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BOorderliNe symptoms and suIcide-related outcomes: proTOcol for a systematic review/meta-analysis and an individual patient data meta-analysis (BONITO study)

Raffaella Calati,1,2 Daniele Romano,1,3 Jorge Lopez-Castroman,2,4,5 Federica Turolla,1 Johannes Zimmermann,6 Fabio Madeddu,1 Philippe Courtet,4,7 Emanuele Preti1

ABSTRACT

Introduction Prevalence of suicidal thoughts and behaviours is higher among patients with borderline personality disorder than the general population. However, evidence concerning the role of specific borderline symptoms for predicting suicide-related outcomes is lacking and no systematic review/meta-analysis (SR/MA) investigated this topic. Our aim will be to investigate the relationship between any borderline symptom (except criterion 5) and suicide-related outcomes both through an SR/MA and an individual patient data meta-analysis (IPD-MA).

Methods We will search PubMed/MEDLINE, Scopus, Web of Science, Embase, PsycINFO, CINAHL and Cochrane Library databases from 1974 until September 2021. Both published and unpublished studies showing the association between any borderline symptom (except criterion 5) and suicide-related outcomes (death wish, suicidal ideation, suicidal plan, non-suicidal self-injury, deliberate self-harm, suicide attempt, suicidal behaviour disorder, suicide) will be included. Two team members will independently perform the selection of the studies and data extraction, with the supervision of two other members in case of discrepancies; and assess each study with study quality assessment tools by National Institutes of Health and Grading of Recommendations Assessment, Development and Evaluation. Each author will be contacted. If possible, we will perform both random-effect meta-analyses on the collected data (odds, risk, rate ratios or correlations) and an IPD-MA on collected databases.

Ethics and dissemination This study does not require an ethical approval. Results will be publicly disseminated, included in research presentations and published in peer-review journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, these will be the first systematic review/meta-analysis (SR/MA) and individual patient data meta-analysis (IPD-MA) investigating the relationship between any borderline symptom and suicide-related outcomes.
⇒ The main limitation of the SR/MA will be the paucity of studies reliably assessing single borderline symptoms together with suicide-related outcomes.
⇒ The main limitation of the IPD-MA will be the difficulty to obtain data sets from the authors as well as the heterogeneity of the data sets.

INTRODUCTION

Borderline Personality Disorder (BPD) is classified in the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition (DSM-5) as a cluster B personality disorder and described as a ‘pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity that begins by early adulthood and is present in a variety of contexts’1. One of the nine diagnostic criteria of BPD includes persistent engagement in self-harming behaviours, which the DSM-5 defines as ‘recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour’ (criterion 5). Recurring self-harming behaviour is one of the primary characteristics of the disorder, with the rate of BPD suicidal patients being almost 50 times higher than that of the general population,2 although relatively lower rates were reported in more recent studies.3,4

According to DSM-5, BPD is diagnosed if five out of a set of nine symptoms are present. In this sense, symptoms are treated as exchangeable, and the diagnosis is based on the number of symptoms rather than on their specific constellations. Although these assumptions are common to polythetic diagnostic systems, they seem unrealistic in the case of BPD.5 Indeed, there is now considerable evidence that BPD is a heterogeneous construct (eg,6 7), suggesting that individual
symptoms/criteria should be considered separately in research. In previous work on BPD symptoms, each borderline criteria was associated with dysfunction in comparison with a control group without BPD criteria, but only the emptiness criterion was a marker of suicidality and history of suicide attempts. Moreover, in a 1-year follow-up study, individuals in psychological treatment who experienced more severe emptiness, impulsivity and self-harm had worse outcomes (more days out of work).³

In this sense, although suicidality is one of the main characteristics of BPD symptoms, there is no clear empirical evidence related to the specific and differential contribution of specific BPD symptoms and traits to such a severe outcome. To our knowledge, in fact, no previous systematic review and/or meta-analysis investigated the association between any single BPD symptom and suicide-related outcomes. Thus, the aim of this project is to assess the relationship between BPD symptoms and suicide-related outcomes independently from the psychiatric diagnosis. This project is ambitious since we aim to perform both a systematic review/meta-analysis (SR/MA) on the collected data/reported effects and an individual patient data meta-analysis (IPD-MA) on collected databases. The results of such an effort will allow to rely on robust results that will fill the gap between a polythetic view of BPD diagnosis and the possibility to consider clinically-significant and empirically-sound predictors of self-destructive outcomes.

OBJECTIVES
The aim of this study is to investigate the association between any borderline symptom and death wish (DW), suicidal ideation (SI), suicidal plan (SP), non-suicidal self-injury (NSSI), deliberate self-harm (DSH), suicide attempt (SA), suicidal behaviour disorder (SBD), suicide. We plan to perform separate analyses for (1) subjects with a full BPD diagnosis, and (2) subjects without a BPD diagnosis.

SR/MA
The primary aim is the calculation of suicidal risk related to any specific BPD symptom separately, with the exception of criterion 5. Secondary aims will be, according to the specific available features of the included studies, to control for all the possible factors contributing to between-study heterogeneity in sensitivity analyses and meta-regressions (socio-demographic features, such as gender and age, clinical features, such as primary and secondary psychiatric diagnoses, methodological features, such as study design).

IPD-MA
The primary aim is the calculation of the BPD symptom specific suicidal risk. With IPD-MA it would be possible to take into account variables that cannot be considered in the SR/MA, such as the number of BPD symptoms for each subject, the diagnosis (BPD symptoms without a full BPD diagnosis, full BPD diagnosis and/or others) and the number of recurrent events (eg, NSSI, SA). The creation of an extended data set will allow to perform further secondary analyses with high statistical power. The use of multilevel models (also known as ‘one-step IPD-MA’) will lead to precise and reliable estimation.⁴ The creation of such a large data set will also offer the opportunity to analyse reliably cross-level interactions or multivariate structures (eg, network analysis).

METHODS AND ANALYSIS
The present protocol has been registered in PROSPERO and is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols statement⁵ (see the supplementary online supplemental appendix A file). The SR/MA will be reported in accordance to the reporting checklist proposed by the Meta-analysis of Observational Studies in Epidemiology group.⁶ We already started to work on BONITO (start date: 1 June 2021) and we plan to conclude by the end of the year 2022.

Studies
Studies will be included if: (1) they are written in English, French, Spanish, German or Italian according to the languages spoken by the authors; (2) they consider at least one DSM BPD symptom (see the borderline symptoms’ paragraph for further details) and at least one suicide-related outcome according to established nomenclature⁷ (see the suicide-related outcomes for further details); (3) they report, or indicate the availability of, data on BPD symptoms and suicide-related outcomes (ie, we will include studies with the availability of our data of interest, even if their primary outcome was not the association between BPD symptoms and suicide-related outcomes and even if this association was not calculated in the original study); (4) they focus on any type of study population (clinical and non-clinical); (5) they have any type of study design (cohort, cross-sectional, case–control studies).

Studies will be excluded if: (1) they are not written in English, French, Spanish, German or Italian; (2) they did not use DSM to screen the BPD symptoms; (3) they consider BPD diagnosis without specific data on any symptom and separate data for any symptom are not available after having contacted the authors; (4) they focus on suicidal patients only; (5) they pool different suicide-related outcomes together (eg, SA and suicide) and separate data are not available after having contacted the authors.

Participants
We will include studies of subjects regardless of age, sex or ethnicity, psychiatric diagnosis, inpatient or outpatient or mixed or community settings.

Measures
Borderline symptoms
We will include studies that examine any borderline symptom according to DSM. In particular:
1. Frantic efforts to avoid real or imagined abandonment.
2. A pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealisation and devaluation.
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating).
5. Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour.
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability or anxiety usually lasting a few hours and only rarely more than a few days).
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

Note that we will include criterion 5, but treat it separately in the evaluation, since it can itself be understood as a suicide-related outcome.

We will consider studies focusing on the DSM-III version or subsequent, since only in DSM-III personality disorders diagnoses have been introduced. We will include both categorical and continuous BPD symptom measures with a clear cut-off for the presence/absence of any symptom. Examples of includable scales are: the Diagnostic Interview for Personality Disorder; the McLean Screening Instrument for Borderline Personality Disorder; the Personality Disorder Questionnaire-4; the Structured Clinical Interview for DSM-5 Personality Disorders and previous versions; the Borderline Personality Disorder section of the Structured Interview for DSM-IV Personality.

**Suicide-related outcomes**

We will refer to established nomenclature of suicide-related outcomes. We will separately consider all the suicide-related events as reported by the original study authors: DW or passive SI (the desire to die or thoughts of being better off dead); active SI (thinking about, considering or planning suicide); SP (the presence of a specific program of action leading to a self-injurious outcome); NSSI (an intentional act of causing physical injury to oneself without wanting to die); DSH (any type of self-injurious behaviour, including SA and NSSI); SA (self-inflicted potentially injurious behaviour with a non-fatal outcome and with the intention to die); SBD (within the last 24 months, the individual has made a SA); suicide (self-inflicted death).

Concerning SI, we will include any standardised rating scale for assessing the presence of SI: it could be an item of a scale assessing depression, such as Montgomery-Åsberg Depression Rating Scale or Hamilton Rating Scale for Depression, or a specific scale for suicidal risk screening, like the Columbia-Suicide Severity Rating Scale. We will consider presence versus absence of any considered suicide-related outcome. In the absence of it (e.g., only mean scores of a specific measure are reported), we will contact the authors. For some outcomes (NSSI, SA), we will also consider number of recurrent events.

For every suicide-related outcome we will consider, when possible, two features: its current and lifetime presence.

**Search methods for identification of studies**

**Electronic searches**

We will search PubMed/MEDLINE, Scopus, Web of Science, Embase, PsyCINFO, CINAHL and Cochrane Library, from 1974 (some years before the introduction of DSM current personality disorders’ criteria) until September 2021 to identify studies reporting the association between any borderline symptom and suicide-related outcomes. Combinations of Medical Subject Headings terms and other keywords will be: “borderline personality disorder” AND (suicide OR suicid* OR “attempted suicide” OR “deliberate self-harm” OR “self injurious behavior” OR “self mutilation” OR “self injur*” OR “self mutil*” OR “self poison*” OR “suicidal ideation” OR “death wish” OR “passive suicidal ideation”). Combinations of Emtree terms (standardised keywords in Embase) will be: borderline state AND (suicide OR suicidal ideation OR suicidal behavior OR suicide attempt OR automutilation OR self-poisoning). See the online supplemental appendix B file for a detailed description of the strings that will be used.

**Reference lists**

The reference lists of all the included studies, relevant papers and previous reviews will be also hand searched for identification of additional studies.

**Data collection**

**Selection of studies**

Two or more students with the supervision of two authors (RC and EP) will independently check titles and abstracts of all the references generated by the search. All studies eligible for inclusion will be added to the preliminary list, and their full texts will be retrieved. RC and EP will then assess all full texts to verify if they meet the inclusion criteria. If the authors disagree, the final decision will be reached through consensus with JL-C, JZ, PC or FM.

**Data extraction and management**

**SR/MA**

Using a standardised data extraction sheet, two or more students with the supervision of RC and EP will independently extract data from the included studies. Any disagreement will be discussed with a third member of the review team (JL-C, JZ, PC or FM), and decisions will be documented. In the case of missing information concerning the outcomes of interest, we will directly contact study authors up to five times to obtain additional information.
The following data will be extracted from all the studies meeting the inclusion criteria: names of all the authors, name and email of the corresponding author and of other authors if present, country, study design, year, sample size, population, setting, period of assessment (years), hazard period (ie, the assessed time period in the case of cohort studies), number and type of assessed BPD symptoms, suicide-related outcomes (type and current/lifetime), percentage of men, age, ethnicity, assessment scales (in particular for the BPD symptoms and the suicide-related outcomes), main results, list of covariates included in design and analysis, crude numbers and measure of association (ORs, risk ratios, rate ratios or correlations) and 95% CIs, and data source in the case of large-scale national or international data sets.

If available, we will use estimates of the association (ORs, risk ratios, rate ratios or correlations) and 95% CIs that have been accounted for potential confounders (eg, age, gender); otherwise, we will include data on the number of cases and non-cases with any BPD symptom to calculate crude estimates of the association, and we will conduct sensitivity analyses separately considering adjusted and unadjusted estimates. If a study shows separate analyses for men and women or for different age ranges, those will be included as separate studies.

In the case of overlapping studies (published on the same data source), we will use the most recently published results, or the largest sample size, or we will evaluate the study case by case. To avoid the risk of overlapping studies for each study, we will extract: (a) the names of the authors and (b) the names of the databases/studies (data source) and we will check for duplicates; then, in the case of doubts, we will directly contact the authors.

**IPD-MA**
To build the largest as possible, comprehensive database, we will maintain the broad already mentioned inclusion criteria. The joint data set will be built on the basis of variables shared in the majority of collected databases.

**Authors’ contact**
The list of all the corresponding authors will be prepared and checked among the research team members. Every author will be contacted at least five times. We will ask to each author both data for the SR/MA and the consent to participate to the IPD-MA. Survey will be sent both via Qualtrics and email, hence every author may choose to use the preferred modality. In the case the corresponding author will not reply, we will contact other authors when possible.

**Assessment of quality, strength of reporting and certainty of evidence in included studies**
Two or more students with the supervision of two authors (RC and EP) will independently assess the quality of the studies using quality assessment tools by National Institutes of Health (NIH) according to different study design (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). We will use in particular the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (14 items) and the Quality Assessment Tool for Case-Control Studies (12 items). Quality of each study will be rated as good, fair or poor, according to the rate to each item (Yes; No; or Other, ie, cannot determine, not applicable or not reported). Items refer to: the research question or objective of the study, the description of the population, participation rate, sample size justification, comparability of cases and controls, time frame, details concerning exposure and outcome measures, blindness, dropout rate and accounting for confounders. Moreover, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology for evaluating the certainty of evidence for each outcome will be used as well. According to GRADE, risk of bias (limitations of design and execution), inconsistency (or heterogeneity), indirectness (Population, Intervention, Comparison and Outcome, and applicability), imprecision (number of events and CIs), and publication bias will be assessed. The certainty of evidence will be classified as: high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) or very low (any estimate of effect is very uncertain).

**Data analysis**

**Main analyses**

**SR/MA**
We will calculate pooled risk measures and 95% CIs. We will assess heterogeneity with the $\chi^2$ goodness of fit and $\Gamma^2$ statistics. Concerning $\Gamma^2$, we will consider Cochrane recommendations. We will consider statistically significant a $p$ value $< 0.05$ (presence of heterogeneity). Data will be analysed using a random effect framework since we hypothesise that the true effect will be similar but not identical across studies. In our statistical analyses we will firstly consider all the included studies on each symptom. In the case of the presence of heterogeneity, we will perform sensitivity analyses and meta-regressions when possible.

We will perform a preliminary analysis aiming at verifying if the quality score of the NIH scales has an impact on results. Then, in the case of a significant impact, the analyses will be performed using the quality score as moderator. All $p$ values will be two-tailed and statistical significance will be set at the 0.05 level.

A funnel plot will be created to reveal the preferential publication of statistically significant results. Tests for funnel plot asymmetry will be used in the presence of at least 10 studies. The Egger’s test will be also used to evaluate the funnel plot asymmetry as well as the Duval and Tweedie’s ‘trim and fill’ method, in the presence of publication bias.
A one-step IPD-MA approach will be preferred to the two-step one. Although the two approaches often yield similar results, the one-step approach has the advantages, among others, of allowing for (1) the simultaneous analysis of all the IPD from all the studies and (2) the inclusion of covariates at an individual level.\(^2^7\) A one-step IPD-MA can be seen as a multilevel model, with participants being nested in studies. The use of (logistic) multilevel models grants the possibility to account for interindividual variability in a given data set. Moreover, they allow to analyse interactions between participant-level and study-level predictors, and to increase the power of the analysis by using all trials at once. We will derive a parsimonious random effects structure by starting from a model that includes a random intercept for the study level and then subsequently testing whether including a random slope for each participant-level predictor improves the model fit (using the Bayesian Information Criterion). We expect that we won’t be able to adopt a ‘maximal’ random structure containing all random slopes,\(^2^9\) a method known to keep under control both type 1 and type 2 errors, as the model will almost certainly not converge. The problem with maximal random structures is related to computational costs and the need of large data set to properly estimate all the parameters of the model.

In the case of systematic missing data, we will select the best method to input missing values, according to the entity of missing and computational costs (eg,\(^2^9\)\(^3^0\)).

When in independent studies different tools have been used to measure the same outcome (eg, suicidal ideation measured with different instruments), if normative data of the tools are available, continuous scores will be standardised at the population level in order to combine different measures of disorder-specific measures and to ensure compatibility of outcomes across studies. We will not standardise dichotomous variables.

**Additional analyses**

**SR/MA**

We will calculate the pooled prevalence for each suicide-related outcome in subjects with each BPD symptom. Moreover, if there is a sufficient number of studies for each suicide-related outcome, we will investigate potential sources of heterogeneity using two different strategies: (1) subgroup analyses by sociodemographic (eg, age, sex, ethnicity, socioeconomic status, social support), clinical characteristics (eg, primary and secondary psychiatric diagnoses, substance use, physical disorders, pain), study design, diagnosis using different versions of DSM; (2) meta-regression models.

**IPD-MA**

If possible, we will consider both between-person associations (eg, based on cross-sectional studies) and within-person associations (eg, based on time series data).\(^3^1\)\(^3^2\) Moreover, if possible, we will consider sex-specific symptom profiles and the repetition of suicide attempts or behaviours in the same subject (follow-up studies).

**Software**

All analyses will be conducted using the statistical environment R (http://www.R-project.org).

**Patient and public involvement**

Agreements will be signed between the Department of Psychology of the University of Milan-Bicocca, Milan, Italy, and every centre agreeing to participate to the consortium. Data will be anonymised or we will follow procedure case by case according to every country rules. Patients and or public will not be involved.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

To our knowledge, these will be the first SR/MA and IPD-MA investigating the relationship between any borderline symptom and suicide-related outcomes. We hope that this study contributes to identifying risk profiles among subjects with a full BPD diagnosis and subjects with subthreshold BPD. In fact, the results could help to establish how specific symptom clusters relate to suicidal events, and also help to respond to the frequent criticism that 256 types of patients with BPD can fit in the current criteria. The implications of our findings might provide evidence to the improvement of the screening, detection and treatment of patients at higher risk for suicide.

Limitations mainly include: the paucity of studies; the paucity of studies reliably assessing single BPD symptoms; the difficulty to obtain longitudinal data; the possible dichotomisation of BPD symptoms (problematic from a psychometric point of view).\(^3^3\)

**ETHICS AND DISSEMINATION**

This study does not require an ethical approval. The results will be publicly disseminated, included in research presentations and published in peer-review journals.

Authors sharing their data will be part of a specific consortium (the BONITO consortium) and they will be coauthors of every paper related to the IPD-MA. At the end of the study, the obtained data set will be made freely available. The consent will be asked to every involved researcher and only the part of the data set of researcher that consented will be included in the free data set.

**Author affiliations**

1Department of Psychology, University of Milano-Bicocca, Milan, Italy
2Department of Adult Psychiatry, Nimes University Hospital, Nimes, France
3Department of History, Society and Human Studies, University of Salento, Lecce, Italy
4France Institute of Functional Genomics, CNRS, INSERM, University of Montpellier, Montpellier, France
5CIBERSAM, Madrid, Spain
6Department of Psychology, University of Kassel, Kassel, Germany
7Department of Emergency Psychiatry and Acute Care, CHU Montpellier, Montpellier, France

**Contributors** RC and EP conceived the project. RC wrote the first draft of the protocol and subsequently incorporated the suggested revisions. DR wrote the
individual patient data meta-analysis statistical section. FT performed preliminary searches and helped in the study design planning. JL-C, JZ, FM and PC supervised the entire project. EP revised each section of the protocol.

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ORCID iDs
Raffaella Calati http://orcid.org/0000-0001-8130-437X
Johannes Zimmermann http://orcid.org/0000-0001-6975-2356
Emanuele Preti http://orcid.org/0000-0001-5207-4579

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