

Predictors and moderators of outcome of psychotherapeutic interventions for mental disorders in young people: Protocol for systematic reviews

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Protocol

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Abstract

Background: Adolescence and young adulthood is a risk period for the emergence of mental disorders. There is strong evidence that psychotherapeutic interventions are effective for most mental disorders. However, very little is known about for whom different psychotherapeutic treatment modalities are effective. This large systematic review aims to address this critical gap within the literature on non-specific predictors and moderators of the outcomes of psychotherapeutic interventions among young people with mental disorders.

Methods: Pubmed and PsycINFO databases were searched for randomized controlled and quasi-experimental/naturalistic clinical trials. Studies were selected according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Risk of bias of all included studies will be assessed by RoB1 and ROBINS-I risk of bias tools. The quality of predictor and moderator variables will be also assessed. A narrative synthesis will be conducted for all included studies.

Discussion: This systematic review will strengthen the evidence base on effective mental health interventions for young people, being the first to explore predictors and moderators of outcome of psychotherapeutic interventions for a wide range of mental disorders in young people.

Systematic review registration: PROSPERO (CRD42020166756)

Background

The transition from childhood to adulthood is a critical developmental period marked by both risk and resilience(1). Young people (YP) aged 13 to 30 years are faced with numerous challenges and developmental demands that span across all aspects of their life(2, 3). Whilst most adolescents adjust to these new challenges, others struggle and exhibit greater vulnerability for mental health problems. Half of all mental disorders will manifest before the age of 14, and three quarters by the age of 24(4, 5), making adolescence and young adulthood a crucial stage for developing mental health disorders.

Studies show that mental health issues impact up to 40% of YP(6, 7), while 20% of them formally meet criteria for functionally impairing mental disorders(8). Mental and substance use disorders are major contributors to disability in children and youth worldwide(9–11), accounting for 16% of the global burden of disease and injury in people aged 10–19 years(12). Moreover, there is strong evidence that mental health disorders in youth, when left untreated, tend to have a recurrent course that persists into adulthood(13). The consequences of untreated disorders not only impair the individual, but affect society in general through, i.e., continuance of psychiatric issues, the increased risk for secondary illnesses resulting in poor general health, as well as impaired social and work performance(8, 14). Failure to address adolescent mental health problems adequately can have devastating implications for both present and future, limiting the opportunities of YP to lead healthy and fulfilling lives as adults(12).

The evidence that adolescence is a sensitive window of opportunity emphasizes the need to address psychopathology at the population level, maximizing the efficiency, efficacy and cost-effectiveness of interventions aimed at improving mental health. Untreated mental disorders are discerned as ‘chronic disease’ of the young, leading to persistent and long-term morbidity and mortality(15), whilst effective psychotherapeutic treatment improves the course of mental disorders, reduces the functional impairment and prevents the recurrence of mental health problems(16). The list of psychotherapeutic interventions developed for YP consisted of over 550 treatments nearly two decades ago(17). Today we know that different psychotherapy modalities (cognitive-behavioural, psychodynamic/psychoanalytic, interpersonal, family systems, humanistic/existential, experiential) are generally effective in treating adolescents and young adults(18, 19).

Nonetheless, service provision for this group of YP still remains disproportionately low (15). Up to three quarters of affected YP do not engage in treatment(20, 21), a statistic that renders YP the least likely population group to seek or to access professional treatment for mental health problems(22). The 1999 British Child and Adolescent Mental Health Survey reported that only half of these YP with mental disorders will access any services, and one fourth of YP with impairing psychiatric conditions access a specialist child and adolescent mental health service(23). Furthermore, YP access treatment following significant delays; for some YP, it may take more than 20 years following the initial onset of symptoms(24). Among those who do access help, many drop out of treatment prematurely(25–27).

While it has been shown that psychotherapeutic interventions provide some reduction in the burden of mental disorders compared to untreated YP(28, 29), their overall effect on mental health outcomes is moderate(30, 31). Furthermore, despite significant advances in psychotherapy research in the last decades, research fails to show improvement of youth psychotherapy outcomes over the years(32, 33). In addition, there is limited knowledge on factors influencing the engagement of YP into psychotherapeutic interventions(34). It is therefore important to investigate and elucidate the factors, which contribute to and influence outcome of psychotherapy interventions among YP in order to provide more effective and personalized care to this at-risk group(35).

Predictors And Moderators Of Psychotherapy Outcome

There is a growing consensus in the field of mental health that the focus of outcome research should be extended from the overall effectiveness of treatments (i.e., “what works in general”) to understanding which clinical factors render a given treatment particularly effective or ineffective (i.e., “what works for whom and under what circumstances”)(36). Such variables that might affect the strength or direction of the treatment response are described as *treatment predictors* and *moderators*. Predictors are *pre-treatment* variables that influence outcome regardless of treatment condition. Moderators, on the other hand, are also pre-treatment variables, but differentially influence outcome depending on treatment allocation.

Identifying patient and therapist characteristics that have an influence on clinical outcomes could help design personalized interventions tailored to the unique needs of YP, thus maximizing their efficacy(37).

The findings of this research would provide a guideline for clinicians to help elucidate which YP would respond better to a particular intervention as compared to others, or for whom a particular psychotherapeutic intervention would prove to be inadequate or even ineffective(38). In terms of policy, identifying these subpopulations of YP might be used to advise service development for both governmental or NGOs' health and mental-health initiatives. The benefits of identifying treatment predictors and moderators extend to research. Knowing which factors predict differential response to treatment can maximise power in future clinical trials by clarifying the variables on which to stratify and improve validity by guiding the choice of exclusion and inclusion criteria(39). Conceptually, moderators may help signal differential processes that operate in specific subgroups, generating search for relevant mediator variables and processes, which is a much-needed direction of psychotherapy research.

Personalized medicine is rapidly emerging as a state-of-the-art approach to diagnostics and therapeutics and is beginning to revolutionize our health care systems, promising better treatment for all(40). However, this is not the case in treatment for mental disorders in YP(37). What patient characteristics (predictors/moderators; e.g., gender, level of interpersonal problems, diagnosis) interfere with specific treatment techniques in youth psychotherapy is unknown. Thus, there is an empirical knowledge gap on personalized mental health treatment for YP, which makes the goals for individualised treatment hard to reach(37, 41).

Recognising this important gap in the literature, the European Cooperation in Science and Technology (COST) funded a 4-year program for the creation of a European Network on Individualised Psychotherapy Treatment of Young People with Mental Disorders (TREATme). The main aim of the TREATme COST action is to create a European multidisciplinary researcher network focusing on stratification tools to individualise psychotherapy for YP with mental disorders. One of the deliverables of this COST action is to conduct a review of the current literature within the field, so to elucidate putative specific markers of changes in different therapeutic modalities.

The overarching aim of the proposed study is to carry out a number of systematic reviews of the published literature on predictors and moderators of the outcomes of psychotherapeutic interventions in YP with mental disorders. The objectives of this review are to: (1) to identify both predictors and moderators of the outcome of psychotherapeutic interventions for a variety of mental disorders among YP; (2) to evaluate the proportion of clinical trials adopting robust methodological practices in the assessment of these predictors and moderators; and (3) to conduct a preliminary assessment of the relationship of these predictors/moderators with treatment outcome.

Methods

Search Strategy

The population, intervention, comparison, outcome and study design (PICOS) strategy(42) was used to specify the research question and guided the forming of the search string for this systematic review (see Table 1 for full PICOS strategy). The review followed the Preferred reporting items for systematic review

and meta-analysis (PRISMA;(43)) and this protocol was written following the PRISMA for protocols guidelines (PRISMA-P(44)) checklist. PubMed and PsycINFO electronic databases were used for a literature search until August 31, 2018. The protocol has been registered at The International Prospective Register of Systematic Reviews (PROSPERO) with a registration number is CRD42020166756.

Table 1
PICOS and Inclusion and Exclusion Criteria

PICOS strategy	Include	Exclude
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PICOS strategy	Include	Exclude
P - Population	<p>Adolescents (12–18 years) and young adults (18–30 years) with a mental disorder diagnosis: anxiety, obsessive-compulsive and trauma-related disorders, depressive and bipolar disorders, psychotic disorders, eating disorders, personality disorders, substance-related disorders, autism, attention deficit/ hyperactivity, conduct disorders.</p> <p>Filters: adolescent OR young adult</p> <p>Keywords:</p> <p>Anxiety Disorders: anxiety disorder; neurotic disorder; panic disorder; agoraphobia; social phobia; social anxiety; mutism; separation anxiety; phobic disorder; phobia; generalized anxiety; obsessive compulsive; ocd; hoarding; body dysmorphic disorder; body image disorder; trichotillomania; hair pulling disorder; excoriation disorder; dermatillomania; skin picking disorder; trauma and stressor related disorders; traumatic stress disorder; posttraumatic stress disorder; stress disorder, post-traumatic; ptsd; acute stress disorder; adjustment disorder; Depressive Disorders: mood disorder; depressive disorder; depression; affective disorder; dysthymic disorder; dysthymia; premenstrual dysphoric disorder; seasonal affective. Bipolar Disorders: bipolar and related disorders; bipolar disorder; mania; manic depression; bipolar depression; pediatric bipolar; cyclothymic disorder; cyclothymia. Psychotic disorders: schizophrenia spectrum and other psychotic disorders; psychotic disorder; psychosis; psychoses; schizophrenia; schizoaffective; schizophreniform; reactive psychosis; reactive psychoses. Eating disorders: feeding and eating disorder; feeding disorder; eating disorder; anorexia; bulimia; binge eating; pica; rumination disorder; avoidant restrictive food intake; arfid; avoidant eating; purging disorder; night eating syndrome; food addiction; orthorexia; ednos; ofsed. Personality disorders: personality disorder, schizotypal personality, schizoid personality; paranoid personality; narcissistic personality; borderline personality; histrionic personality; antisocial personality; obsessive compulsive personality; avoidant personality; dependent personality; character pathology; character neurosis; axis II disorder. Substance use disorders: substance related disorder; substance use disorder; substance abuse; substance misuse; substance dependence; addiction; drug use; drug abuse; drug addiction; alcohol related disorder; alcohol use disorder; alcohol abuse; alcohol dependence; alcoholism; amphetamine; cocaine; inhalant ; marijuana; cannabis; opioid; heroin; opium; morphine; hallucinogen; tobacco; nicotine; smoking; polydrug; stimulant; substance induced psychosis; substance induced psychotic disorder; drug psychosis; drug psychoses. Autism: autistic spectrum disorder; autism spectrum disorder; autistic disorder; autism; asperger syndrome; asperger; asperger's; child development disorders, pervasive; pervasive child development disorder. ADHD: attention deficit disorder; adhd; hyperkinetic disorder; attention deficit hyperactivity disorder; conduct; conduct disorder; oppositional defiant; defiant disorder; externalizing behavior; externalizing behavior; antisocial behavior; antisocial behaviour</p>	<p>Age range or mean age of participants under 12 or over 30 years</p> <p>Participants not being diagnosed or having disorder specific symptoms bellow the agreed-upon cut-off point</p>

PICOS strategy	Include	Exclude
I - Intervention	<p>Psychotherapeutic interventions:</p> <p>Keywords: Psychotherapy; Psychotherapeutic treatment; Psychotherapeutic intervention; Psychological therapy; Psychological treatment; Psychological intervention; Psychosocial therapy; Psychosocial treatment; Psychosocial intervention; Supportive therapy</p> <p>Supportive treatment; Counselling; Counseling; Motivational interviewing; Psychoeducation; Psychoeducational; Cognitive therapy; Cognitive analytic therapy; Behavioral therapy; Behavioural therapy;</p> <p>CBT; Psychoanalysis; Psychodynamic therapy; Psychoanalytic therapy;</p> <p>Dynamic therapy; Transference focused (therapy); Mentalization based (therapy); Metacognitive therapy; Interpersonal therapy; Interpersonal and social rhythm therapy; Schema therapy; Schema-focused therapy;</p> <p>Acceptance and Commitment Therapy; Acceptance based (therapy); Problem solving therapy; Problem solving treatment; Insight oriented therapy; Rational emotive; Solution focused therapy; Family therapy</p> <p>Family systems therapy; Parenting intervention; Parent management training; Group therapy; Mind-Body Therapy; Art Therapy; Dance Therapy; Music Therapy; Play Therapy; Expressive therapy; Cognitive remediation; Cognitive training; Behavioral activation; Behavioural activation; Behavior activation; Behavioral weight control; Behavioural weight control; Applied behavior analysis; Applied behaviour analysis; Attention bias modification; Exposure and response prevention; Exposure therapy; Systematic Desensitization; Eye movement desensitization reprocessing; EMDR; Psychology biofeedback; Hypnosis; Mindfulness; Relaxation</p>	<p>Prevention programs</p> <p>Studies testing interventions using only medication arms</p> <p>Studies with interventions targeting only parents</p>
C - Comparison		No exclusion criteria
O - Outcome	Quantitative studies including pre- and post- measurement published in peer-review journals	<p>Qualitative studies</p> <p>Dissertations</p> <p>Book Chapters</p>
S – Study design	<p>Clinical outcome trials: RCT, controlled trials, empirical trials, naturalistic setting, case studies</p> <p>Filters: Clinical Trial OR Comparative study</p>	Case studies where n < 10 or results not being reported in group level

Searches were conducted combining search strings for: (a) psychotherapeutic interventions search terms; (b) mental disorder search terms; (c) age range search terms and (d) study type terms. Controlled descriptors (i.e., PubMed MeSH terms, PsycINFO thesaurus) and their synonyms (key words) were verified in each database. The search terms were combined using the Boolean operators 'AND' and 'OR'.

Searches were conducted separately for each mental disorder. The following mental disorder categories were chosen for inclusion: (a) anxiety, obsessive-compulsive and trauma-related disorders; (b) depressive and bipolar disorders; (c) psychotic disorders; (d) eating disorders; (e) personality disorders; (f) substance-related disorders; (g) autism spectrum disorders; (h) attention deficit/hyperactivity disorder; and (i) conduct disorders.

To ensure successful identification of relevant studies for the specific age group targeted, we added age filters for 'adolescents' and 'young adults.' To identify clinical trials, we used the filter for study type, including 'clinical study' OR 'comparative study' in Pubmed and 'clinical case study' OR 'clinical trial' OR 'empirical study' OR 'treatment outcome' in PsycINFO. Preliminary manual searches that were carried out with relevant search terms (clinical trial treatment response, treatment outcome, random allocation, controlled trial, efficacy, effectiveness) yielded comparable results to the filters selected. This was used to determine that the chosen filters had adequate sensitivity.

Capitalizing on the culturally diverse background of our research team, we had no a priori restriction regarding the language of the published full text, in order to increase the yield of appropriate articles and, thus, generalizability of our findings. However, it was decided that the title and abstract must be available in English so as to be searchable by English keywords and all team members to be able to appraise the study design.

One researcher (VG) formed the final search strings in collaboration with information specialists and conducted the searches. Two researchers (EV and SP) performed the searches independently to cross-check the results. The open access bibliographic software Mendeley was used to store, organize and manage all the references and ensure a systematic and comprehensive search. Duplicate publications from the database search results were removed. An example of a search strategy for the PubMed database for anxiety disorders is presented in Table 2.

Table 2.
Search Strategy for Anxiety Disorders on PubMed.

Search terms for all disorders:

1. Treatments:

"psychotherapy"[MeSH Terms] OR "psychotherapy"[All Fields] OR "psychotherapeutic treatment"[All Fields] OR "psychotherapeutic treatments"[All Fields] OR "psycho-therapeutic treatment"[All Fields] OR "psychotherapeutic intervention"[All Fields] OR "psychotherapeutic interventions"[All Fields] OR "psychological therapy"[All Fields] OR "psychological therapies"[All Fields] OR "psychological treatment"[All Fields] OR "psychological treatments"[All Fields] OR "psychological intervention"[All Fields] OR "psychological interventions"[All Fields] OR "psychosocial therapy"[All Fields] OR "psychosocial therapies"[All Fields] OR "psychosocial treatment"[All Fields] OR "psychosocial treatments"[All Fields] OR "psychosocial intervention"[All Fields] OR "psychosocial interventions"[All Fields] OR "supportive therapy"[All Fields] AND "supportive therapies"[All Fields] OR "supportive treatment"[All Fields] OR "supportive treatments"[All Fields] OR "counseling"[MeSH Terms] OR

"counselling"[All Fields] OR "counseling"[All Fields] OR "motivational interviewing"[All Fields] OR "psychoeducation"[All Fields] OR "psychoeducational"[All Fields] OR "psycho-education"[All Fields] OR "psycho-educational"[All Fields] OR "cognitive therapy"[All Fields] OR "cognitive therapies"[All Fields] OR "behavioural therapy"[All Fields] OR "behavioural therapies"[All Fields] OR "behavioral therapy"[All Fields] OR "behavioral therapies"[All Fields] OR "cbt"[All Fields] OR "psychoanalysis"[MeSH Terms] OR "psychoanalysis"[All Fields] OR "psychodynamic therapy"[All Fields] OR "psychodynamic therapies"[All Fields] OR "psychoanalytic therapy"[All Fields] OR "psychoanalytic therapies"[All Fields] OR "dynamic therapy"[All Fields] OR "dynamic therapies"[All Fields] OR "transference focused"[All Fields] OR "mentalization based"[All Fields] OR "metacognitive therapy"[All Fields] OR "metacognitive therapies"[All Fields] OR "interpersonal therapy"[All Fields] OR "interpersonal therapies"[All Fields] OR "interpersonal and social rhythm therapy"[All Fields] OR "schema therapy"[All Fields] OR "Schema-focused Therapy"[All Fields] OR "Schema-focused Therapy"[All Fields] OR "acceptance and commitment therapy"[All Fields] OR "acceptance based"[All Fields] OR "problem solving therapy"[All Fields] OR "problem solving therapies"[All Fields] OR "problem solving treatment"[All Fields] OR "problem solving treatments"[All Fields] OR "insight oriented therapy"[All Fields] OR "insight oriented therapies"[All Fields] OR "rational emotive"[All Fields] OR "solution focused therapy"[All Fields] OR "solution focused therapies"[All Fields] OR "family therapy"[All Fields] OR "family therapies"[All Fields] OR "family systems therapy"[All Fields] OR "parenting intervention"[All Fields] OR "parenting interventions"[All Fields] OR "parent management training"[All Fields] OR "group therapy"[All Fields] OR "group therapies"[All Fields] OR "mind-body therapies"[MeSH Terms] OR "mind body therapy"[All Fields] OR "mind body therapies"[All Fields] OR "art therapy"[All Fields] OR "art therapies"[All Fields] OR "dance therapy"[All Fields] OR "dance therapies"[All Fields] OR "music therapy"[All Fields] OR "music therapies"[All Fields] OR "play therapy"[All Fields] OR "play therapies"[All Fields] OR "expressive therapy"[All Fields] OR "expressive therapies"[All Fields] OR "cognitive remediation"[All Fields] OR "cognitive training"[All Fields] OR "behavioral activation"[All Fields] OR "behavior activation"[All Fields] OR "behavioural activation"[All Fields] OR "applied behavior analysis"[All Fields] OR "applied behaviour analysis"[All Fields] OR "behavioral weight control"[All Fields] OR "behavioural weight control"[All Fields] OR "attention bias modification"[All Fields] OR (("attention"[MeSH Terms] OR "attention"[All Fields]) AND bias-modification[All Fields]) OR "exposure and response prevention"[All Fields] OR (exposure[All Fields] AND "response prevention"[All Fields]) OR "exposure therapy"[All Fields] OR "systematic desensitization"[All Fields] OR "eye movement desensitization reprocessing"[All Fields] OR "emdr"[All Fields] OR "psychology biofeedback"[All Fields] OR "hypnosis"[All Fields] OR "mindfulness"[All Fields] OR "relaxation"[MeSH Terms]

2. Age:

("adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescents"[All Fields]) OR ("young adult"[MeSH Terms] OR "young adult"[All Fields] OR "young adults"[All Fields])

3. Anxiety:

"anxiety disorders"[MeSH Terms] OR "anxiety disorders"[All Fields] OR "anxiety disorder"[All Fields] OR "neurotic disorders"[MeSH Terms] OR "neurotic disorders"[All Fields] OR "neurotic disorder"[All Fields] OR "panic disorder"[All Fields] OR "panic disorders"[All Fields] OR "agoraphobia"[All Fields] OR "social phobia"[All Fields] OR "social phobias"[All Fields] OR "social anxiety"[All Fields] OR "mutism"[All Fields] OR "separation anxiety"[All Fields] OR "phobic disorders"[All Fields] OR "phobic disorder"[All Fields] OR "phobia"[All Fields] OR "phobias"[All Fields] OR "generalized anxiety"[All Fields] OR ("obsessive-compulsive"[All Fields] AND "disorder"[All Fields]) OR "obsessive compulsive disorder"[All Fields] OR ocd[All Fields] OR "hoarding disorders"[All Fields] OR "hoarding disorder"[All Fields] OR "body dysmorphic disorders"[All Fields] OR "body dysmorphic disorder"[All Fields] OR "body image disorder"[All Fields] OR "trichotillomania"[All Fields] OR "hair pulling"[All Fields] OR excoriation[All Fields] OR dermatillomania[All Fields] OR "skin picking"[All Fields] OR "Trauma and Stressor Related Disorders"[MeSH Terms] OR "traumatic stress disorder"[All Fields] OR "traumatic stress disorders"[All Fields] OR "posttraumatic stress disorder"[All Fields] OR "posttraumatic stress disorders"[All Fields] OR "stress disorders, post-traumatic"[MeSH Terms] OR "post-traumatic stress disorders"[All Fields] OR "ptsd"[All Fields] OR "acute stress disorder"[All Fields] OR "acute stress disorders"[All Fields] OR "adjustment disorders"[All Fields] OR "adjustment disorder"[All Fields]

4. Filters (Article types):

Clinical Study[ptyp] OR Comparative Study[ptyp]

5. Date Filter

"0001/01/01"[PDAT] : "2018/08/31"[PDAT]

Combined Total Results: 1581

Study Selection Criteria

Eligibility of outcome studies were determined with the following criteria, specified by two researchers (BT, VG): (a) clinical outcome study (b) with at least one treatment condition involved being a psychotherapeutic intervention of any length or orientation for (c) adolescents or young adults aged 12–30 years (d) with specified mental disorders (e) as determined by DSM-5, ICD-10, or other diagnostic criteria or high level of symptoms on at least one relevant self-report measure (above the defined cut-off point for that measure), that (f) reports on the relationship between baseline variables and treatment outcome. Moreover, the clinical study should report at least two assessment points: pre-treatment (compulsory) and post-treatment (compulsory). Follow-up assessment was not compulsory for study inclusion; however, to be considered a follow-up at least one month between post-treatment and follow-up was necessary for the third assessment point. In addition, the study must be published in a peer-review journal, and at least title and abstract must be published in English.

In this study, psychotherapeutic interventions were defined as well-known psychotherapy approaches and other psychosocial interventions previously known to show promising evidence on treatment outcome for chosen disorders. A more detailed summary of the participants, interventions, comparators and outcomes considered, as well as the type of studies included according to PICOS strategy, is provided in Table 1.

Moderators of treatment outcome were defined as variables (a) measured at baseline that (b) interact with treatment to change outcome for each sub-group, and (c) the interaction is related to outcome in the linear model with or without a main effect. Predictors of treatment outcome were defined as (a) baseline variables that (b) affect outcome (significant main effect only) but do not interact with the allocated intervention. Both terms have been described in the literature under different terminology⁽³⁶⁾. To avoid making any assumptions on the definition of relevant predictors and moderators for treatment outcome in advance, we first conducted systematic search to identify eligible outcome studies, and from that pool of clinical studies, predictor and moderator studies will be searched manually.

Screening Procedure

Screening of studies was conducted using a three-stage screening process. Stage one included screening of all titles and abstracts, performed independently by two researchers for each diagnostic group. During stage two, the pair of researchers independently screened each full text article. Any discrepancies in screening of titles/abstracts and full text articles were resolved via discussion between the pair until consensus was reached, and when necessary, a third reviewer was called in to adjudicate. In the event that a full-text article was not available in the databases the research team had access to, the researchers contacted the corresponding authors.

The final, third step, is in progress. The eligible outcome studies will be screened for predictors and moderators of treatment outcome. The pair of reviewers will independently screen eligible studies for candidate predictors and moderators and will reach a consensus on which relevant moderator studies

should be included. All predictor variables will be included, as long as they are assessed pre-randomization and do not change as a response to treatment(45).

Data Extraction And Coding

This is an ongoing study. Screening of articles by independent reviewers is close to completion, but data extraction has not begun. We plan to extract data from the final list of included studies in the following categories (1) identification of the study (article title; journal title; authors; publication year; host institution of the study (hospital; university; research centre; single institution; multicentre study); (2) methodological characteristics (study design; sample characteristics, e.g., sample size, gender, age, race; diagnostic procedures and measures; intervention groups and controls; length of follow-up; statistical analysis); (3) predictor or moderators (4) relationship between predictor/moderator and outcome.

The coding of predictors and moderator variables was based on the structure found in Knopp et al.(46). Variables will be coded as: (a) non-specific *predictors* of outcome, if the main effect of a predictor on outcome was assessed for the sample as a whole; and (b) *moderators*, if the effect of the baseline variable on outcome was assessed through a direct test of the interaction between the baseline variable and the intervention(s).

Variables identified through the splitting of the data into groups will be coded as predictors of outcome. Several strategies for such subgroup analysis can be found in the literature (see(46)). One approach includes assessing the main effect of a predictor on outcome only for the treatment or control group. Another approach is to select patients from the treatment and control groups based on a baseline characteristic and compare intervention with control patients within that subgroup (for example, comparing efficacy of intervention vs. control among male participants). Another possibility is to split the overall sample into two groups and look at the effect of the predictor on outcome for both groups separately (e.g., splitting the sample into those with and without co-morbid mental disorders and assessing outcome for both groups separately).

For data extraction, a minimum of two independent reviewers will extract and summarize the data from each included study. If the outcome data in the original article is unclear, the corresponding author will be contacted via email for clarification.

Quality Assessment

As the study is ongoing, quality assessment of included studies has not yet started. First, in order to estimate the possible sources of bias in RCTs, we will use the four criteria of the Cochrane Collaboration Risk of Bias Tool (RoB1 tool;(47)), where overall ratings vary from low, to unclear and to high risk of bias. The criteria are (a) *random sequence generation* - the adequate generation of the allocation sequence, (b) *allocation concealment* – concerning the concealment of allocation to conditions, (c) *blinding of outcome assessment* – i.e., blinding of outcome assessors and considering how subjective or objective an outcome is, and d) *incomplete outcome data* – the manner in which incomplete data were addressed.

The Risk of Bias assessment will be made by two independent raters and disagreements will be discussed and resolved by reaching consensus.

Second, in order to assess the possible sources of bias in non-randomized controlled studies or NRCTs, the ROBINS-I tool will be used(48). ROBINS-I uses seven domains at three moments in time: pre-intervention, intervention, and post-intervention. At pre-intervention, selection bias is assessed in the form of (1) bias due to the presence of confounding factors affecting outcome and (2) bias in selection of some participants into the study. During intervention, bias is assessed in terms of (3) biases in classification of interventions. At post-intervention wise, four other domains are assessed: (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported results. The risk level of each domain is classified as low, moderate, serious, or critical. As in the case of the RoB1 tool, in the current research, two independent reviewers will perform the risk of bias assessment and disagreements will be discussed and resolved by reaching consensus. A review-level narrative summary of the risk of bias will also be provided.

To assess the quality of predictor and moderators, we will employ the criteria developed by Pincus et al. (49) and Sun et al.(50), implemented in the study by Knopp et al.(46). These include: (a) predictor and moderator variables are assessed through validated assessment tool; (b) predictor and moderator variables are measured pre-randomization (non-applicable for non-modifiable variables, such as gender or age); (c) fewer than five predictors tested in the model; (d) predictor and moderator variables tested through a priori hypothesis of anticipated effects; (e) for moderator variables, analysis of direct test of interaction between moderator and treatment type is conducted.

Data Analysis

The final stage of the systematic review will be a data synthesis of the different predictors and moderators of outcomes of psychotherapeutic interventions. Given the anticipated heterogeneity of clinical studies, we will conduct a narrative synthesis of extracted data, a method that has been carried out in similar studies(46). Data will be organized by predictor/moderator variable and by targeted disorder.

Discussion

The study protocol for assessing predictors and moderators of treatment outcome in psychotherapeutic interventions of YP aged 12–30 years has been described above. The key strength of this protocol is that it can be reproduced and used to facilitate the structuring of other systematic reviews. The protocol was carefully discussed by an interdisciplinary team of early career and senior clinical academics and practitioners, including psychologists, psychiatrists and a neurologist. They have a range of psychotherapeutic backgrounds including cognitive-behavioural, psychodynamic/psychoanalytic, integrative, interpersonal, family therapy/systemic, humanistic/existential and experiential approaches. The team is composed of researchers from a range of European countries mastering a wide range of languages, which allows a wider selection of studies to be included. The search strategy and protocol has

been continuously discussed with experts outside this research team to further improve the quality of the study.

The review is based on state-of-the-art review methods. The PICOS strategy(42) was used to specify the research question and guided the forming of the search strings for this systematic review, and the PubMed and PsycINFO electronic databases were used for the literature search. The review was based on the PRISMA guidelines(43, 44) with initial independent selection of papers by a minimum of two researchers followed by a consensual final selection aided by advice from external experts when required. The RoB(47) and ROBINS-I(48) tools will be used for the rating of bias of studies identified and the review was registered within PROSPERO (CRD42020166756).

Given the strengths of this protocol, future studies aiming to develop systematic reviews could use this protocol as a guideline for formulating the research question, search strings, data extraction, critical appraisal, data synthesis and reporting of results. By including non-randomized and non-controlled studies, the review also provides information on psychotherapeutic interventions and disorders, which have only been subjected to a limited amount of research. It may thereby provide information that can be of interest to several stakeholder groups, such as YP and their families, psychologists, clinicians, school counsellors and policymakers, as well as providing an impetus for further studies of less explored treatment approaches.

One of the limitations of this protocol was that searches only included studies published until 31st August 2018, thus excluding more recent publications. This could be addressed by updating the search immediately before the intended publication of the systematic review to include more recent papers. In addition, the number of researchers involved in the review may have led to delays in the research process as each step of the protocol was discussed at length until agreed upon by the whole team. Despite these limitations, to our knowledge, this is the first systematic attempt to map the current knowledge base on factors influencing the effectiveness of psychotherapeutic interventions in YP.

List Of Abbreviations

COST: European Cooperation in Science and Technology

MeSH: Medical Subject Heading

PICOS: The population, intervention, comparison, outcome and study design (PICOS) strategy

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RoB1: Cochrane Collaboration Risk of Bias Tool

ROBINS-I: Risk of Bias in non-randomized controlled studies

TREATme: European Network on Individualised Psychotherapy Treatment of Young People with Mental Disorders

YP: Young People

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The dataset is stored in a protected data repository at the University of Copenhagen and can be accessed by requesting it from the first (EV) or the last author (SP). After publishing the systematic reviews, the dataset will be published in a public, open access data repository and will be also uploaded as supplementary information.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RU and SP conceived the original idea; all authors participated in the planning and design of the study protocol. VG, with the assistance of SP and EV, developed the search strategy; VG and EV planned the data extraction. BTT, VG, and EV developed the eligibility criteria.

IRP and EV developed the quality assessment plan. EV wrote the first draft and NC, AS, LJGL, HLS, TP, VG and SP provided critical insights into the manuscript. All authors have approved and contributed to the final written manuscript.

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