

STUDY PROTOCOL

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The (cost-)effectiveness of early intervention (MBT-early) versus standard protocolized treatment (CBT) for emerging borderline personality disorder in adolescents (the EARLY study): a study protocol for a randomized controlled trial

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Abstract

Background Although clinical guidelines prioritize the treatment of depression and anxiety in young persons, there is accumulating evidence that the presence of symptoms of borderline personality disorder (BPD) is associated with the limited effectiveness of these standard treatments. These findings stress the need for interventions addressing early-stage BPD in young people with presenting symptoms of anxiety and depressive disorders. The aim of this study is to investigate the (cost-)effectiveness of an early intervention programme for BPD (MBT-early) compared to first-choice psychological treatment for depression and anxiety according to Dutch treatment guidelines (CBT), in adolescents with either depression, anxiety, or both, in combination with early-stage BPD.

Methods This study is a multi-centre randomized controlled trial. A total of 132 adolescents, presenting with either depression, anxiety, or both and significant BPD features will be randomized to either MBT-early or CBT. The severity of BPD, symptoms of depression and anxiety, personality, social and academic functioning, and quality of life will be assessed at baseline, end of treatment, and at 12-, 18-, and 24-month follow-up, along with medical costs and costs of productivity losses for cost-effectiveness analyses.

Discussion This study will provide an empirical evaluation of the potential surplus value of early intervention in young people for whom treatment oriented at common mental disorders like anxiety and depression may be insufficient given their underlying personality problems.

Trial registration Netherlands Trial Register, NL9569. Registered on June 15, 2021.

Keywords Adolescent, Borderline personality disorder (BPD), Early intervention, Mentalization, Cognitive behavioural therapy (CBT), Depressive disorder, Anxiety disorder, Randomized controlled trial (RCT)

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Administrative information

Note: The numbers in curly brackets in this protocol refer to the SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see <http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/>).

Title {1}	The (cost-)effectiveness of early intervention (MBT-early) versus standard protocolized treatment (CBT) for emerging borderline personality disorder in adolescents (the EARLY study): a study protocol for a randomized controlled trial
Trial registration {2a and 2b}	Netherlands Trial Register: NL9569. Registered June 15, 2021. https://onderzoekmetmensen.nl/nl/trial/27931
Protocol version {3}	Version 3 of 30–8-2022
Funding {4}	This study is in part funded by ZonMw, which is the Netherlands Organization for Health Research and Development (grant. no. 636310021).
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Role of sponsor {5c}	De Viersprong is the sponsor and responsible for the study design, data collection, data management, data analysis and interpretation of the data, and writing and submitting reports for publication. The funder (ZonMw) monitors the project through yearly reports and evaluations. The funder has no role in the study design and collection, analysis, and interpretation of the data.
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Introduction

Background and rationale {6a}

Borderline personality disorder (BPD) is a severe mental disorder associated with a range of unfavourable outcomes in several areas of mental, social, and occupational functioning [1–3]. Longitudinal data suggest that adult BPD typically is a chronic condition, characterized by patterns of remission and relapse at PD symptom level, but with more pervasive and persistent disabilities in psychosocial functioning [4, 5]. Community studies show that over half of the individuals with BPD are unemployed [6]. In addition, people with BPD often have poor physical health [3] and excess mortality from medical conditions [1] resulting in a high burden of disease and considerable societal costs [7, 8].

From an individual, societal, and (health-)economic perspective, it makes sense to switch from a focus on the late-stage treatment of BPD in adulthood to addressing emerging BPD in adolescence [9]. Symptoms of BPD typically emerge in adolescence [10], and evidence consistently suggests that negative outcomes, such as educational challenges, unemployment, and increased health care utilization and costs, are already prevalent during the transition from adolescence to young adulthood in persons with BPD [11, 12]. Accumulating data show that early intervention for BPD is time-sensitive, indicating adolescence as a critical juncture in the development of BPD, determining its course and long-term outcomes [13].

Despite this need for appropriate strategies for early intervention to reduce the short-term burden and prevent long-term disabilities, several studies suggest that current mental health services often do not provide an appropriate response to the health needs of these young persons. Data from the Netherlands [14] as well as Australia [15] show that young persons with BPD remain largely undetected in primary services, are not referred to appropriate treatment, and are rarely provided appropriate, evidence-based treatments. Brief psychosocial treatments that are common in primary care seem to be less effective for young people with BPD. For example, in a prospective follow-up study of young people receiving

cognitive behavioural therapy (CBT) for depression, the subgroup of females with both depressive problems and BPD showed poor distal outcomes. These young people, compared to those without BPD, had up to four times higher likelihood of experiencing recurrent depressive episodes [16]. The limited effects of brief treatments for these young people seem to be in large part due to the considerable dropout rate from these treatments. Approximately 40–50% of young people with BPD drop out from treatment prematurely, even though they experience high levels of distress and suffering [17]. This suggests that these treatment approaches may not be adequately tailored to the specific needs and problems of young people with emerging BPD. In addition, current services are primarily organized based on a ‘stepped-care’ strategy; initiating care for these young people with brief and generic interventions which are subsequently upscaled in the case of poor response. Yet, poor or non-response in these young people is the rule rather than the exception. In a study on primary care in Australia for 12- to 25-year-olds, for instance, patients with BPD symptoms showed no progress or deteriorated in terms of social and occupational functioning (45%), psychological stress (60%), and quality of life (69%) [15]. Importantly, aside from the lack of efficiency in attaining, this approach generated iatrogenic damage in these youngsters as failed treatment attempts lead to disappointment in and distrust of mental health services [18], which may undermine future care-seeking or treatment success.

In response to the need for appropriate and in-time treatments, and the lack of evidence of treatment programmes for young people with BPD, the past decades have witnessed the development and evaluation of a range of treatment programmes for young people with BPD features, based on adaptations of treatments for BPD in adults. These include dialectical behaviour therapy (DBT-A) [19], mentalization-based treatment (MBT-A) [20], and transference-focused psychotherapy [21]. The evidence base for these adaptations is rather scarce. A recent review identified only ten randomized clinical trials [22–31]. The results indicate that the majority of these trials did not show the superiority of the specialized treatments compared with treatment as usual. Dropout rates varied widely, ranging from 15 to 75%. Moreover, the heterogeneity of the samples involved in these studies is typically large [17, 22]. Compared with treatments for adults with BPD, the majority of psychosocial treatments for young people with BPD were relatively brief (e.g. HYPE, consisting of sixteen sessions [23]) or were characterized by low treatment intensity (e.g. DBT-A, involving weekly sessions [26]). This matches a clinical staging perspective, with increasing consensus that such interventions, whether

brief or low-intensity, may be best suited for addressing the early stages of BPD, characterized by low to moderate risk profiles [32]. However, these interventions are likely to be insufficient for young people with BPD at a later stage of development. A clinical staging approach may enable better matching of treatment to the clinical needs of these young people [10, 33]. Staged care has been introduced as an alternative to stepped care [34]. The advantages of such an approach are clear. Staged care does not require individuals to fail prior treatment to be assigned to more specialist services and it enables to match the type and level of care to the clinical needs associated with the stage of illness, also minimizing the probably of early dropout and dissatisfaction with and disbelief in mental health treatments.

Objectives {7}

The primary aim of this study is to investigate the effectiveness of an early intervention approach for BPD (mentalization-based treatment-early [MBT-early]) compared to first-choice psychological treatment for depressive and anxiety disorders according to Dutch treatment guidelines (which is cognitive behavioural therapy [CBT]) for young people referred for treatment of depression, anxiety, or both, presenting with symptoms indicative of early-stage BPD. Treatment effects will be evaluated on the primary outcome (severity of borderline symptoms) and secondary outcomes (symptoms of depression and anxiety, personality functioning, social functioning, and academic functioning). Adolescents receiving MBT-early are expected to show superior outcomes in terms of severity of BPD symptoms and personality functioning, social functioning, and academic functioning compared to adolescents receiving CBT, but MBT-early will be non-inferior to CBT in reducing symptoms of depression and anxiety.

The secondary aim of this study is to compare the cost-effectiveness of both treatments based on costs per quality-adjusted life year (QALY). We expect MBT-early to be cost-effective compared to CBT.

Trial design {8}

This multi-centre study is a parallel-group, randomized controlled trial, where an early BPD intervention, MBT-early, is compared to first-choice psychological treatment, CBT, as recommended by the Dutch treatment guidelines, for adolescents with presenting symptoms of depression, anxiety, or both and emerging BPD symptoms. This study is a superiority trial comparing MBT-early and CBT at baseline, end of treatment, and at 12-, 18-, and 24-month follow-up. The allocation rate is 1:1.

Methods: participants, interventions, and outcomes

Study setting {9}

Three mental healthcare institutions in the Netherlands participate in this study: Mentaal Beter (Bergen op Zoom, Roosendaal, Etten-Leur, and Breda), GGz Breburg (Breda), and de Viersprong (Bergen op Zoom). All three of these institutions provide treatments for young people referred for (emerging) mental health problems and offer interventions for a wide range of mental health problems. GGz Breburg provides both MBT-early and CBT, while Mentaal Beter only provides CBT and de Viersprong solely provides MBT-early. Consequently, adolescents referred to Mentaal Beter and randomized to MBT-early will receive treatment administered by therapists from de Viersprong, while those referred to de Viersprong and randomized to CBT will be treated at Mentaal Beter.

Eligibility criteria {10}

Adolescents are eligible for this study if they meet the following criteria: (a) adolescents between 12 and 18 years old; (b) a depression, anxiety disorder, or both as assessed by the Structural Clinical Interview for DSM-5 Syndrome Disorders (SCID-5-S; [35]); and (c) early stage BPD, defined as three to six features of BPD and mild and moderate disabilities in either school, with family, or with peers or in multiple areas as assessed using the structural clinical interview for DSM-5 Personality Disorders (SCID-5-P; [36]). The exclusion criteria are (a) a primary diagnosis that requires other specialist treatment (e.g. severe autism spectrum disorder, chronic psychotic disorder, severe eating disorder, or severe substance abuse disorder), (b) $IQ < 75$, or (c) severe disability with regard to functioning in school, at home, and in the peer group representative for later stage BPD [10].

Who will take informed consent? {26a}

All consecutively referred adolescents between 12 and 18 years old referred to the above mental health care institutions for treatment of presenting symptoms of depression, anxiety, or both, and their parents, will be informed about the study during the first consultation with a mental health professional. They will receive an information letter with detailed information about the study and the screening process. If the adolescent agrees to participate in the screening process, the mental health professional obtains informed consent for the screening process from the adolescent, and from both parents if aged under 16, and asks permission to share their contact information with the research team. The adolescent and parents have at least 1 week to consider their decision about participating in the screening process. After approval for the screening, a research assistant contacts the family to plan

the screening. If the inclusion criteria are met, the mental health professional will inform the family that the adolescent is eligible to participate in the study during the second consultation. Again, the adolescent and parents have at least 1 week to consider their decision about participating in the study. If they agree, the research assistant will obtain informed consent for participating in the study from the adolescent, and from both parents if aged under 16, and plan the baseline assessment. After baseline assessment, the adolescent will be randomly assigned to MBT-early or CBT (for more details, see the ‘Assignment of interventions: allocation’ section).

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Adolescents will be informed that they may withdraw their consent at any moment, while highlighting that data collected up to the point of withdrawal will be used for the study. In addition, they will be asked to give permission to access their data for the purpose of monitoring, by other people from the research team and regulatory authorities that are mentioned in the information letter. Adolescents are also asked if their coded data may be used in follow-up research and if they may be contacted for future research related to this study. Through the consent form, they (and both parents if the adolescent is under [16]) provide their consent for these conditions. This study does not involve the collection of biological specimens.

Interventions

Explanation for the choice of comparators {6b}

To investigate the effectiveness of early intervention for BPD symptoms in adolescents with presenting depression, anxiety, or both and emerging BPD, CBT for depression and anxiety will be compared to MBT-early. CBT is currently offered as the first-choice psychological treatment for adolescents with presenting symptoms of depression and anxiety, according to the Dutch treatment guidelines [37], following a stepped care approach, where the presenting symptoms of depression and anxiety are typically addressed first, even in the presence of underlying BPD symptoms. Hence, CBT is an appropriate comparative treatment option in the current study as it is currently typically offered to these young people in the Netherlands.

Intervention description {11a}

CBT CBT [38] is a psychotherapeutic intervention that adolescents with presenting symptoms of depressive and anxiety disorders receive according to the Dutch treatment guidelines [37] as a first-choice psychological

treatment. CBT is an evidence-based, goal-directed approach utilizing cognitive restructuring and behavioural interventions. This therapeutic model aims to identify and modify maladaptive thought patterns and behaviours, equipping individuals with practical coping skills to mitigate symptoms and enhance overall emotional resilience. In this study, CBT is offered as an individual treatment following a manualized treatment protocol [39]. The treatment consists of an average duration of 12–16 sessions, encompassing assessment and case formulation, a treatment phase, and a closure phase. Additionally, post-treatment relapse prevention booster sessions may be offered within the first 3 months after treatment.

Assessment and case formulation

This initial phase involves the assessment of the adolescent's issues and the formulation of a case conceptualization to identify specific problems and tailor treatment accordingly (2–3 sessions). Collaboratively, the therapist and the adolescent establish goals such as symptom reduction, coping skills development, and improvement in daily functioning.

Treatment phase

The next phase of treatment involves interventions such as psychoeducation, teaching coping strategies (breathing and relaxation techniques, problem-solving skills, and distraction techniques), cognitive restructuring (addressing automatic negative thoughts), and exposure exercises (involving gradual exposure to fearful objects or situations), as well as strengthening coping skills and activation (enhancing daily structure such as attending school, engaging in hobbies, and participating in social activities to counteract passive behaviour and avoidance associated with depression) aimed at improving depressive and anxiety symptoms. Parents are provided with information regarding the adolescent's presenting symptoms and the treatment plan. They are asked to actively engage in facilitating and executing exposure exercises. Additionally, supplementary supportive interventions for parents may be added, if needed [39].

Closure phase

This phase is aimed at reinforcing and maintaining the skills learned during therapy, preventing potential relapse or setbacks. Sessions focus on the evaluation of the treatment gains in relation to the predetermined goals and teaching of relapse prevention (2–3 sessions). Booster sessions involve additional sessions or follow-up sessions

scheduled within the first 3 months after treatment completion (2–4 sessions). The booster sessions aim to consolidate progress, address any emerging issues, and fine-tune strategies to ensure the sustained effectiveness of the treatment over time.

MBT-early MBT was originally developed as an intervention for adults with BPD. Several types of MBT for BPD are empirically supported [40–42]. MBT-early, developed at de Viersprong and implemented since 2014, has offered preliminary support from a small naturalistic pilot study [43].

The aim of MBT-early is to improve the capacity for mentalizing and social learning (i.e. epistemic trust). Impairments in these fundamental capacities are assumed to underly psychopathology [44]. MBT-early aims to facilitate adolescents and their parents to better understand their own and others' thoughts, feelings, intentions, and motivations and to foster epistemic trust, i.e. nurturing confidence in one's own perceptions and beliefs, as well as developing trust in others' perspectives.

MBT treatment programmes vary in terms of treatment components, duration, and intensity. MBT-early shares with all other MBT programmes that it is highly structured and systemically planned. The three C's, consistency, constancy, and coherence, form a foundational principle for all MBT treatment programmes (see a detailed description elsewhere, [45]) and thus for MBT-early.

MBT-early is a time-limited specialized treatment for emerging BPD and comprises two phases: an initial intensive treatment phase of 16 weeks, followed by a 6-month booster treatment phase.

Intensive treatment phase

The intensive treatment phase consists of an assessment phase (3–4 sessions), a middle phase (10 sessions), and a final phase (2 sessions). The sessions include 16 individual sessions, 3 family sessions, 2 treatment review sessions, and, if necessary, psychiatric consultations and case management (e.g. consultation with school). These treatment modalities are delivered by 1 therapist, and interventions are tailored to the specific needs of the adolescent and his/her family (e.g. case management may partially replace individual sessions if problems manifest primarily at school). However, this standard package can be downscaled in cases of rapid improvement or upscaled when needed.

Booster treatment phase

The intensive treatment phase is followed by a booster phase with follow-up sessions 1, 2, 4, and 6 months after the end of the first phase. At the final session, the treatment progress is assessed to determine if the therapy can conclude or if a new phase of care is necessary. Additional care can be provided in consultation with the family and the treatment team, even after the closure of the adolescent's case.

Criteria for discontinuing or modifying allocated interventions {11b} Adolescents can withdraw from the study at any time for any reason if they wish to do so without any consequences for their treatment, i.e. they can complete their current assigned treatment (either MBT-early or CBT), but will not be contacted for further assessments. Previously collected data will be included in the analyses.

The research team will register and follow up all potential serious adverse events (SAEs) that might be associated with the treatment (e.g. suicide), which may ultimately lead to the ending of the study. These SAEs will also be reported and discussed at a trial steering committee (TSC). The TSC may decide to end the study prematurely if a significant difference in SAEs (> 5) is shown between the two treatment conditions. For more details on the SAEs, see 'Adverse event reporting and harms {22}' section.

Strategies to improve adherence to interventions {11c} Both the CBT and MBT-early teams consist of therapists with broadly ranging level of experience, background, and educational level. All therapists involved in the study are certified psychologists, sociotherapists, remedial educationalists, or psychotherapists. Clinicians within the CBT teams who are involved in the study have successfully completed a certified CBT basic course or are further trained in CBT. CBT therapists have weekly one-on-one supervision to review case material with their supervisor. MBT-early therapists who are involved in the study have successfully completed a certified MBT basic course at the minimum or are further trained in MBT. Within the MBT-early programme, biweekly team supervision focuses on reviewing case material to increase therapists' comprehension of mentalizing theory and their competency in working with the principles of MBT and the spectrum of mentalizing interventions. In order to test for adherence, ten randomly selected individual sessions of both CBT as well as the MBT-early will be scored on an, for the treatment appropriate, adherence scale.

Relevant concomitant care permitted or prohibited during the trial {11d} By default, no other interventions will take place during the intensive phase of treatment. However, when it is deemed clinically necessary to add other psychological interventions, concomitant care can be offered within the same mental healthcare institution as the assigned treatment or somewhere else.

Provisions for post-trial care {30} Throughout the treatment, the mental health professional will, in collaboration with the adolescent, evaluate whether the allocated treatment is sufficiently beneficial or if an alternative treatment might be more appropriate, either within the same mental healthcare institution or elsewhere. After dropping out or completing the allocated treatment, participants can also receive the non-assigned treatment (e.g. receiving MBT-early after completing CBT or vice versa). Based on the intention-to-treat principle, adolescents dropping out of the allocated treatment will be followed for research purposes, unless they withdraw their consent to participate in the follow-up assessments.

The sponsor has a liability insurance which is in accordance with Article 7 of the WMO (Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen [WMO]). The risks of participating in this study are minimal. The interviews and assessments may be somewhat burdensome but do not carry specific risks. For this reason, the sponsor is dispensed from the obligation to provide insurance for participating in medical research by the Medical Research Ethics Committee (in Dutch: medisch-ethische toetsingscommissie [METC]) of the Erasmus Medical Center (MC).

Outcomes {12}

Table 1 presents an overview of the time points for each outcome measure.

Primary outcome

Severity of BPD symptoms The primary outcome variable is the reduction in severity of BPD symptoms from baseline to end of treatment assessed using the Borderline Personality Disorder Symptom Severity Index for Adolescents (BPDSI-IV-ado). The BPDSI-IV-ado is a semi-structured interview to assess the severity of BPD symptoms in adolescents and to detect short-term changes [46]. The BPDSI-IV-ado consists of 72 questions, spread over the 9 criteria for BPD. The total scale ranges from 0 to 90, and the subscales range from 0 to 10. The interview is designed to obtain detailed scores for each BPD symptom and to assess the severity of BPD

Table 1 Time point of each outcome measure

	Measures			Assessment				
	Measure	Respondent	Type	Baseline	End of treatment	12-month follow-up	18-month follow-up	24-month follow-up
Severity of BPD	BPDSI-IV-ado	A	Interview	x	x			x
Severity of depression and anxiety	PHQ-9 ^a	A	Questionnaire	x	x	x	x	x
	GAD-7 ^a	A	Questionnaire	x	x	x	x	x
	C-SSRS ^a	A	Interview	x	x			x
Personality functioning	BSI	A	Questionnaire	x	x	x	x	x
	CBCL	P	Questionnaire	x	x	x	x	x
	LPFS-BF 2.0 ^a	A	Questionnaire	x	x	x	x	x
Social functioning	RFQ-8	A	Questionnaire	x	x	x	x	x
	WHODAS 2.0 ^a	A	Questionnaire	x	x	x	x	x
	KIDSCREEN-10 ^a	A	Questionnaire	x	x	x	x	x
Academic functioning	EQ-5D-NL	A	Questionnaire	x	x	x	x	x
	NRS-BSV	A	Questionnaire	x	x	x	x	x
Economic evaluation	School attendance	A	Questionnaire	x	x	x	x	x
	TiC-P	P	Questionnaire		x	x	x	x
Demographic variables	Questions about extra time investment treatment	P	Questionnaire		x	x	x	x
	Questions about living situation, nationality, level of education, current school, and/or work status	A	Questionnaire	x				

^a Recommended by ICHOM

symptoms over the past 3 months. The internal consistency of the BPDSI-IV-ado is moderate to high (Cronbach's α ranging from 0.62 to 0.94) and the BPDSI-IV-ado has been demonstrated to be a reliable and valid instrument for the assessment of the severity of borderline symptoms in adolescents [46].

Secondary outcomes

Severity of depression and anxiety The Patient Health Questionnaire (PHQ) is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders [47]. The PHQ-9 is the depression module, which scores each of the nine DSM-IV criteria from 0 (not at all) to 3 (nearly every day). It is used to monitor the severity of depression and response to treatment. The Generalized Anxiety Disorder Scale (GAD-7) is a diagnostic self-report scale for screening, diagnosis, and severity assessment of anxiety disorders [48]. The GAD-7 is based on seven items, which are scored from 0 (not at all) to 3 (nearly every day). Both PHQ and GAD-7 have been recommended by the International Consortium for Health Outcome Measurement (ICHOM; [49]).

In line with recommendations by ICHOM [49] for personality disorders, and for depressive and anxiety

disorders, the Columbia Suicide Severity Rating Scale (C-SSRS; [50]) will be used to assess suicidal thoughts and behaviours. The screener version of the scale assesses whether adolescents meet the criteria for specific forms of suicidal behaviour and consists of 3–6 'yes/no' questions (the number of questions depends on the answers given).

To compare the results of this trial with those of other MBT trials, the Brief Symptom Inventory (BSI; [51]) and the Child Behavior Checklist (CBCL; [52]) are also included. The BSI is a self-report questionnaire that also covers depression and anxiety dimensions and can also be used as a global severity index. Adolescents score each item on a 5-point scale ranging from 0 (not at all) to 4 (extremely). Scores represent the intensity of distress over the past week. The Dutch version of the BSI has a good reliability (Cronbach's α ranging from 0.71 to 0.88, test–retest reliability ranging from $r=0.71$ to 0.89) [51]. The CBCL is a child behaviour questionnaire completed by parents. It assesses the competences and emotional and behavioural problems (e.g. depression and anxiety) of the adolescent in a standardized format. The scores on the different domains indicate possible problem areas for the adolescent, from a parental perspective [52].

Personality functioning Improvement of personality functioning will be assessed by the Level of Personality Functioning Scale – Brief Form, version 2.0 (LPFS-BF 2.0; [53]), as a secondary outcome. This self-report measure consists of 12 items rated on a 4-point Likert scale ranging from 0 (very false or often false) to 3 (very true or often true), reflecting the 12 facets of the LPFS as described in section III of the DSM-5 [54]. The internal consistency of the LPFS-BF 2.0 is satisfactory, and sensitivity to change is high [53]. The LPFS-BF 2.0 fits into the recent tradition of dimensional measures of personality problems and has been recommended by ICHOM [49].

Related to improvements in personality functioning are improvements in mentalizing abilities. The Reflective Functioning Questionnaire (RFQ; [55]) is a brief self-report screening measure of reflective functioning. It consists of eight items (e.g. ‘People’s thoughts are a mystery to me’), which are scored on a 7-point Likert scale ranging from 1 (completely disagree) to 7 (completely agree). This instrument assesses the level of certainty (RFQc) and uncertainty (RFQu) about mental states. Internal consistency of RFQc and RFQu respectively are $\alpha = 0.65$ and $\alpha = 0.77$ in a clinical sample and $\alpha = 0.67$ and $\alpha = 0.63$ in a non-clinical sample, respectively [55].

Social functioning The World Health Organization Disability Assessment Scale (WHODAS 2.0) assesses disability in psychiatric populations [56]. The 12-item version assesses impairment in six domains: mobility, self-care, understanding and communication, interpersonal relationships, life activities, and community participation. The WHODAS 2.0 has also been recommended by the ICHOM [49].

The adolescents’ quality of life will also be assessed as a measure of social functioning. The KIDSCREEN-10 is an international cross-culturally comparable quality-of-life assessment instrument validated for children and adolescents between 8 and 18 years. It consists of ten items, which provide a global measure of health-related quality of life [57]. The KIDSCREEN-10 has also been recommended by the ICHOM [49]. The EQ-5D-5L is a self-report questionnaire comprising five dimensions for measuring health-related quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into five levels (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems). The adult version of the EQ-5D-5L will be used to consistently assess the quality of life during the study, as the youth version of this questionnaire was designed to be used in adolescents up to age 15 years [58].

To assess how social relationships improve, the Dutch translation of the Network of Relationships Inventory-Behavioural Systems Version (NRI-BSV; [59]) is used. Adolescents answer 24 items regarding their relationships with important people in their social network on a 5-point Likert scale (1 = little or none; 5 = the most), which assess support and conflict in social relationships. The NRI-BSV will also be administered to parents to include their assessment of changes in the parent–child relationship.

Academic functioning To assess academic functioning, adolescents will answer questions concerning their school attendance in the past month (e.g. ‘Have you been to school in the past month?’, ‘Why did you not go to school in the past month?’, ‘Did you skip classes in the past month?’), taking school holidays into account.

Economic evaluation The intervention costs of MBT-early and CBT will be calculated using a mixture of bottom-up and top-down approaches and will include personnel costs, implementation costs (e.g. hosting and coaching), and overhead costs associated with the treatment (e.g. facilities for coaches).

An adapted version of the Trimbos/iMTA questionnaire for Costs associated with psychiatric illness (TiC-P; [60, 61]) will be used to calculate medical costs beyond the intervention costs specific to MBT-early and CBT. We will use the parent-form questionnaire (TiC-P Kinderen, in Dutch) to assess health care utilization at baseline, end of treatment, and at 12-, 18-, and 24-month follow-up. We slightly adapted the questionnaire by adding questions about the frequency and duration of (suicidal) crisis (with hospitalization needed) and removing questions that are not related to the problems of the target population (e.g. ‘How many appointments did your child have with a dietician in the past 3 months’).

In line with the iMTA Valuation of Informal Care Questionnaire [62], additional costs of parents that are needed for the treatment of their child will be assessed separately (e.g. taking leave from work to bring their child to therapy, transportation costs, having less leisure time). Parents will answer questions concerning this invested time (e.g. ‘Did you take leave from work for your children’s therapy at “Mentale Beter/GGz Breburg/de Viersprong” in the past 4 weeks?’ or ‘Did you make any extra costs because your child had therapy in the past 4 weeks? E.g. extra travel expenses or arranging a babysitter’). These questions will be assessed at the end of treatment and at 12-, 18-, and 24-month follow-up. QALYs

will be estimated by calculating the area under the Euro-Qol EQ-5D/time curve [63].

Demographic variables At the initial assessment (prior to randomization), adolescents will answer questions regarding demographic variables including their living situation, nationality, level of education, and their current school status, employment, or both.

Participant timeline {13}

Figure 1 shows the participant timeline.

Sample size {14}

The sample size is determined by the predicted difference between the groups on the primary outcome, the BPDSI-IV-ado [46]. Consistent with previous studies on MBT for adolescents [43, 64] and MBT for adolescents compared with treatment as usual [27], we expect a medium effect size (Cohen’s $d=0.50$) difference between MBT-early and CBT. Based on the BPDSI-IV-ado and

with a two-sided $\alpha=0.05$, a power of 0.80 and a correlation of 0.50 between the repeated measures, based on Bales et al. [65] and Hutsebaut et al. [43], we require 59 participants in each treatment group (118 in total) with at least 1 follow-up measurement. Because of the vulnerable and unpredictable target population, we anticipate a 10% attrition rate and therefore intend to recruit at least 66 participants per group.

Recruitment {15}

Adolescents will be recruited at three mental health-care institutions in the Netherlands: Mentaal Beter, GGz Breburg, and de Viersprong. These settings treat young people referred for (emerging) mental health problems and offer interventions for a wide range of mental health problems. Adolescents and their parents are informed during the admission by the clinician about participating in this study and will receive written information. The information folder also includes an infographic about the study. The research team is available to answer questions about the study and will ask for informed consent, if the

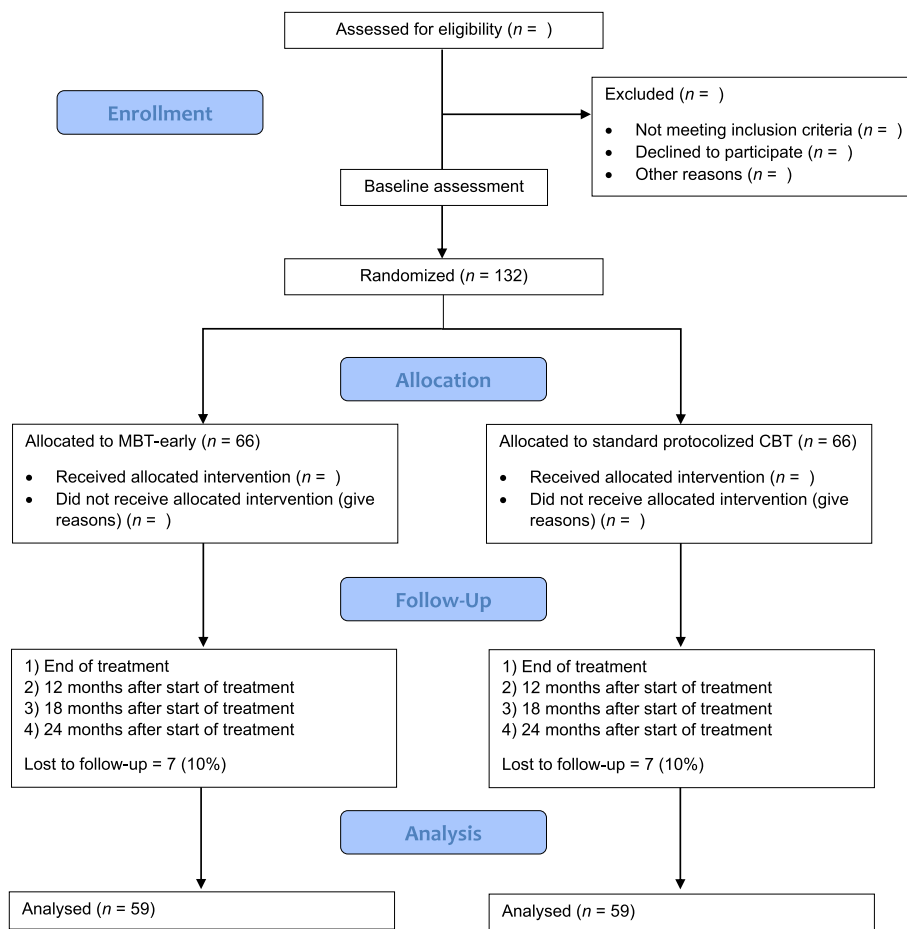


Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow chart

adolescent is eligible. In cooperation with the involved institutions and local government, informative meetings will be scheduled to inform referrers about this study and the information folders will also be made available to referrers.

Assignment of interventions: allocation

Sequence generation {16a}

Participants will be randomized to either MBT-early or CBT using a computerized 1:1 allocation sequence generated by an independent statistician. Randomization will be blocked with random permuted blocks of sizes 4, 6, and 8.

Concealment mechanism {16b}

Participants are randomized by an independent researcher, following a password-protected computer list with the 1:1 allocation sequence. Allocation will be only revealed to the adolescent, therapist and trial coordinator upon randomization by the independent researcher. The research assistants will not be informed about the allocation.

Implementation {16c}

After informed consent is provided and baseline assessment has taken place, an independent researcher will generate the allocation and inform the trial coordinator about the result. To keep the research assistants blind for the allocation, the trial coordinator directly informs the adolescent (and parents) and therapist about the assigned treatment.

Assignment of interventions: blinding

Who will be blinded {17a}

Research assistants are kept blind for the treatment allocation. The trial coordinator, adolescent (and parents), and therapist will not be blinded but are strongly inculcated to not disclose the assigned treatment during end-of-treatment assessment and follow-up assessments. To check whether research assistants are still blinded for the assigned treatment during the study, research assistants are asked after each assessment to which treatment the adolescents was allocated.

Procedure for unblinding if needed {17b}

N/A. Only research assistants will be blinded. There is no need to unblind research assistants, as the trial coordinator, participants, and therapists are all not blind in this trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

To assess the primary outcome, semi-structured interviews will be administered by trained research assistants at baseline, end of treatment and at 24-month follow-up. To assess the secondary outcomes, questionnaires will be collected through the online database BergOp (<https://www.bergop.info>), to minimize data entry errors. For a detailed description of the instruments used in this trial, see the 'Outcomes {12}' section. For the administration of the BPDSI-IV-ado and C-SSRS, research assistants will be trained and supervised by senior researchers. The research assistant writes a report on the results of the BPDSI-IV-ado and, if requested, provides this report to the adolescent.

All data will be anonymized and saved in a folder on a secured server of 'de Viersprong', which can only be accessed by the research team. The data will be stored, coded, and cleaned before analyses (e.g. checking for duplicates, coding of missings and date of entry) in SPSS.

Plans to promote participant retention and complete follow-up {18b}

Research assistants will follow and motivate adolescents for the assessments during the study. To limit the burden related to follow-up, questionnaires are provided through an online program, and semi-structured interviews will only be administered at the end of treatment and 24-month follow-up. Adolescents have the opportunity to do the interviews at the location or through video conference. Travel expenses will be refunded and adolescents receive a small gift (with a value of €15) after every completed assessment.

Adolescents are allowed to refuse to participate in an assessment and are not obliged to give a reason for not participating. They will be invited for the next assessment planned unless they withdraw their consent for participating in the study. Adolescents may withdraw from the trial at any time for any reason, without any consequences (i.e. they can complete their assigned treatment) and will not be contacted for further assessments.

Data management {19}

Every adolescent receives a unique key code, not based on their initials, birthdate or medical record. In the data files, used for monitoring inclusion and data collection, and for the statistical analyses, only the unique key code of each adolescent will be used and no personal identifiable data. The identification code list that connects adolescents with the research data is encrypted and only available to the research team.

Questionnaires will be administrated online through BergOp (<https://www.bergop.info>), and the results are stored in SPSS. The output of the interviews is also kept in SPSS, and the written reports are stored in a secured folder. Any data on paper (e.g. scoring forms) is stored in a locked room at de Viersprong. All data stored in a secured folder on the network of de Viersprong can only be accessed by the research team. All changes made to the raw data and steps taken in the analyses will be kept in a logbook.

Confidentiality {27}

As stated under the ‘[Data management {19}](#)’ section, in the research data only the unique key code will be used and no personal identifiable data. Only the research team can store, manage, and access the research data. No personal identifiable data will be reported in publications. Data will be stored for 15 years at de Viersprong, according to the Medical Ethical Committee guidelines.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

N/A. No biological specimens will be collected or stored in this study.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Data analysis will be conducted using SPSS Statistics. Treatment outcomes of the primary outcome, severity of BPD symptoms, over time will be examined using multilevel modelling. Multilevel modelling is able to model data from different time points, correcting for the dependency of observations by adding a within-subject correlation structure to the regression model. Another advantage of multilevel modelling is that it is able to handle missing data, by using the available data irrespective of the number of repeated measurements. In other words, adolescents with an incomplete number of follow-up measurements are also included in the treatment outcome analyses.

The interventions will be compared with the intention-to-treat adolescent sample, that is, with all adolescents randomized to either MBT-early or CBT.

A deviance test using restricted maximum likelihood will be used to assess whether random or fixed slopes should be assumed in models for each outcome variable. Subsequently, time will be included as appropriate (i.e. linear, logarithmic) and included in the model together with the treatment group and time by group interactions if likelihood ratio tests show significant improvement. The primary effect size of the treatments

will be estimated from baseline to end of treatment and secondary effect sizes from baseline to 12-, 18-, and 24-month follow-up. Additional treatment offered in the follow-up period will be included as a covariate in the estimation of the multilevel models and effect sizes from baseline to 12-, 18-, and 24-month follow-up, as well as a predictor of treatment outcomes at 12-, 18-, and 24-month follow-up.

The secondary outcomes will be analysed similarly using multilevel modelling, in which the type of model is adapted to the outcome if needed (i.e. binary in case of the C-SSRS) from baseline to end of treatment, 12-, 18-, and 24-month follow-up. As noted, additional treatment offered in the follow-up period will be included as a covariate in the estimation of the multilevel models and effect sizes from baseline to 12-, 18-, and 24-month follow-up, as well as a predictor of treatment outcomes at 12-, 18-, and 24-month follow-up.

To examine the possible influence of missing data, we will repeat the analyses described using datasets in which missing data are imputed with state-of-the-art data imputation methods [66].

To investigate the cost-effectiveness of MBT-early compared to CBT, an economic evaluation will be performed using a ‘piggyback economic evaluation’, which means that health economic data will be collected alongside the clinical trial and will be analysed using the same time horizon as the trial. The economic evaluation will be performed from a societal perspective, and all analyses will be conducted according to the intention-to-treat principle, in which we adhere to the related guidelines [67–69]. For example, parameter uncertainty will be covered by, for example, sensitivity analyses in which imputed uncertainty is also taken into account by repeating the economic evaluation on the imputed dataset and sampling uncertainty will be taken into account by providing a cost-effectiveness acceptability curve and frontier [67].

To investigate the potential differences between the adolescents in the MBT-early group and the adolescents in the CBT treatment group, parametric and nonparametric descriptive statistics will be used, as appropriate.

Interim analyses {21b}

N/A. No interim analysis will be conducted because the adverse effects of participating in this study are minimal for the participants.

Methods for additional analyses (e.g. subgroup analyses) {20b}

N/A. There are no additional analyses planned.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Based on the intention-to-treat principle, adolescents will be analysed according to their assigned treatment and excluded from the analyses if they withdraw their consent after being randomized. There will be no replacement of adolescents after withdrawal. To examine the possible influence of missing data, we will repeat the analyses described using datasets in which missing data are imputed with state-of-the-art data imputation methods [66].

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The datasets used or analysed, as well as the statistical code, will be made available by the corresponding author upon reasonable request and in consultation with the research team of this study.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The overarching research team consists of the principal investigator, senior researchers, the trial coordinator, and research assistants of de Viersprong. The daily coordination of the trial will be done by the principal investigator and trial coordinator. The trial coordinator and the research assistants are responsible for day-to-day contact with the participants and the therapists at the involved institutions. Each institution has a contact person, with whom the principal investigator and trial coordinator have regular meetings to monitor the progress of the trial at the specific institution. To monitor the overall progress of the trial, the overarching research team will meet every month, or if necessary, more frequently. Participants can consult an independent expert with questions about the trial.

A TSC will be established, consisting of the principal investigator and manager from each treatment location, professors from different universities, and the chair of the Client Council of de Viersprong. This committee can be consulted for advice and monitor the serious adverse events (SAE) during the trial. The TSC will meet two to three times a year, or if necessary, more frequently. The TSC may decide to discontinue or terminate the trial prematurely if there is a significant difference in SAEs (>5) between the two treatment conditions.

Composition of the data monitoring committee, its role, and reporting structure {21a}

N/A. A data safety monitoring board (DSMB) is not applicable for this trial, due to its relatively small size and

the fact that the treatments being investigated are not experimental. However, as mentioned in the '[Composition of the coordinating centre and trial steering committee {5d}](#)' section, a TSC will be established, which can be consulted for advice and monitor the SAEs during the trial.

Adverse event reporting and harms {22}

Adverse events (AEs) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure. Adverse events, including self-harm or family crises, are considered to be related to the nature of the mental problems of these adolescents/families and will be managed by the therapist as part of the regular treatment. The therapist will discuss these adverse events with the adolescent. Reporting for research purposes will only occur in case of an SAE.

The following SAEs will be monitored, recorded, and reported:

- Lethal suicide attempts or suicide attempts that require hospitalization
- Any other behaviour that may be related to the patients' presenting problems that requires inpatient hospitalization or that may result in persistent or significant disability/incapacity (e.g. very serious self-harm, overdose)

An elective hospital admission will not be considered as a serious adverse event.

All SAEs occurring from the time of written consent until 90 days after cessation of the trial treatment will be recorded in the case report form.

For each SAE, the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality (i.e. relatedness to trial intervention/investigation), in the opinion of the investigator
- Whether the event would be considered expected or unexpected

Events will be followed up until the event has been resolved or a final outcome has been reached.

The research assistant will report all SAEs to the trial coordinator and principal investigator without undue delay after obtaining knowledge of the events, within one

working day. The principal investigator informs the trial steering committee in case of a SAE.

The trial coordinator will also report the SAEs through the web portal *ToetsingOnline* to the accredited Medical Ethical Committee that approved the protocol, within seven working days of first knowledge for SAEs that result in death or are life-threatening followed by a period of a maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of a maximum of 15 days after the trial coordinator has first knowledge of the SAE.

Frequency and plans for auditing trial conduct {23}

De Viersprong has an internal and external audit cycle certified on the basis of the NEN 15224, with regard to the support of activities for the provision of Top Clinical Psychiatric Care, specialist diagnostic research, and treatment programmes for adolescents and adults with complex psychiatric problems and personality disorders. The research team also meets monthly to review trial conduct.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Changes made to the research protocol which may have an impact on the conduct of the study and after a favourable opinion by the METC of the Erasmus MC has been given will require a formal amendment to the research protocol. Substantial amendments will first be proposed to the METC of the Erasmus MC and changes will only be implemented after ethical approval. ZonMw, as one of the funders of this study, will be notified about the ethically approved amendments. Non-substantial amendments will not be notified to the METC of the Erasmus MC and ZonMw but will be recorded and filed by the sponsor.

Dissemination plans {31a}

Results will be published in national and international peer-reviewed journals. Both positive, negative, and null results will be reported. Additionally, the results will be presented at national and international conferences. Local stakeholders will be informed through the websites, social media, and newsletters of the involved mental healthcare institutions (e.g. de Viersprong, GGz Breburg and Mentaal Beter). A client board will be asked to provide feedback on the results and advise on how to inform adolescents and parents who opted in to receive results on a study level.

Discussion

This study will provide an empirical evaluation of the potential value of detecting and treating symptoms of BPD in an early stage. It extends current research in the field of clinical staging and early intervention, which has been proven to be valuable in other somatic (e.g. oncology) [70] and mental (e.g. psychosis) disorders [71], to the domain of personality disorders.

This study has several strengths. First, to the best of our knowledge, this is the first study to use an early intervention paradigm, including a model of clinical staging, to identify a specific subsample of referred adolescents in an early stage of BPD, as opposed to merely treating BPD at an early age with a fixed treatment package. Second, this study possesses a high degree of external validity due to the specific target group of adolescents who are routinely referred to the involved institutions for the treatment of either depressive symptoms, anxiety symptoms, or both. Third, we will include not only the reduction of psychopathology as a desired outcome of treatment, but also social and academic functioning and lifestyle, thereby studying the impact of both interventions on areas of functioning that may determine health and quality of life in the long term more than a reduction of symptoms. The selected outcome measures represent domains of outcome that are of both scientific and societal value, as they are based on the ICHOM standard sets for depression, anxiety, and personality disorders [49] and reflect outcomes that matter to patients.

The results of this study may open new perspectives on early intervention for young people with BPD and may identify a group of young people for whom traditional protocolized treatment of depressive and anxiety disorders may be insufficient given their underlying borderline symptoms. An early focus on personality impairments may generate more long-lasting resilience as compared to classic interventions that target the presenting symptoms and therefore may be a cost-effective treatment choice. Ultimately, this study may lay the basis for a validated paradigm of early and stage-tailored interventions in the management of BPD.

Trial status

Trial NL9569, the current protocol is version 3, dated 30 August 2022. The first participant was enrolled on 12 August 2021. Recruitment is expected to be completed by the third quarter of 2024.

Abbreviations

AEs	Adverse event
BPD	Borderline personality disorder
CBT	Cognitive behavioural therapy
DBT-A	Dialectical behavioural therapy for adolescents
DSMB	Data safety monitoring board

ICHOM	International Consortium for Health Outcomes Measurement
MBT-A	Mentalization-based treatment for adolescents
MBT-early	Mentalization based treatment-early
METC	Medical Research Ethics Committee (in Dutch: Medisch-ethische toetsingscommissie)
NEN	Royal Netherlands Standardization Institute (in Dutch: Stichting Koninklijk Nederlands Normalisatie Instituut)
PD	Personality disorder
RCT	Randomized controlled trial
SAEs	Serious adverse events
TSC	Trial Steering Committee
WMO	Medical Research Involving Human Subjects Act
QALY	Quality-adjusted life year

Acknowledgements

We would like to thank all the adolescents and their parents for their time, commitment, and willingness to participate in this study and all the participating therapists from Mentaal Beter, GGz Breburg, and de Viersprong. We would like to thank all the research assistants for their hard work in collecting the data.

Authors' contributions (31b)

Conception and design: JH, DF, MR, RS, and PL. Drafting of the manuscript: MR in collaboration with JH and DF. Study coordination: DF and JH. Patient recruitment: MR and SC. Statistical analysis: HE. All authors contributed to and approved the final manuscript.

Funding (4)

This study is in part funded by ZonMW, which is the Netherlands Organization for Health Research and Development (grant no. 636310021). The funder does not have a role in the collection, analysis, and interpretation of the data or in the writing of the manuscript.

Availability of data and materials (29)

The research team working for the sponsor has access to the dataset. Any data used or analysed during the study will be made available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate (24)

Ethical approval was assigned by the Medical Ethical Committee of Erasmus Medical Center, Rotterdam, The Netherlands (NL76087.078.20). All participating adolescents (and parents if the adolescent is younger than 16 years old) will provide written informed consent.

Consent for publication (32)

The informed consent forms can be obtained from the corresponding author.

Competing interests (28)

JH and PL have been involved in the development, training, and dissemination of mentalization-based treatment. MS has been involved in the dissemination of mentalization-based treatment. SD has been involved in the training and dissemination of cognitive behavioural therapy. The other authors declare that they have no competing interests.

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Received: 25 March 2024 Accepted: 3 April 2024

Published online: 15 April 2024

References

- Fok ML, Hayes RD, Chang CK, Stewart R, Callard FJ, Moran P. Life expectancy at birth and all-cause mortality among people with personality disorder. *J Psychosom Res.* 2012;73(2):104–7.
- Grant BF, Chou SP, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry.* 2008;69(4):533–45.
- Moran P, Stewart R, Brugha T, Bebbington P, Bhugra D, Jenkins R, et al. Personality disorder and cardiovascular disease: results from a national household survey. *J Clin Psychiatry.* 2007;68(1):69–74.
- Wright AG, Zalewski M, Hallquist MN, Hipwell AE, Stepp SD. Developmental trajectories of borderline personality disorder symptoms and psychosocial functioning in adolescence. *J Pers Disord.* 2016;30(3):351–72.
- Zanarini MC, Frankenburg FR, Reich DB, Fitzmaurice G. Attainment and stability of sustained symptomatic remission and recovery among patients with borderline personality disorder and axis II comparison subjects: a 16-year prospective follow-up study. *Am J Psychiatry.* 2012;169(5):476–83.
- Hastrup LH, Kongerslev MT, Simonsen E. Low vocational outcome among people diagnosed with borderline personality disorder during first admission to mental health services in Denmark: a nationwide 9-year register-based study. *J Pers Disord.* 2019;33(3):326–40.
- Soeteman DI, Verheul R, Busschbach JJ. The burden of disease in personality disorders: diagnosis-specific quality of life. *J Pers Disord.* 2008;22(3):259–68.
- Soeteman DI, Hakkaart-van Roijen L, Verheul R, Busschbach JJ. The economic burden of personality disorders in mental health care. *J Clin Psychiatry.* 2008;69(2):259–65.
- Chanen AM, McCutcheon LK, Germano D, Nistico H, Jackson HJ, McGorry PD. The HYPE Clinic: an early intervention service for borderline personality disorder. *J Psychiatr Pract.* 2009;15(3):163–72.
- Hutsebaut J, Videler AC, Verheul R, Van Alphen SPJ. Managing borderline personality disorder from a life course perspective: clinical staging and health management. *Personal Disord.* 2019;10(4):309–16.
- Hastrup LH, Jennum P, Ibsen R, Kjellberg J, Simonsen E. Welfare consequences of early-onset borderline personality disorder: a nationwide register-based case-control study. *Eur Child Adolesc Psychiatry.* 2022;31(2):253–60.
- Wertz J, Caspi A, Ambler A, Arseneault L, Belsky DW, Danese A, et al. Borderline symptoms at age 12 signal risk for poor outcomes during the transition to adulthood: findings from a genetically sensitive longitudinal cohort study. *J Am Acad Child Adolesc Psychiatry.* 2020;59(10):1165–77 e2.
- Hutsebaut J, Clarke SL, Chanen AM. The diagnosis that should speak its name: why it is ethically right to diagnose and treat personality disorder during adolescence. *Front Psychiatry.* 2023;14:1130417.
- Laurensen EMP, Hutsebaut J, Feenstra DJ, Van Busschbach JJ, Luyten P. Diagnosis of personality disorders in adolescents: a study among psychologists. *Child Adolesc Psychiatry Ment Health.* 2013;7(1):3.
- O'Dwyer N, Rickwood D, Buckmaster D, Watsford C. Therapeutic interventions in Australian primary care, youth mental health settings for young people with borderline personality disorder or borderline traits. *Borderline Personality Disord Emot Dysregul.* 2020;7(1):23.
- Kiviruusu O, Strandholm T, Karlsson L, Marttunen M. Outcome of depressive mood disorder among adolescent outpatients in an eight-year follow-up. *J Affect Disord.* 2020;266:520–7.
- Jørgensen MS, Storebø OJ, Stoffers-Winterling JM, Faltinsen E, Todorovac A, Simonsen E. Psychological therapies for adolescents with borderline personality disorder (BPD) or BPD features—a systematic review of randomized clinical trials with meta-analysis and Trial Sequential Analysis. *PLoS One.* 2021;16(1):e0245331.
- Li ET, Midgley N, Luyten P, Sprecher EA, Campbell C. Mapping the journey from epistemic mistrust in depressed adolescents receiving psychotherapy. *J Couns Psychol.* 2022;69(5):678–90.

19. Miller AL, Rathus JH, Linehan MM. Dialectical behavior therapy with suicidal adolescents. New York (NY): Guilford Press; 2006.
20. Bleiberg E, Rossouw T, Fonagy P. Adolescent breakdown and emerging borderline personality disorder. 2012.
21. Foelsch PA, Schlüter-Müller S, Odom AE, Arena HT, Borzutzky A, Schmeck K. Adolescent identity treatment: an integrative approach for personality pathology. Heidelberg (DE): Springer International Publishing; 2014.
22. Beck E, Bo S, Jorgensen MS, Gondan M, Poulsen S, Storebo OJ, et al. Mentalization-based treatment in groups for adolescents with borderline personality disorder: a randomized controlled trial. *J Child Psychol Psychiatry*. 2020;61(5):594–604.
23. Chanen AM, Jackson HJ, McCutcheon LK, Jovev M, Dudgeon P, Yuen HP, et al. Early intervention for adolescents with borderline personality disorder: quasi-experimental comparison with treatment as usual. *Aust N Z J Psychiatry*. 2009;43(5):397–408.
24. Gleeson JF, Chanen A, Cotton SM, Pearce T, Newman B, McCutcheon L. Treating co-occurring first-episode psychosis and borderline personality: a pilot randomized controlled trial. *Early Interv Psychiatry*. 2012;6(1):21–9.
25. McCauley E, Berk MS, Asarnow JR, Adrian M, Cohen J, Korslund K, et al. Efficacy of dialectical behavior therapy for adolescents at high risk for suicide: a randomized clinical trial. *JAMA Psychiat*. 2018;75(8):777–85.
26. Mehlum L, Tormoen AJ, Ramberg M, Haga E, Diep LM, Laberg S, et al. Dialectical behavior therapy for adolescents with repeated suicidal and self-harming behavior: a randomized trial. *J Am Acad Child Adolesc Psychiatry*. 2014;53(10):1082–91.
27. Rossouw TI, Fonagy P. Mentalization-based treatment for self-harm in adolescents: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2012;51(12):1304–13 e3.
28. Salzer S, Cropp C, Jaeger U, Masuhr O, Streeck-Fischer A. Psychodynamic therapy for adolescents suffering from co-morbid disorders of conduct and emotions in an in-patient setting: a randomized controlled trial. *Psychol Med*. 2014;44(10):2213–22.
29. Santisteban DA, Mena MP, Muir J, McCabe BE, Abalo C, Cummings AM. The efficacy of two adolescent substance abuse treatments and the impact of comorbid depression: results of a small randomized controlled trial. *Psychiatr Rehabil J*. 2015;38(1):55–64.
30. Schuppert HM, Timmerman ME, Bloo J, van Gemert TG, Wiersma HM, Minderaa RB, et al. Emotion regulation training for adolescents with borderline personality disorder traits: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2012;51(12):1314–23 e2.
31. Schuppert HM, Giesen-Bloo J, van Gemert TG, Wiersma HM, Minderaa RB, Emmelkamp PM, et al. Effectiveness of an emotion regulation group training for adolescents—a randomized controlled pilot study. *Clin Psychol Psychother*. 2009;16(6):467–78.
32. Hutsebaut J, Debbané M, Sharp C. Designing a range of mentalizing interventions for young people using a clinical staging approach to borderline pathology. *Borderline Personal Disord Emot Dysregul*. 2020;7(1):1–10.
33. Chanen AM, Berk M, Thompson K. Integrating early intervention for borderline personality disorder and mood disorders. *Harv Rev Psychiatry*. 2016;24(5):330–41.
34. McGorry PD, Mei C. Clinical staging for youth mental disorders: progress in reforming diagnosis and clinical care. *Annu Rev Dev Psychology*. 2021;3(1):15–39.
35. Arntz A, Kamphuis JH, Derks JL. SCID-5-S: Gestructureerd klinisch interview voor DSM-5 Syndroomstoornissen. Amsterdam: Boom; 2018. p. 454.
36. Arntz A, Kamphuis JH, Derks JL. SCID-5-P: Gestructureerd klinisch interview voor DSM-5 persoonlijkheidsstoornissen. Amsterdam: Boom; 2017. p. 120.
37. Landelijke Stuurgroep Multidisciplinaire Richtlijnontwikkeling in de GGZ. Multidisciplinaire richtlijn persoonlijkheidsstoornissen. Utrecht: Trimbos-Instituut; 2008.
38. Davidson KM. Cognitive therapy for personality disorders: a guide for therapists. Oxford; Boston: Butterworth-Heinemann; 2000.
39. Braet C, Bögels SM. Protocolaire behandelingen voor kinderen en adolescenten met psychische klachten. Amsterdam: Boom; 2020.
40. Stoffers-Winterling JM, Storebø OJ, Kongerslev MT, Faltinsen E, Todorovac A, Sedoc Jørgensen M, et al. Psychotherapies for borderline personality disorder: a focused systematic review and meta-analysis. *Br J Psychiatry*. 2022;221(3):538–52.
41. Hajek Gross C, Oehlke S-M, Prillinger K, Goreis A, Plener PL, Kothgassner OD. Efficacy of mentalization-based therapy in treating self-harm: a systematic review and meta-analysis. *Suicide Life-Threat Behav*. 2024;00:1–21.
42. Byrne G, Murphy S, Connon G. Mentalization-based treatments with children and families: a systematic review of the literature. *Clin Child Psychol Psychiatry*. 2020;25(4):1022–48.
43. Hutsebaut J, Feenstra D, Keur E, Schäfer B, Bales D. Tijdig herkennen en behandelen van borderlineproblematiek bij jongeren met MBT-early. *Tijdschr Psychother*. 2017;43(5):330–44.
44. Luyten P, Campbell C, Allison E, Fonagy P. The mentalizing approach to psychopathology: state of the art and future directions. *Annu Rev Clin Psychol*. 2020;16(1):297–325.
45. Bateman A, Fonagy P. Psychotherapy for borderline personality disorder: mentalization-based treatment. New York (NY): Oxford University Press; 2004.
46. Schuppert HM, Bloo J, Minderaa RB, Emmelkamp PM, Nauta MH. Psychometric evaluation of the Borderline Personality Disorder Severity Index-IV—adolescent version and parent version. *J Pers Disord*. 2012;26(4):628–40.
47. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–13.
48. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092–7.
49. International Consortium for Health Outcomes Measurement. Boston (MA): ICHOM. Patient-Centered Outcome Measures. Available from: <https://www.ichom.org/patient-centered-outcome-measures/>. Cited 2022 December 15.
50. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266–77.
51. De Beurs E. Brief Symptom Inventory 18-BSI 18-Handleiding herziene editie. Leiden: PITS BV; 2011.
52. Verhulst F, Van der Ende J. Handleiding ASEBA-Vragenlijsten voor leeftijden 6 t/m 18 jaar: CBCL/6–18. Rotterdam: YSR en TRF, ASEBA; 2013.
53. Weekers LC, Hutsebaut J, Kamphuis JH. The level of Personality Functioning Scale-Brief Form 2.0: update of a brief instrument for assessing level of personality functioning. *Personal Ment Health*. 2019;13(1):3–14.
54. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Washington (DC): American Psychiatric Association Publishing; 2013.
55. Fonagy P, Luyten P, Moulton-Perkins A, Lee YW, Warren F, Howard S, et al. Development and validation of a self-report measure of mentalizing: the Reflective Functioning Questionnaire. *PLoS One*. 2016;11(7):e0158678.
56. Üstün TB, Kostanjsek N, Chatterji S, Rehm J. Measuring health and disability: manual for WHO Disability Assessment Schedule (WHODAS 2.0). Geneva: World Health Organization; 2010. p. vii + 84.
57. Ravens-Sieberer U, Erhart M, Rajmil L, Herdman M, Auquier P, Bruil J, et al. Reliability, construct and criterion validity of the KIDSCREEN-10 score: a short measure for children and adolescents' well-being and health-related quality of life. *Qual Life Res*. 2010;19(10):1487–500.
58. Versteegh MM, Vermeulen KM, Evers SM, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. *Value in health*. 2016;19(4):343–52.
59. Van Aken M, Hessels C. Nederlandse vertaling van de Network of Relationships Inventory—Behavioral System Version. Utrecht: Ontwikkelingspsychologie, Universiteit Utrecht; 2012.
60. iMTA Productivity and Health Research Group. Handleiding iMTA Productivity Cost Questionnaire (iPCQ). Rotterdam: iMTA, Erasmus Universiteit; 2018.
61. Bouwmans C, De Jong K, Timman R, Zijlstra-Vlasveld M, Van der Feltz-Cornelis C, Tan Swan S, et al. Feasibility, reliability and validity of a questionnaire on healthcare consumption and productivity loss in patients with a psychiatric disorder (TiC-P). *BMC Health Serv Res*. 2013;13(1):217.
62. Hoefman R, Van Exel N, Brouwer W. iMTA Valuation of Informal Care Questionnaire (iVICQ). Version 1.0 (December 2011). Rotterdam: IBMG/iMTA; 2011. 2013.
63. Brooks R, Rabin R, De Charro F. The measurement and valuation of health status using EQ-5D: a European perspective: evidence from the EuroQol BIOMED Research Programme. Dordrecht (NL): Springer Science & Business Media; 2013.

64. Laurensen EM, Hutsebaut J, Feenstra DJ, Bales DL, Noom MJ, Busschbach JJ, et al. Feasibility of mentalization-based treatment for adolescents with borderline symptoms: a pilot study. *Psychotherapy (Chic)*. 2014;51(1):159–66.
65. Bales DL, Timman R, Andrea H, Busschbach JJ, Verheul R, Kamphuis JH. Effectiveness of day hospital mentalization-based treatment for patients with severe borderline personality disorder: a matched control study. *Clin Psychol Psychother*. 2015;22(5):409–17.
66. Smits ML, Feenstra DJ, Eeren HV, Bales DL, Laurensen EMP, Blankers M, et al. Day hospital versus intensive out-patient mentalisation-based treatment for borderline personality disorder: multicentre randomised clinical trial. *Br J Psychiatry*. 2020;216(2):79–84.
67. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II—an ISPOR Good Research Practices Task Force report. *Value Health*. 2015;18(2):161–72.
68. Huseareau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health*. 2013;16(2):231–50.
69. Zorginstituut Nederland. Richtlijnen voor het uitvoeren van economische evaluaties in de gezondheidszorg. Diemen: Zorginstituut Nederland; 2016.
70. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio I, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30(8):1194–220.
71. McGorry PD, Killackey E, Yung A. Early intervention in psychosis: concepts, evidence and future directions. *World Psychiatry*. 2008;7(3):148.

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