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What works for whom and why? Treatment effects and their moderators among forcibly displaced people receiving psychological and psychosocial interventions: study protocol of a series of individual patient data meta-analyses

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Abstract

Introduction: Due to ongoing wars more than 110 million people worldwide have been forced to flee their homes. Forcibly displaced people (FDP) are exposed to many stressors before, during, and after displacement resulting in a high risk of developing mental disorders such as post-traumatic stress (PTS) disorder. Providing adequate mental healthcare for FDP is crucial but despite overall efficacy of existing interventions in reducing PTS symptoms, a large proportion of FDP do not benefit from treatment, highlighting the necessity of further investigating factors contributing to individual differences in treatment trajectories. Yet, the few studies that have explored moderators of treatment effects in this population often lack sufficient statistical power. Therefore, the present Individual Patient Data meta-analysis (IPD-MA) will investigate treatment effects and their moderators - variables related to beneficiaries, providers, intervention, and study characteristics in relation to PTS outcomes.

Methods and analysis: After a systematic literature search, articles will be screened for eligibility. Randomised controlled trials on adult FDP receiving psychological and psychosocial interventions aimed at alleviating PTS symptoms compared to a non-active control will be included in this IPD-MA. Subsequently, authors will be contacted to request individual patient data. All datasets obtained will be synthesised into one large dataset which will be analysed using a one-stage approach by conducting mixed-effect linear regression models.

Ethics and dissemination: We issued a clarification of responsibility for which the local ethic committee of the canton of Zurich, Switzerland, confirmed that this IPD-MA does not require ethical approval. The results will be published in international peer-reviewed journals.

The protocol of this IPD-MA has prospectively been registered on PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=299510).

Strengths and limitations of this study

- This is the first individual patient data (IPD) meta-analysis of treatment effects and their moderators among forcibly displaced people receiving psychological and psychosocial support.
- IPD, compared to aggregate data meta-analysis, will allow more complex analyses to identify moderators of treatment effects while standardisation of variables is facilitated, and missing values can be accounted for.
- This study can contribute important information towards identifying factors that affect treatment trajectories, attendance, drop-out, and adverse effects.
- IPD meta-analysis is limited by the availability of IPD and their quality.

Introduction

According to the United Nations High Commissioner for Refugees (UNHCR, 2023a), an unprecedented 108.4 million people worldwide have been forced to flee their homes at the end of 2022 as a result of persecution, conflict, violence, and other reasons. Due to a number of ongoing wars and, most recently, the conflict in Sudan, this number has eclipsed 110 million people for the first time (UNHCR, 2023b). Forcibly displaced people (FDP) are exposed to many stressors before, during, and after displacement (e.g., Drescher et al., 2021; Steel et al., 2009). Not surprisingly, FDP are at a high risk of developing mental disorders with estimates, for example, around 32% for post-traumatic stress (PTS) disorder (e.g., Blackmore et al., 2020; Patanè et al., 2022).

Due to the substantial personal suffering and the high economic costs of untreated mental health problems, it is crucial for hosting countries to provide adequate mental healthcare for FDP (Schick et al., 2016). Different treatment approaches have been taken to treat FDP including therapies delivered by specialists (e.g., cognitive behaviour therapy; CBT; Crumlish & O'Rourke, 2010), low-intensity interventions delivered by non-specialists (e.g., Problem Management Plus; PM+; Sijbrandij et al., 2020), and (un)guided self-help programs (e.g., Step-by-Step; SbS; Cuijpers et al., 2022). The task-sharing approach of scalable psychological interventions delivered by non-specialists seems to be a viable solution for settings which are burdened by a scarcity of specialised mental health services in low- and middle-income countries (Barbui et al., 2020; van Ginneken et al., 2021) or where adequate mental healthcare is hindered by language barriers and limited access to facilities in high-income countries (Lange, 2021). While several meta-analyses have shown different psychological interventions to effectively reduce PTS, there is a considerable heterogeneity among studies (e.g., Kip et al., 2020) which may be attributed to differences in characteristics related to beneficiaries, providers, intervention, and study design. However, factors contributing to this heterogeneity have not yet been explored.

Despite overall efficacy of existing interventions, beneficiaries with a forced displacement background compared to those without such a background benefit less from the same interventions (ter Heide & Smid, 2015), while a large proportion of FDP (up to 60%; e.g., ter Heide et al., 2016) *do not improve* following treatment, highlighting the necessity of further investigating factors contributing to individual differences in treatment outcome. Yet, relatively little is known about factors impacting individual differences in treatment trajectories of PTS in this population. The few studies that have made an attempt to explore this matter (e.g., Haagen et al., 2017) have been often limited by small sample sizes and thus lack the necessary statistical power to yield reliable findings.

Therefore, to explore treatment effects and their moderators, the present study aims to conduct an Individual Patient Data meta-analysis (IPD-MA), in which datasets from separate randomised-controlled trials (RCT) will be synthesised. IPD-MAs are considered the *gold standard* of statistical approaches when synthesising and analysing evidence from multiple studies (Broeze et al., 2010). By merging different IPD datasets with each other, a much larger sample size is reached than when looking at a single-study dataset, an advantage which allows for more complex analyses with statistical power and precision large enough to detect significant moderators of treatment effects and examine predictors of rare events such as adverse outcomes (Smith et al., 2011). In particular, we aim to *1)* investigate treatment effects and *2)* identify beneficiary, provider, intervention, and study characteristics that moderate treatment outcome with regard to PTS symptom reduction among adult FDP receiving psychological and psychosocial interventions compared to controls in the non-active treatment condition.

Methods and analysis

Eligibility criteria

We will include trials that *a)* used an RCT study design including *b)* adult (≥ 18 years) FDP (i.e., refugees, asylum seekers, or internally displaced persons, as defined by the UNHCR, 2022) receiving

c) psychological and psychosocial interventions (e.g., specific interventions such as CBT, low-intensity interventions such as PM+, or (un)guided self-help programs such as SbS) or *d)* a non-active control condition such as no treatment, waiting list, psychoeducation, or (enhanced) care-as-usual, and which *e)* assess PTS symptoms as outcome. Trials which included only a subsample of individuals with a forced-displacement background will be still included in this IPD-MA, if the target sample in the dataset can be identified.

Identification and selection of studies

We will conduct a systematic literature search in the databases MEDLINE, PsycINFO, PTSDpubs, Cochrane, and Embase using search terms related to the population (i.e., FDP), intervention (i.e., psychological and psychosocial interventions), mental health outcomes (i.e., general distress, PTS, depression, or anxiety), and study design (i.e., RCT). The search terms were identified through researchers and clinicians from the field; however, the target population was not consulted. Inclusion of studies will be restricted to the following languages: English, German, French, Spanish, Portuguese, and Dutch. Additionally, we will search the bibliographies and citations of 29 reviews and meta-analyses related to the topic. Their references, the detailed search syntax, and the full search strings of each database can be seen here: https://osf.io/cbw3q/?view_only=2c42dff3c25a440cbd5a833e29e35c0b. Before conducting any analyses, we will add the citations and bibliographies of all included articles to the screening process.

First, titles and abstracts of retrieved records will be screened independently by two raters to identify studies that potentially meet the inclusion criteria outlined above. Second, the full-texts of these potentially eligible studies will be retrieved and independently assessed for eligibility by the same raters. Any disagreement between raters will be resolved through discussion with a senior rater where necessary.

Data collection, extraction, and preparation

Authors of relevant trials identified in the selection process will be contacted to request anonymised data of their studies, i.e., IPD including, but not limited to, the following variables: beneficiaries' sociodemographic (e.g., education), migratory (e.g., time spent in host country), and clinical characteristics (e.g., trauma history) and providers' (e.g., degree of training), intervention (e.g., format), and study characteristics (e.g., study setting).

After gathering all primary datasets of the eligible studies, data accuracy will be checked by comparing the frequencies of sociodemographic and clinical variables, as well as their mean scores and standard deviations of continuous scales. Inconsistencies (e.g., extreme values or discrepancies between the reported values and the delivered data) will be discussed and clarified with the authors of the primary trials. After confirming the accuracy of each dataset, we will first synchronise variables of interest and then merge the data into one large IPD meta-analytic dataset. Finally, PTS outcome measures will be standardised by converting them to z-scores for each trial separately if multiple measures had been used for the same outcome (according to the procedure used by Karyotaki et al., 2015).

Quality assessment

The quality of included studies will be checked by two independent raters using the Revised Cochrane tool (RoB2.0) for assessing risk of bias in RCT (Sterne et al., 2019). This tool assesses several domains including bias from the randomisation process, deviations from intended interventions, and measurement of the outcome. Two bias categories, i.e., "bias from missing outcome data" and "selection from the reported result", will not be assessed with the RoB tool. Instead, multiple imputation will be used to account for missing outcome data. The bias category "selection of the reported result" is not applicable for IPD-MA as we will have access to the full datasets of all included studies. Each item will be evaluated regarding its risk resulting in a low or high risk of bias judgement per domain. Authors will be contacted in case of unclear items.

Statistical analysis

The primary outcome will be PTS symptoms assessed at post-intervention (PT) and follow-up (FU). Secondary outcomes will include positive mental health outcomes (e.g., well-being), psychopathology (e.g., depression), disability, functioning, and quality of life at PT and FU assessments, as well as adverse outcomes, attendance, and drop-out.

The analyses will be conducted according to the intention-to-treat principle, i.e., all randomised participants will be included in the analyses with the exception of resettlement as rationale for exclusion. Multiple imputation will be conducted using 100 imputations through the mvn method in STATA software, StataCorp, as recommended by Graham, Olchowski, and Gilreath (2007). To estimate the missing values, complete baseline variables will be used (e.g., PTS symptom levels at baseline, age, gender, etc.). To assess the difference between imputed and complete values we will conduct a sensitivity analysis using complete cases only. For the primary analyses, we will use the one-stage approach with IPD. Additionally, to compare effects of both type of trials, i.e., those that provided IPD and those that did not, a conventional aggregate data meta-analysis using a two-stage approach will be conducted. This is particularly advisable when a large proportion of authors did not share their datasets (Riley et al., 2007; Stewart & Tierney, 2002). Results from both the one- and two-stage approach will be compared and discrepancies will be discussed (Burke et al., 2017). Variables will be included as moderators in the analyses if they are represented by at least three studies.

One-stage approach: analysis of IPD (primary analyses). To investigate treatment effects of psychological and psychosocial interventions, we will perform a multilevel mixed-effects linear regression model with intervention condition (treatment vs. control) as the independent variable whilst controlling for trial and severity of PTS symptoms at baseline. The severity of PTS symptoms at PT and FU will be used as the dependent variable. To identify moderators of treatment effects, we will add an interaction between each potential moderator and PTS outcome into the multilevel

mixed-effects linear regression model. This procedure will be repeated for all aforementioned secondary outcome variables.

Two-stage approach: analysis of aggregate data (secondary analyses). First, we will calculate effect sizes for each trial separately and then compare them across studies by running conventional aggregate data meta-analyses including both, trials providing IPD and studies providing only meta-data, in order to examine potential discrepancies in results. Thus, we will run multivariate meta-analyses with standardised mean differences using a random-effects model accounting for differences in trials (Bartlett, 1937; Viechtbauer, 2010). In order to identify moderators of treatment effects, we will run several multiple linear regression models, including intervention condition and all potential moderators as independent variables and PTS symptom scores at PT and FU assessments as dependent variables for each trial separately. Subsequently, we will run several multivariate regression models with a random effect controlling for trial and standardised regression coefficients as dependent variables for each moderator separately. This procedure will be repeated for all secondary outcome variables mentioned above.

Heterogeneity (two-stage approach). To quantify variation among studies we will conduct analyses of heterogeneity by using Cochran's *Q*, prediction intervals, and I^2 statistic (Borenstein et al., 2009; Ioannidis et al., 2007; Vo et al., 2021). I^2 is a measure which quantifies the proportion of observed heterogeneity representing the difference between effects sizes that are not due to sampling error but to differences in, for example, the populations or measures that are studied. It ranges from 0-100% including increments of 0%, 25%, 50%, and 75%, indicating no, low, moderate, and high heterogeneity, respectively (Borenstein et al., 2009).

Publication bias. We will assess publication bias by creating "funnel plots" for a visual evaluation of asymmetry and applying the "trim and fill" method (Duval & Tweedie, 2000). Additionally, we will conduct an Egger's regression test to check whether this asymmetry is statistically significant (Egger, Smith, & Minder (1967).

Ethics and dissemination

We issued a clarification of responsibility for which the local ethic committee of the canton of Zurich, Switzerland, confirmed that this IPD-MA does not require ethical approval (Req-2022-00496). Only anonymised datasets will be requested from authors. With signing our data transfer agreement, authors warrant that the provided data had been legally obtained and all necessary consents for the transfer to and use by a third party had been secured. The results will be published in international peer-reviewed journals.

Discussion

Considering the rapidly growing number of FDP worldwide and their increased risk of developing mental disorders, immediate response from host countries with adequate mental healthcare is crucial to avoid high individual and societal costs. Exploring factors related to beneficiary, provider, intervention, and study characteristics, that moderate treatment effects may help inform who benefits most from which interventions, who needs additional care, clarify whether existing treatments need further improvement, and may guide the focus of future research and public health initiatives. To our knowledge, this is the first IPD-MA investigating treatment effects and their moderators among FDP.

Current status

The literature search, as well as the screening of titles and abstracts and the full-text review have been partially conducted for this IPD-MA. The systematic literature search in the aforementioned databases had been carried out on 12th January 2022 and will be updated prior to conducting the analyses.

Authors' contributions

All authors contributed to the design of the study. JK drafted the manuscript of this study protocol while AA, EK, PC, RR, NM, and MS were involved in revising the manuscript critically for intellectual content. All authors read and approved the final manuscript.

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Competing interests

The authors declare no conflict of interests.

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 5-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p. 6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 8-9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	p. 6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 7-8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 8-9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 8-9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 8-9
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p. 9

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	NA
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	NA
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	NA
	23b	Discuss any limitations of the evidence included in the review.	NA
	23c	Discuss any limitations of the review processes used.	NA
	23d	Discuss implications of the results for practice, policy, and future research.	NA
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

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

BMJ Open

What works for whom and why? Treatment effects and their moderators among forcibly displaced people receiving psychological and psychosocial interventions: study protocol for an individual patient data meta-analysis

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What works for whom and why? Treatment effects and their moderators among forcibly displaced people receiving psychological and psychosocial interventions: study protocol for an individual patient data meta-analysis

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Abstract

Introduction: Forcibly displaced people (FDP) have a high risk of developing mental disorders such as post-traumatic stress (PTS) disorder. Providing adequate mental healthcare for FDP is crucial but despite overall efficacy of many existing interventions, a large proportion of FDP does not benefit from treatment, highlighting the necessity of further investigating factors contributing to individual differences in treatment outcome. Yet, the few studies that have explored moderators of treatment effects are often insufficiently powered. Therefore, the present Individual Patient Data meta-analysis (IPD-MA) will investigate treatment effects and their moderators - variables related to beneficiaries, providers, intervention, and study characteristics in relation to PTS outcomes.

Methods and analysis: A systematic literature search will be conducted from database inception in the databases PsycINFO, Cochrane, Embase, PTSDpubs, and Web of Science. Only studies published in English, German, French, Spanish, Portuguese, and Dutch will be considered. Retrieved records will be screened for eligibility. Randomised controlled trials on adult FDP receiving psychological and psychosocial interventions aimed at alleviating symptoms such as PTS compared to a control condition without intervention will be included in this IPD-MA. Subsequently, authors of eligible studies will be contacted to request individual patient data (IPD). All datasets obtained will be synthesised into one large dataset which will be analysed using a one-stage approach by conducting mixed-effect linear regression models (i.e., primary analysis). Additionally, an aggregate data meta-analysis using a two-stage approach by conducting a multivariate regression model including all IPD (transformed) and available meta-data from study reports (i.e., secondary analysis). PTS will serve as primary outcome measure, while mental health outcomes other than PTS, attendance, attrition, treatment non-response, and adverse outcomes will be examined as secondary outcomes.

Ethics and dissemination: This IPD-MA does not require ethical approval. The results will be published in international peer-reviewed journals.

Study registration: PROSPERO, CRD42022299510.

Strengths and limitations of this study

- This individual data patient meta-analysis (IPD-MA), compared to traditional meta-analyses, will allow more complex analyses to identify moderators of treatment effects at patient-level while the standardisation of variables is facilitated, and missing values can be accounted for.
- By merging different datasets into one large dataset, this IPD-MA has the potential to investigate predictors of rare events such as adverse outcomes.
- This study can contribute important information towards identifying factors that affect treatment outcome, response, attendance, attrition, and adverse effects.
- IPD meta-analysis is limited by the availability of IPD and their quality.

INTRODUCTION

According to the United Nations High Commissioner for Refugees [1], an unprecedented 108.4 million people worldwide have been forced to flee their homes at the end of 2022 as a result of persecution, conflict, violence, and other reasons. Due to a number of ongoing wars and, most recently, the conflict in Sudan, this number has eclipsed 110 million people for the first time [2]. Forcibly displaced people (FDP) are exposed to many stressors before, during, and after displacement [3-4]. Not surprisingly, FDP are at a high risk of developing mental disorders with estimates, for example, around 32% for post-traumatic stress (PTS) disorder [5-6].

Due to the substantial personal suffering and the high economic costs of untreated mental health problems, it is crucial for hosting countries to provide adequate mental healthcare for FDP [7]. Different treatment approaches have been taken to treat FDP including therapies delivered by specialists (e.g., cognitive behaviour therapy; CBT; [8]), low-intensity interventions delivered by non-specialists (e.g., Problem Management Plus; PM+; [9]), and guided (e.g., Step-by-Step; SbS; [10]) or unguided self-help programs. The task-sharing approach of scalable psychological interventions delivered by non-specialists seems to be a viable solution for settings which are burdened by a scarcity of specialised mental health services in low- and middle-income countries [11] or where adequate mental healthcare is hindered by language barriers and limited access to facilities in high-income countries [12]. While several meta-analyses have shown different psychological interventions to effectively reduce PTS, there is a considerable heterogeneity among studies [13-14], some of which have been investigated and attributed to differences in study characteristics. For example, [15] found that treatment effects of narrative exposure therapy increase if the providers themselves have a displacement background. While randomised-controlled trials (RCT) and trials with an active control group seem to be associated with smaller treatment effects [16-17], findings with regard to treatment dose (i.e., number of sessions) tend to be mixed, with evidence for more sessions boosting the treatment effect [16-17] or having no impact [13]. However, many tested

moderators did not seem to influence treatment effects across studies including medication rate, time since displacement [13], residence status [18], use of interpreter [16], type of PTS assessment [16-17], study quality, country where trial was conducted, or ethnicity [17].

Despite many existing interventions showing overall efficacy, beneficiaries with a forced displacement background compared to those without such a background benefit less from the same interventions [19], while a large proportion of FDP (up to 60%; e.g., [20]) *do not improve* following treatment. A recent Individual Patient Data meta-analysis (IPD-MA) combining data from several PM+ trials found that although the intervention seemed to effectively reduce PTS among recipients overall, a third of them had persisting symptoms of hyperarousal [21]. These findings highlight the necessity of further investigating factors contributing to individual differences in treatment outcome. Yet, this matter has been explored by only a few studies [22] which were often limited by small sample sizes and thus lack the necessary statistical power to yield reliable findings. One IPD-MA on PM+ and SbS trials which is currently carried out (see [23], for the study protocol) will hopefully shed light on moderators influencing treatment effects of such low-threshold interventions. However, results will be limited to PM+ and SbS trials only.

To paint a more complete picture, the present study aims to conduct an IPD-MA, in which datasets from separate RCTs including both psychological and psychosocial interventions will be synthesised. IPD-MAs are considered the *gold standard* of statistical approaches when synthesising and analysing evidence from multiple studies [24]. By merging different IPD datasets with each other, a much larger sample size is reached than when looking at a single-study dataset, an advantage which allows for more complex analyses with statistical power and precision large enough to detect significant moderators of treatment effects and examine predictors of rare events such as adverse outcomes [25]. Additionally, the use of an IPD-MA will allow us to shed light also on moderators of treatment effects at client-level, something previous traditional meta-analyses using reported meta-data could not address as they are restricted to moderators at study-level [26].

Moreover, by including trials using specialised and low-threshold interventions we will be able to examine whether interventions delivered by specialists and non-specialists differ in terms of treatment effects and moderators thereof. Specifically, for this IPD-MA we aim to: *1)* investigate treatment effects; *2)* identify beneficiary, provider, intervention, and study characteristics that moderate treatment outcome with regard to PTS symptom reduction among adult FDP receiving psychological and psychosocial interventions compared to controls receiving no intervention; and *3)* extend the latter analysis to secondary outcomes including mental health outcomes other than PTS, non-response, attendance, attrition, and adverse outcomes (see section "statistical analysis" for more details).

METHODS AND ANALYSIS

Eligibility criteria

We will include trials that *a)* used an RCT study design including *b)* adult (≥ 18 years) FDP (i.e., refugees, asylum seekers, or internally displaced persons, as defined by the [27]) receiving *c)* psychological and psychosocial interventions (e.g., specific interventions such as CBT, low-intensity interventions such as PM+, or guided (e.g., SbS) or unguided self-help programs) or *d)* a control condition without intervention (i.e., no treatment, waiting-list, or case-as-usual), and which *e)* assess PTS symptoms as outcome. Trials which included only a subsample of individuals with a forced-displacement background will be still included in this IPD-MA, if the target sample in the dataset can be identified.

Identification and selection of studies

We conducted a systematic literature search in the databases MEDLINE, PsycINFO, PTSDpubs, Cochrane, and Embase using search terms related to the population (i.e., FDP), intervention (i.e., psychological and psychosocial interventions), mental health outcomes (i.e., general distress, PTS, depression, or anxiety), and study design (i.e., RCT). The search terms were identified through

researchers and clinicians from the field; however, the target population was not consulted. The time range was not specified. Inclusion of studies were restricted to the following languages: English, German, French, Spanish, Portuguese, and Dutch. Additionally, we searched the bibliographies and citations of 29 reviews and meta-analyses related to the topic. This search for relevant records provided by newly published reviews and meta-analytic work will be repeated before conducting the analyses. Their references, the detailed search syntax, and the full search strings of each database can be seen here: https://osf.io/cbw3q/?view_only=2c42dff3c25a440cbd5a833e29e35c0b. The full search strategy is included in the **supplementary file**. Before conducting any analyses, we will add the citations and bibliographies of all included articles to the screening process.

First, titles and abstracts of retrieved records will be screened independently by two raters to identify studies that potentially meet the inclusion criteria outlined above. Second, the full-texts of these potentially eligible studies will be retrieved and independently assessed for eligibility by the same raters. Any disagreement between raters will be resolved through discussion with a senior rater where necessary. Retrieved records will be evaluated throughout the review process with the software COVIDENCE (https://www.covidence.org/).

Data collection, extraction, and preparation

Authors of relevant trials identified in the selection process will be contacted to request anonymised data of their studies, i.e., IPD including, but not limited to, the following variables: beneficiaries' sociodemographic (e.g., education), migratory (e.g., time spent in host country), and clinical characteristics (e.g., trauma history) and providers' (e.g., degree of training), intervention (e.g., format), and study characteristics (e.g., study setting). According to [28], the success to obtain IPD from authors is moderator (i.e., 58% success rate). In order to incentivise authors to share their data, we will offer two co-authorships per trial and contact all authors of each article at least three times, as suggested by [29].

After gathering all primary datasets of the eligible studies, automated data quality checks for IPD will be run and data accuracy will be checked by comparing the frequencies of sociodemographic and clinical variables, as well as their mean scores and standard deviations of continuous scales. Inconsistencies (e.g., extreme values or discrepancies between the reported values and the delivered data) will be discussed and clarified with the authors of the primary trials. After confirming the accuracy of each dataset, we will first synchronise variables of interest to the same scale or categorical order and then merge the data into one large IPD meta-analytic dataset. If variables were assessed by several measures, the method with the highest quality standard will be selected (e.g., clinical interviews will be favoured over self-report measures). Finally, outcome measures will be standardised by converting them to z-scores for each trial separately if multiple measures had been used for the same outcome (according to the procedure used by [30]).

Quality assessment

The quality of included studies will be checked by two independent raters using the Revised Cochrane tool (RoB2.0) for assessing risk of bias in RCT [31]. This tool assesses several domains including bias from the randomisation process, deviations from intended interventions, and measurement of the outcome. Two bias categories, i.e., “bias from missing outcome data” and “selection from the reported result”, will not be assessed with the RoB tool. Instead, multiple imputation will be used to account for missing outcome data. The bias category “selection of the reported result” is not applicable for IPD-MA as we will have access to the full datasets of all included studies. Each item will be evaluated regarding its risk resulting in a low or high risk of bias judgement per domain. Authors will be contacted in case of unclear items.

Statistical analysis

As PTSD is the most prevalent mental disorder in FDP [5], the primary outcome will be PTS symptoms assessed at post-intervention (PT; i.e., immediately after treatment) and follow-up (FU; at any later time). However, in order to paint a more complete picture, we will run analyses with

secondary outcomes including positive mental health outcomes (e.g., well-being), psychopathology (e.g., depression), disability, functioning, and quality of life at PT and FU assessments, as well as adverse outcomes, attendance, attrition, and treatment non-response. Moderator variables at client-level will depend on available IPD provided by the authors and will be included as moderators in the analyses if they are represented by at least three studies. Moderator variables at study-level will be extracted from the published manuscript and will consist of variables such as region where study was conducted (i.e., low-/middle-income vs. high-income countries), time of assessments, and quality of study (assessed in the risk of bias quality assessment). In order to examine differences in treatment effects, we will include type of intervention (i.e., low-threshold interventions vs. specialised therapy) as a moderator in the analyses. Before running any main analyses (see below), we will first test all assumptions necessary for linear regression models using DHARMa (https://cran.r-project.org/web/packages/DHARMa/vignettes/DHARMa.html).

The analyses will be conducted according to the intention-to-treat principle, i.e., all randomised participants will be included in the analyses regardless of rationale for exclusion. Multiple imputation per trial will be conducted using 100 imputations through the mvn method in STATA software, StataCorp, as recommended by [32]. To estimate the missing values, complete baseline variables will be used (e.g., PTS symptom levels at baseline, age, gender, etc.). To assess the difference between imputed and complete values we will conduct a sensitivity analysis using complete cases only. For the primary analyses, we will use the one-stage approach with IPD. Additionally, to compare effects of both type of trials, i.e., those that provided IPD and those that did not, an aggregate data meta-analysis using a two-stage approach including all IPD (transformed) and available meta-data from study reports will be conducted. This is particularly advisable when a large proportion of authors did not share their datasets [33-34]. Results from both the one- and two-stage approach will be compared and discrepancies will be discussed [35]. As we will run several analyses with different outcome variables, we will correct for multiple testing (i.e., Bonferroni adjusted p-values) for analyses including secondary outcome variables. Analyses of the one-stage

approach will be conducted using the STATA software, while all analyses of the two-stage approach and assumptions tests will be performed using the statistical program R (https://www.r-project.org/).

One-stage approach: analysis of IPD (primary analyses)

To investigate treatment effects of psychological and psychosocial interventions, we will perform a multilevel mixed-effects linear regression model with a random effect for each trial and fixed effects for intervention condition (treatment vs. control) and severity of PTS symptoms at baseline. The severity of PTS symptoms at PT and FU will be used as the dependent variable. To identify moderators of treatment effects, we will add an interaction between each potential moderator and PTS outcome into the multilevel mixed-effects linear regression model. This procedure will be repeated for all aforementioned secondary outcome variables.

Two-stage approach: analysis of aggregate data (secondary analyses)

First, we will calculate effect sizes for each trial separately and then compare them across studies by running aggregate data meta-analyses including both, trials providing IPD and studies providing only meta-data, in order to examine potential discrepancies in results. Thus, we will run multivariate meta-analyses with standardised mean differences (i.e., Hedges *g;* [36]) using a random-effects model estimated by restricted maximum likelihood accounting for differences in trials [37-38]. In order to identify moderators of treatment effects, we will first run several multiple linear regression models, including all potential moderators as independent variables and change in PTS symptom scores from baseline to PT and FU assessments as dependent variables for each trial separately. The obtained standardised regression coefficients will then be used as dependent variables when running several multivariate regression models with a random effect controlling for trial for each moderator separately. This procedure will be repeated for all secondary outcome variables mentioned above.

Heterogeneity (two-stage approach)

To quantify variation among studies we will conduct analyses of heterogeneity by using Cochran's *Q*, prediction intervals, and I^2 statistic [39-41]. I^2 is a measure which quantifies the proportion of observed heterogeneity representing the difference between effects sizes that are not due to sampling error but to differences in, for example, the populations or measures that are studied. It ranges from 0-100% including increments of 0%, 25%, 50%, and 75%, indicating no, low, moderate, and high heterogeneity, respectively [39].

Publication bias (two-stage approach)

We will assess publication bias by creating "contour-enhanced funnel plots" for a visual evaluation of asymmetry [42] and applying the "trim and fill" method [43].

Certainty of evidence

To evaluate the confidence in evidence we will apply the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology for the primary outcome measure [44].

Patient and public involvement

None.

ETHICS AND DISSEMINATION

We issued a clarification of responsibility for which the local ethic committee of the canton of Zurich, Switzerland, confirmed that this IPD-MA does not require ethical approval (Req-2022-00496). Only anonymised datasets will be requested from authors. With signing our data transfer agreement, authors warrant that the provided data had been legally obtained and all necessary consents for the transfer to and use by a third party had been secured. The results will be published in international peer-reviewed journals.

Current status

The literature search, as well as the screening of titles and abstracts and the full-text review have been partially conducted for this IPD-MA. The systematic literature search in the aforementioned databases had been carried out on 12th January 2022 and will be updated prior to conducting the analyses. This project is expected to be completed by December 2025.

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Contributors

All authors contributed to the design of the study. JK drafted the manuscript of this study protocol while AA, EK, PC, RB, NM, and MS were involved in revising the manuscript critically for intellectual content. All authors read and approved the final manuscript. NM holds the role of the guarantor.

Competing interests

The authors declare no competing interests.

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POTENTIAL project - Full search strategy

We conducted a systematic literature search in the databases MEDLINE, PsycINFO, PTSDpubs, Cochrane, and Embase using search terms related to the population (i.e., FDP), intervention (i.e., psychological and psychosocial interventions), mental health outcomes (i.e., general distress, PTS, depression, or anxiety), and study design (i.e., RCT). The search terms were identified through researchers and clinicians from the field; however, the target population was not consulted. The time range was not specified, the start date therefore depended on the inception of the databases. Inclusion of studies were restricted to the following languages: English, German, French, Spanish, Portuguese, and Dutch. Additionally, we searched the bibliographies and citations of 29 reviews and meta-analyses related to the topic. This search for relevant records provided by newly published reviews and meta-analytic work will be repeated before conducting the analyses. Before conducting any analyses, we will add the citations and bibliographies of all included articles to the screening process.

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Search strings

- Embase
  Advanced search - ALL FIELDS:
  (refugee OR 'asylum seeker*' OR 'forcibly displaced' OR 'forced displacement' OR 'internally displaced' OR 'civilian war survivor*' OR 'civilian survivor*' OR 'civilian war victim*') AND (treatment* OR intervention* OR therap* OR psychother* OR counsel* OR behavio* OR psycholog* OR psychosoci* OR program* OR low) AND (pts OR 'post-traumatic stress' OR ptsd OR 'post-traumatic stress disorder' OR 'post-traumatic symptom*' OR 'mental health' OR 'mental illness' OR 'mental disorder' OR 'mental distress' OR 'emotion* distress' OR 'psycho* distress' OR*

anxiety OR depression OR mdd) AND (rct OR random OR trial* OR controlled OR allocat* OR assign*)*

- Cochrane
  Advanced search – Title Abstract Keywords:
  (refugee OR "asylum seeker*" OR "forcibly displaced" OR "forced displacement" OR "internally displaced" OR "civilian war survivor*" OR "civilian survivor*" OR "civilian war victim*") AND (treatment* OR intervention* OR therap* OR psychother* OR counsel* OR behavio* OR psycholog* OR psychosoci* OR program* OR low) AND (PTS OR "post-traumatic stress" OR PTSD OR "post-traumatic stress disorder" OR "post-traumatic symptom*" OR "mental health" OR "mental illness" OR "mental disorder" OR "mental distress" OR "emotion* distress" OR "psycho* distress" OR anxiety OR depression OR MDD) AND (RCT OR random* OR trial* OR controlled OR allocat* OR assign*)*
- PTSDpubs
  Advanced search – Anywhere:
  (refugee OR "asylum seeker*" OR "forcibly displaced" OR "forced displacement" OR "internally displaced" OR "civilian war survivor*" OR "civilian survivor*" OR "civilian war victim*") AND (treatment* OR intervention* OR therap* OR psychother* OR counsel* OR behavio* OR psycholog* OR psychosoci* OR program* OR low) AND (PTS OR "post-traumatic stress" OR PTSD OR "post-traumatic stress disorder" OR "post-traumatic symptom*" OR "mental health" OR "mental illness" OR "mental disorder" OR "mental distress" OR "emotion* distress" OR "psycho* distress" OR anxiety OR depression OR MDD) AND (RCT OR random* OR trial* OR controlled OR allocat* OR assign*)*
- Medline
  Advanced search - Select a field (optional):
  (refugee OR "asylum seeker*" OR "forcibly displaced" OR "forced displacement" OR "internally displaced" OR "civilian war survivor*" OR "civilian survivor*" OR "civilian war victim*") AND (treatment* OR intervention* OR therap* OR psychother* OR counsel* OR behavio* OR psycholog* OR psychosoci* OR program* OR low) AND (PTS OR "post-traumatic stress" OR*
  PTSD OR "post-traumatic stress disorder" OR "post-traumatic symptom" OR "mental health" OR "mental illness" OR "mental disorder" OR "mental distress" OR "emotion* distress" OR "psycho* distress" OR anxiety OR depression OR MDD) AND (RCT OR random* OR trial* OR controlled OR allocat* OR assign*)*
- PsycINFO
  Advanced search - Select a field (optional):
  (refugee OR "asylum seeker*" OR "forcibly displaced" OR "forced displacement" OR "internally displaced" OR "civilian war survivor*" OR "civilian survivor*" OR "civilian war victim*") AND (treatment* OR intervention* OR therap* OR psychother* OR counsel* OR behavio* OR psycholog* OR psychosoci* OR program* OR low) AND (PTS OR "post-traumatic stress" OR PTSD OR "post-traumatic stress disorder" OR "post-traumatic symptom*" OR "mental health" OR "mental illness" OR "mental disorder" OR "mental distress" OR "emotion* distress" OR "psycho* distress" OR anxiety OR depression OR MDD) AND (RCT OR random* OR trial* OR controlled OR allocat* OR assign*)*

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review => report is identified as a protocol of an individual patient data meta-analyses, see p. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such => NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number => see line 25
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author => see p. 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review => see lines 240-243
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments => NA
Support:		
Sources	5a	Indicate sources of financial or other support for the review => see lines 236-239
Sponsor	5b	Provide name for the review funder and/or sponsor => see lines 236-239
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol => see lines 240-243
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known => see lines 38-76
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) => see lines 89-95
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review => see lines 100-107
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage => see lines 109-121
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated => see lines 119-121
Study records:		

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review => see lines 126-127 / 137-147
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) => see lines 122-127
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators => see lines 129-136
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications => see lines 129-133 / 166-169
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale => see lines 159-164
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis => see lines 149-157 / 166-169
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised => see lines 164-166
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) => see lines 211-216
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) => see lines 195-198 / 199-210
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned => NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) => see lines 217-219
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) => see lines 220-222

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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