on language problems or other special clinical features, which may hinder participation in this study.

The following measures were assessed in the patients in the beginning (pre) and in the end (post) of their rehabilitation treatment:

- ADN-8: all patients admitted to the hospital were routinely screened with the “Adjustment Disorder - New Module 8; ADN-8”<sup>5</sup>, which asks for adjustment disorder criteria in reference to the ICD-11<sup>1</sup>. The introduction reads: “Which life events stick in your mind and are most burdensome?”, followed by the items “1. I have to think about the stressful situation repeatedly”; “2. I have to think about the stressful situation a lot and this is a great burden to me”; “3. Since the stressful situation, I find it difficult to concentrate on certain things”; “4. I constantly get memories of the stressful situation and can’t do anything to stop them”; “5. My thoughts often revolve around anything related to the stressful situation”; “6. Since the stressful situation, I do not like going to work or carrying out the necessary tasks in everyday life”; “7. Since the stressful situation, I can no longer sleep properly”; “8. Overall, the stressful situation affected me strongly in my personal relationships, my leisure activities, or other important areas of life”. Items are answered on a Likert scale (1 = never to 4 = often). Patients with an ADN-8 total score  $\geq 18$  are suspect of adjustment disorder and were suitable for the present study.
- SCL-90: the “Symptom Checklist” (“SCL-90-R”) was used to record physical and especially psychological symptoms. The impairment of the last seven days is inquired. The “SCL-GSI” gives an indication of the

extent of impairment in general <sup>16</sup> and can be seen as a measure of subjective distress.

- BDI: the “Beck Depression Inventory” (“BDI-II”) was used to assess depressive symptoms. A total of 21 statements about different possible depressive symptoms have to be selected on a four-point scale (0–3). The total score is an indication of the extent of current depressive symptomatology with a suspicious threshold of 13 <sup>17</sup>.
- DLB scale: the “Differential Life Burden Scale” (“DLB Scale”) was used to record subjective stress in a variety of life domains. The scale starts with the words: “When I think about...”, connected with different areas of life such as “family”, “work”, or “the future”. Each area of life can be rated on a six-point scale (0 = “very negative”, 1 = “negative”, 2 = “somewhat negative”, 3 = “somewhat positive”, 4 = “positive”, 5 = “very positive”). The total score provides information about the extent of general stress in life <sup>18</sup>. Items with a rating of 0 = “very negative” or 1 = “negative” indicate that this life area is burdensome for the patient;
- The “Multidimensional Wisdom Scale” (“MDW”) is a questionnaire for evaluating a person’s wisdom level. This can be seen as resilience factor in coping with difficult problems in life <sup>19</sup>. Wisdom-related items must be answered on a five-point scale ranging from “not true” – “definitely true” <sup>20</sup>.
- PTED interview: the “PTED interview” <sup>21</sup> is a standardized diagnostic interview conducted by a specially trained psychotherapist. The interviewer has to make a judgement whether patients suffered from a critical negative life event which they experience as unjust and unfair, whether they show a distinct feeling of embitterment related to the triggering event and which is not due to some other mental disorder, whether the patient feels helpless towards what happened, whether there are intrusive and distressing memories, whether the overall subjective well-being is impaired since the critical event, and whether the problem exists for longer than six months.
- Embitterment: at the end of the ADN-8 questionnaire, two additional questions were added: “Thinking about what happened, I have the desire for revenge” and “Thinking about what happened, I feel disparagement, injustice, and embitterment”. These items represent embitterment. Their combined score ranges from 2 to 8.
- Sociodemographic data: data such as age, gender, and education were recorded.
- Group allocation: all patients had to have a minimal score of  $\geq 18$  on the ADN-8 scale, indicating adjustment disorder problems. These patients were divided into three groups. The first group included all

patients who were diagnosed as suffering from PTED according to the standardized interview (PTED-group). Next, patients with a score of 5 to 8 on the embitterment items were allocated to the embittered group (E-group). The remaining patients who were neither diagnosed as PTED nor had an increased embitterment score were grouped as pure adjustment disorders (A-group).

### Ethics

The study was supported by a research grant of the Federal Pension Fund Berlin-Brandenburg (10-R-40.07.05.07.018). Patients gave their informed consent for participation in the study. The data have been processed anonymously. The study was approved by the ethical committee of the Charité University Medicine Berlin (AS57(bB)/2019), registered with and approved by the Clinical Trial office and the data security office of the Charité University Medicine Berlin, the clinical trial data security department of the Federal Pension Fund Berlin-Brandenburg, and was registered with the German Trial Register (DRKS00016895).

### Results

A total of 186 patients were included in the study. There were 15 patients (8.1%) with adjustment problems who also fulfilled the diagnostic criteria for PTED (PTED-group), 66 patients (35.5%) with adjustment problems who also reported feelings of embitterment and revenge but did not fulfil PTED criteria (E-group), and 105 patients (56.5%) with adjustment problems according to the ADN-8  $\geq 18$ , but no signs for embitterment (A-group).

There were no significant differences between the three groups in regard to age (53.39 years, range 29–65, SD = 7.87;  $F = .339$ ;  $p = .713$ ), gender (74.2% female;  $\chi^2 = 1.01$ ;  $p = .603$ ), marital status (55.4% married;  $\chi^2 = 4.222$ ;  $p = .647$ ), educational level (33.3% college;  $\chi^2 = 0.616$ ;  $p = .735$ ), ability to work at admission (56.5% fit for work;  $\chi^2 = 2.646$ ;  $p = .266$ ), duration of incapacity (41.0% longer than six months;  $\chi^2 = 7.142$ ;  $p = .521$ ), and ability to work at discharge (55.9% fit for work;  $\chi^2 = 7.135$ ;  $p = .129$ ).

Table I shows the differences between groups in the standardized diagnostic interview. The differentiation between PTED-patients on one side and E- and A-patients on the other side is the judgement of the interviewer on the presence of an embitterment affect. All patients in all three groups complained about some negative life event, as this was the inclusion criterion according to the ADN-8. All PTED- and 85% of E-patients called this an experience of injustice and unfairness in comparison to 64% in A-group. PTED- and E-patients also expressed significantly more about feelings of de-

TABLE I. PTED interview.

Item	PTED n = 15	Embittered n = 66	Pure adjustment n = 105	$\chi^2$ -Test
Suffered a critical life event	100%	100"	100"	
Observer rating: embitterment affect	86.7"	7.6"	1.9"	98.75; p = < .001
Subjectively perceived as unjust or unfair	100"	84.8"	63.8%	15.04; p = < .001
Subjective complaints about despair and anger	100%	97"	81.9"	11.26; p = .004
Feeling helpless towards the critical life event or perpetrator	93.3"	95.5"	77.1"	11.52; p = .003
Intrusive memories	100%	90.9%	93.3%	1.59; p = .451
Agitated when remembering event?	80%	63.6%	52.4%	5.20; p = .074
Minimum 4 additional symptoms?	100"	86.4"	75.2"	7.07; p = .029
Current general mood depressed?	100"	90.9"	87.6"	2.34; p = .311
Normal mood prevails when distracted?	86.7"	92.4"	89.5"	0.64; p = .726
Additional mental and emotional problems in the past	26.7"	45.5"	26.7"	6.76; p = .034
Current condition can be explained by previous or other mental disorder? (A4a)	6.7"	25.8"	14.3"	5.03; p = .081
Duration of mental impairment to date > 6 months?	100%	92.4%	97.1%	2.93; p = .232

spair and anger, helplessness towards the critical event and the perpetrator. The E-group showed more cases with additional mental problem in the past, which were also more often seen as cause of the present problems. All groups, but most pronounced in the PTED-group, reported a high degree of intrusive memories and agitation when reminded of the event. The PTED- and the E-group showed more symptoms in general. There was in all groups a generally impaired mood state, but not an impairment in mood modulation, as this would be characteristic for depressive disorders. The duration of illness was longer than half a year in almost all cases, including the A-group, which contradicts the diagnostic requirement of the ICD-11, which sees adjustment disorders as transient disorders which should subside in half a year.

The ADN-8 total score is across all patients at admission 27.8 (SD = 3.44), and 28.6 (SD = 3.76) in the PTED group, 28.45 (SD = 3.01) in the E-group, and 27.28 (SD = 3.59) in the A-group, speaking for a trend of a lower score in the A-group as compared to both embitterment groups ( $F = 2.78$ ;  $p = .06$ ). At discharge the overall score is 23.9 (SD = 5.3), and 26.6 (SD = 4.4) in the PTED group, 26.8 (SD = 2.8) in the E-group, 21.7 (SD = 5.3) in the A-group, indicating a significantly lower score in the A-group as compared to both embitterment groups ( $F = 25.7$ ;  $p < .001$ ). Figure 1 shows the percentage of patients which report on the ADN-8 scale, that they "often" suffer from respective problems. The comparison of the three groups shows that all patients report about repeated negative thoughts also in

the ADN-8, that both embitterment groups find these more burdensome, and that especially the PTED-group is more impaired as indicated by problems in concentration, the fulfilment of daily tasks, or sleep disorders. Table II gives an overview on general symptoms and the present well-being of patients in the three groups. Significant differences were found for the symptom checklist (GSI) pre and post, and the BDI pre and post. Post-hoc tests show that these differences are preferably due to differences between the E- and A-group at pre-test, but also between the A- and PTED-group at post-test, with no differences between the two embitterment groups.

The wisdom score, as a measure of resilience, does not show any group differences at pre assessment but a significantly higher score in the A-group as compared to the embitterment groups at post assessment.

When looking at eliciting life burdens, as measured with the DLB scale, significant differences are found between groups with highest scores in the A-group, lowest in the E-group, and the PTEDgroup in between (Tab. II). This suggests that E-patients complain most about burdens across different areas in life. The same is found at the post assessment.

Figure 2 shows the percentage of patients with a rating of 0 or 1 (negative and very negative) for each DLB item by group. Across all areas, the A-group shows lower numbers of burdening. The E-group shows relatively higher scores in relation to family at large and future and lifetime balance. PTED- and E-patients show increased rates predominantly in regard to work, health,

**TABLE II.** Differences in subjective complaints between groups. Means (standard deviation) are reported.

Item	All	PTED	Embittered	Pure adjustment	Group differences	PTED - E	PTED - A	E - A
SCL GSI (pre)	1.12 (.58)	1.24 (.42)	1.38 (.62)	0.94 (.50)	F = 13.211; p = <b>.000</b>	P = .650	P = .155	P = <b>.000</b>
SCL GSI (post)	0.76 (.58)	0.96 (.57)	1.09 (.65)	0.53 (.40)	F = 24.058; p = <b>.000</b>	P = .688	P = <b>.014</b>	P = <b>.000</b>
BDI total (pre)	24.53 (10.60)	25.67 (8.76)	28.47 (11.27)	21.92 (9.67)	F = 8.366; p = <b>.000</b>	P = .632	P = .415	P = <b>.000</b>
BDI total (post)	14.62 (11.34)	19.93 (11.44)	20.58 (11.98)	10.13 (8.64)	F = 23.4; p = <b>.000</b>	P = .975	P = <b>.003</b>	P = <b>.000</b>
MDW (pre)	54.9 (8.33)	52.64 (11.07)	54.25 (9.20)	55.67 (7.20)	F = 1.059; p = .349	P = .812	P = .453	P = .609
MDW (post)	57.53 (8.82)	51.69 (11.13)	54.66 (7.3)	60.17 (8.50)	F = 11.618; p = <b>.000</b>	P = .508	P = <b>.003</b>	P = <b>.000</b>
DLB (pre)	46.96 (12.02)	47.500 (10.12)	40.25 (13.01)	51.21 (9.50)	F = 17.694; p = <b>.000</b>	P = .088	P = .500	P = <b>.000</b>
DLB (post)	52.65 (12.22)	52.29 (8.416)	45.37 (12.76)	57.43 (9.9)	F = 21.154; p = <b>.000</b>	P = .108	P = .264	P = <b>.000</b>

and politics and PTED-patients especially in regard to colleagues and politics.

## Discussion

Embitterment is a reactive emotion which may manifest in different forms<sup>13</sup>, ranging from transitory emotional surges, which reside in a short amount of time on one side, to PTED on the other side, a distinct disorder with great impairment, severe suffering for the affected person, and also burdens for the environment. In between there are people who feel that they have been treated unfairly and unjustly and harbor feelings of aggression and revenge towards the perpetrator, but do not fulfil the criteria for a PTED diagnosis. Finally, there are people who suffer from past burdens in their lives, but do not experience feelings of embitterment. Embitterment can be conceived similar to anxiety, which is also a reactive, normal and universal emotion. Both emotions can cause disabling mental disorders, depending on their intensity, duration, or context. A clinical and scientific problem for both is, to discriminate between the different manifestations of these emotions. This is especially of interest in the differentiation between adjustment disorders with embitterment (similar to adjustment disorders with anxiety) on one hand, and PTED as special embitterment disorder (similar to PTSD as specific anxiety disorder) on the other hand. While there is a large amount of research in regard to anxiety, there is a lack of data in regard to embitterment. To our knowledge, this is the very first study which looks at embitterment in

patients with adjustment disorders, trying to delineate those which suffer from PTED.

The very first and important result is that among patients suspicious of adjustment disorder, only 8.1% were classified as PTED cases. Nevertheless, 35.5% more patients reported thoughts of embitterment and revenge, which together accounts for almost every second patient. Embitterment therefore is a highly prevalent emotion in patients with adjustment problems and should therefore get proper clinical and scientific attention<sup>15,22,23</sup>.

The second result is that feelings of embitterment do not equal PTED in all cases. This suggests that a distinction should be made. Again, this is similar to anxiety. The majority of people with anxiety do not fulfil criteria for PTSD<sup>24</sup>.

Similarly, adjustment problems and feeling burdened is not the same as feeling downgraded and humiliated. Not every person who is burdened by negative life events is also harbouring feelings of embitterment. Even people who are complaining about experiences of injustice or unfairness do not necessarily harbour feelings of embitterment and desires for revenge.

There are no differences in regard to sociodemographic data like age, gender family status or education. This suggests that embitterment cannot be explained by structural factors and obviously can affect everybody<sup>14,25</sup>.

Differences are that E-patients are suffering the most and are particularly impaired in general, as reflected in regard to burdensome thoughts, concentration, restric-

tion of daily activities, the ADN-8 sum score and the symptom load as measured with the SCL-90, the BDI, and the DLB sum score. As embitterment is regularly associated with negative mood and multiple other unspecific psychosomatic symptoms, one might expect that the E- and the PTED group similarly suffer from such additional symptoms. Contrary to this assumption our data suggest the the E-patients suffer more in this regard than PTED-patients. An explanation may be that the E- and PTED-group both felt to be the victim of disparagement, injustice, and embitterment and were harbouring the desire for revenge. But this negative emotion was qualified as “embitterment” in the very sense only in the PTED-group. The E-patients seem more generally to be at odds with the world, which can explain their increased general suffering. It is also a warning notice that self-ratings are not enough to diagnose PTED, which is also known from self-ratings in other areas <sup>26</sup>. When looking at the types of burdensome life events, as reflected in the DLB scale, E-patients show the highest scores in partnership, sex, children, parents, the future, and life balance as compared to the other groups. Together with PTED-patients, they also show high scores in regard to work, health, and environment. In summary, this also gives the impression that E patients are dissatisfied, reproachful, and overburdened in regard to life in general. PTEDpatients report problems with colleagues, work, and politics, suggesting a more focussed type of eliciting event. A-patients show the lowest scores across all domains.

In regard to resilience, no significant differences are seen in the pre-assessment, while in the post-assessment, PTED- and E-patients have significantly lower scores than A-patients. This suggests and confirms that embitterment is a negative prognostic factor and can impair therapeutic developments <sup>7,27,28</sup>.

## Conclusions

In summary, the data show that reports about feelings of embitterment coincide with a greater overall severity of the present disorder. Therefore, it is reasonable to distinguish cases with embitterment from those without. In spite of the prevasiveness and destructiveness of embitterment, this emotion is often overlooked and not taken properly into account.

In spite of their difference, one may also discuss, whether the similarities between PTED and embittered patients in contrast to A-patients would not rather suggest that the diagnostic criteria for PTED are too restrictive and both types of patients should get the same clinical diagnosis.

This is not only a problem of differential diagnosis but also of sensitivity and specificity. The present diagnostic criteria have been designed in order to avoid overdiagnosis. More sound epidemiological data are needed in order to answer this problem. Until then, it may be reasonable to stay with the present diagnostic classes of PTED, adjustment disorder with embitterment, and adjustment disorder without embitterment. Linden & Arnold <sup>29</sup> have suggested that unspecific feelings of being at odds with the world, including subjective feelings of embitterment and desires of revenge, should best be coded in ICD-11 under “adjustment disorders (6B43)” <sup>1</sup>, while PTED should be considered as “specified disorder specifically associated with stress” (ICD-11 6B4Y).

## Limitation

The study has been done in a convenience sample of psychosomatic inpatients. The results may be different in other groups. There were no standardized diagnostic interviews available, which might have added important information on the full illness spectrum.

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## Conflict of interest statement

The Authors declare no conflict of interest.

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## Author contributions

ML: is the principal investigator who designed the study, guided the data analyses and prepared the manuscript; CA: is a study scientist, who did the data analyses and helped to write the paper; BL: is the director of the Heinrich-Heine-hospital and supervised the conduct of the study; MR: is the director of the Department of Psychosomatic Medicine at the Charité and principal applicant of the research grant; BM: collaborated in the analyses, interpretation and writing up of the data.

## Ethical consideration

The Authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. APA ethical standards were obeyed.

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