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TITLE OF THE DOCTORAL THESIS

THE RE-DEFINE PROJECT AND THE EFFECTIVENESS OF SH+ IN PREVENTING MENTAL DISORDERS IN REFUGEES AND ASYLUM SEEKERS RESETTLED IN EUROPE: A MULTICENTRE RANDOMISED CONTROLLED TRIAL

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SUMMARY

Background: The RE-DEFINE project aims to provide effective community-based health care implementation strategies to scale-up the delivery and uptake of psychosocial interventions for preventing the onset of mental disorders in refugees and asylum seekers (RAS) resettled in middle-income and in high-income countries (HICs). Self Help Plus (SH+) is a group-based psychosocial intervention developed by the World Health Organization for managing psychological distress in conditions of adversity. RE-DEFINE aimed to assess the effectiveness of SH+ in preventing the development of mental disorders in RAS resettled in Europe.

Methods: A randomized controlled trial was conducted at six sites in five European countries. Participants were adult asylum seekers and refugees with psychological distress (General Health Questionnaire ≥ 3), but without a formal psychiatric diagnosis as assessed with the Mini International Neuropsychiatric Interview (M.I.N.I.). The intervention comprised five group-based audio-recorded sessions on stress management, complemented with an illustrated book. Sessions were led by peer-facilitators receiving appropriate training. Participants were randomized to either SH+ or treatment as usual (TAU) on a 1:1 basis. The frequency of any mental disorder was measured with the M.I.N.I. at post-intervention (secondary outcome) and six months after start of the intervention (primary outcome) in the intention-to-treat population. Secondary outcomes also included self-identified problems, symptoms of depression and post-traumatic stress disorder, functional impairment, quality of life, and subjective wellbeing at post-intervention and at six-month follow-up. Assessors were masked to allocation.

Findings: Of 1475 individuals assessed for eligibility, 459 were included in the trial and randomly assigned to SH+ or TAU. Compared with controls, we found lower incidence of any mental disorders at post-intervention for SH+ (Cramer's V 0.13, p= 0.01, Risk Ratio (RR) 0.50, 95% Confidence Interval (CI) 0.29 to 0.87), but not at follow-up (Cramer's V 0.007, p= 0.90, RR 0.96, 95% CI 0.52 to 1.78). We also found statistically significant improvements for SH+ for four out of six secondary outcomes at post-intervention, and for the outcome wellbeing at six-month follow-up. Eight adverse events were reported, none of which was considered to be associated with the intervention.

Interpretation: This is the first study showing that it is possible to prevent the development of mental disorders in asylum seekers and refugees resettled in HICs. As the preventative effect was observed at post-intervention only, modalities to maintain the beneficial effect of SH+ in the long-term need to be identified. SH+ may be safely offered as a public health indicated prevention strategy to RAS resettled in HICs.

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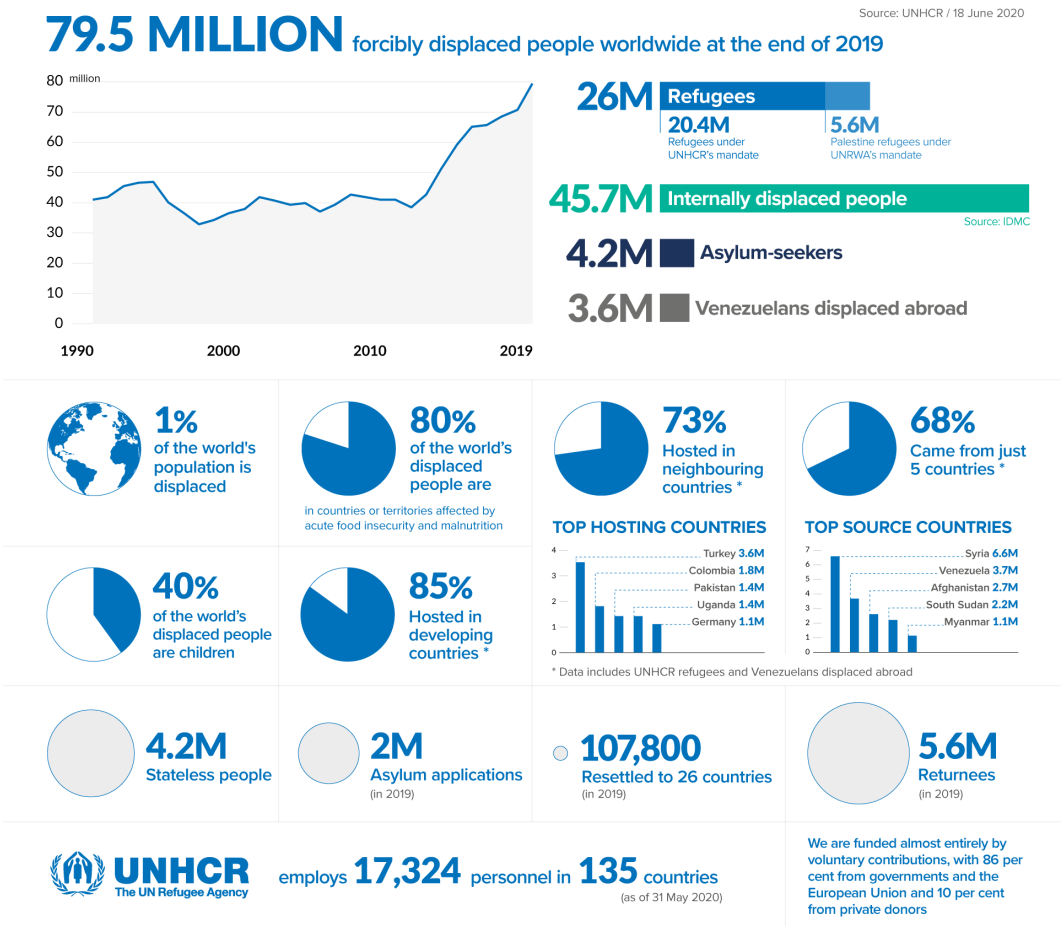
1. BACKGROUND

1.1 Refugees and asylum seekers in Europe and in bordering countries

Worldwide, around 79.5 million people are forcibly displaced from their country of origin, including 26 million refugees, and over 4.2 million awaiting resolution of their asylum application.[1] These are the highest numbers since World War II. The number of people seeking refugee status has progressively increased in the last years, driven by the wars in Syria and Iraq, alongside conflicts and instability in Afghanistan, Eritrea, Somalia and elsewhere (Figure 1, Table I).[2 3]

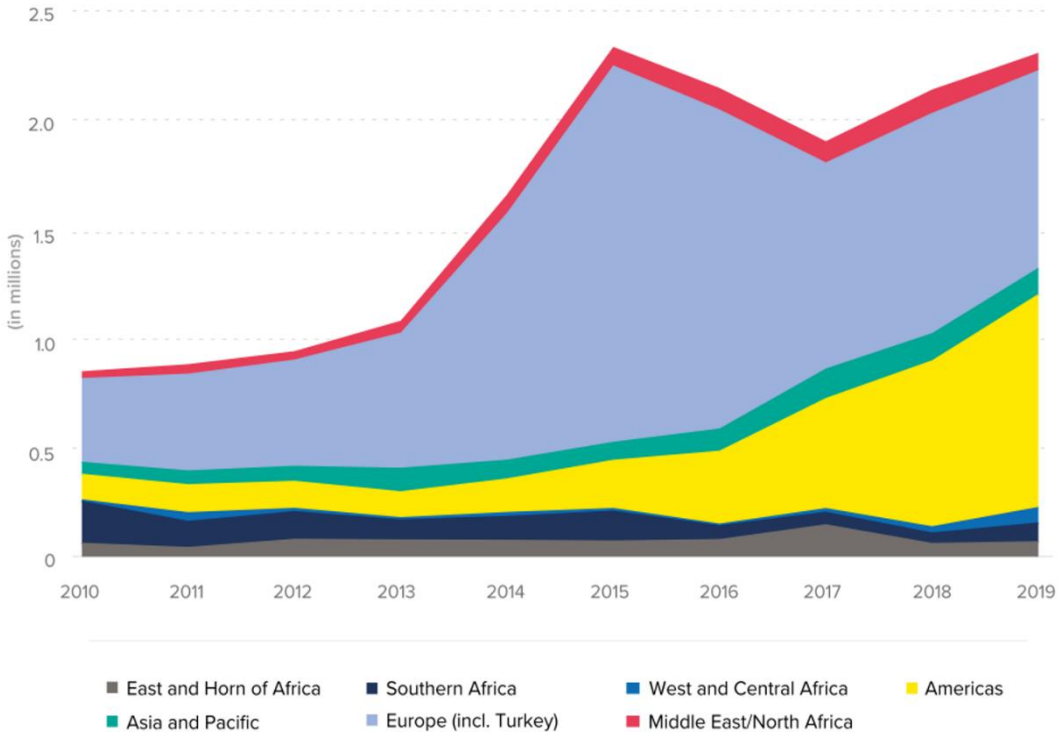
Figure 1. UNHCR data on refugees and asylum seekers (updated June 2020).



In the last decade, Europe registered 9.2 million asylum claims (Figure 2). Analysis of asylum trends highlighted a spike in the number of new asylum seekers in 2014, largely because of the outbreak of conflict in eastern Ukraine. It experienced another spike in new asylum requests in 2015. As the war in Syria intensified and

conflicts in Iraq and Afghanistan worsened, an increasing number of people risked their lives to cross the Mediterranean Sea in search of safety and protection. More than one million people arrived in Europe by boat – the vast majority from these three refugee-producing countries. More than 1.5 million new asylum claims were lodged in the major European destination countries, including Germany and Sweden. Arrivals in Cyprus, Greece, Malta, Italy and Spain continued in subsequent years, standing at about 200,000 between 2017 and 2019.

Figure 2. UNHCR data on asylum applications registered by regions, updated to 2019.



The number of asylum applications registered in the European Union (EU) then dropped by 43% in march 2020 as compared to February 2020, as asylum systems slowed or came to a halt with countries closing borders or implementing strict border restrictions in response to COVID-19.[3] The 2019 coronavirus pandemic (SARS-CoV2) exacerbated the already difficult living conditions in the hosting countries, with physical sequelae of the spread viral infection, and higher levels of marginalization, poverty, stigma, and mental health problems.[4] Healthcare systems are being overwhelmed by the management of the SARS-CoV2 pandemic, and this disproportionally impacts the most vulnerable population groups.[5 6] The refugee

crisis imposes highly challenging demands on health systems in Europe and bordering countries. Some European countries (i.e., Italy, Austria, Germany, Finland, and the UK) already have very limited specialised mental health care services for refugees and asylum seekers (RAS). In other bordering countries, such as Turkey, the mental health services required to meet the psychological needs of millions of RAS are inadequate or insufficient, and their health systems are overburdened to meet basic survival needs and more chronic health problems.[7 8] The provision of services to address the psychological conditions of millions of RAS is often conducted by non- government organisations (NGOs) and coordinated by international organisations, including the World Health Organization (WHO), the United Nations High Commissioner of Refugees (UNHCR), and the International Federation of Red Cross and Red Crescent Societies. An effective, evidence-based response from health systems in countries inside and outside Europe is still incomplete and therefore an urgent issue.

Table I. Definition of asylum seeker, refugee, and economic migrant.

An **asylum seeker**, defined according to the 1951 United Nations convention, is a person who has fled his/her own country and formally applies to the government of another country for asylum but the application has not yet been concluded; they remain asylum-seekers while they are awaiting a decision on their application for refugee status. People move from asylum seeker status to **refugee** status once the country they have applied for asylum in accepts their claim. **Economic migrants** are defined as "people that move from one country to another to advance their economic and professional prospects". Economic migrants are a different population not included in the RAS definition. The government's definition of RAS is adopted also in the international scientific literature in this field.

1.2 Mental health of refugees and asylum seekers

RAS often endure great physical and mental challenges either before or during displacement, and suffer continuing hardships after arrival in a High-Income Country (HIC).[9] RAS may be exposed to a constellation of stressors (i.e., poverty, violence, persecution, armed conflict, resettlement stressors) causing them to be much more vulnerable than the general population to some common mental health

conditions (post-traumatic stress disorder, anxiety, depression and other forms of disabling psychological distress).[10 11]

RAS have complex health needs, and many of them experience trauma before and during their deleterious journey.[12 13] Furthermore, they may face the effects of continued disadvantage, poverty and dependence in their new country, which are determinants of both poor physical and mental health. This is compounded by difficulty/lack of communication due to language barriers, unfamiliarity with the local environment and healthcare systems, and cultural differences.[14] These have consequences for provision of various services, including access to healthcare and a requirement for comprehensive screening and cohesive medical support systems.[15]

A recent literature review on physical and mental health of refugees showed that infectious diseases requiring treatment in refugees are a minority; whilst non-communicable diseases and musculoskeletal conditions are prevalent. Many refugees arrive with complex health needs. 1 out of 6 refugees have a physical health problem severely affecting their lives and 2 out of 3 experience mental health problems.[16]

A systematic review and meta-analysis comparing the prevalence of depression and anxiety in labor migrants and refugees shows that the combined prevalence rates for depression are 20% among labor migrants vs 44% among refugees; for anxiety, the combined estimates are 21% among labor migrants vs 40% among refugees.[17] These results highlight the primary importance of assessing mental health conditions of RAS, not only in specialized contexts, but also at a screening level.[18] Mental health conditions that affect this specific population can be divided into three categories: relapse of pre-existing psychiatric symptoms; development of new psychological-psychiatric problems caused by violence and trauma in the country of origin or during the migration progress; issues connected with adjustment and coping with the adversities after migration to the host country.

Recent research studies[19] have shown substantial variability in the prevalence of mental disorders (such as Psychotic Disorders, Mood and Anxiety Disorders, Substance Use Disorders) among RAS. For refugees only, data suggest that, in general, the prevalence of mental disorders is not substantially higher than the

overall prevalence in host populations. An exception is PTSD, which is more frequent in RAS than in host populations.

The prevalence of PTSD in refugees is higher than estimates for host country populations (9% vs 1-3%).[10 20] There is evidence that the prevalence of PTSD is even higher in refugees who have been exposed to potentially traumatic experiences, in child and adolescent refugees and in asylum seekers. Also, comorbidity of PTSD and depression is common: some studies report that as many as 40% of refugees with PTSD also have clinical depression.[10]

Risk factors for mental disorders may be experienced before migration (pre-migration), during migration (peri-migration) and/or after resettlement in the host country (post-migration) (Table II).[21]

Table II. Risk factors for mental disorders in RAS.

Pre-migration risk factors	
Persecution for political, ethnical, religious reasons	*Torture, imprisonment, witnessing death of family members, violation of human rights*
Exposure to armed conflicts	*Witnessing destruction and death, torture, direct combat involvement*
Extreme economic hardships	*Lack of food, water, shelter and other basic needs and resources*
Peri-migration risk factors	
Physical harm (including sexual violence)	*Infectious diseases*
Extortion	*Human trafficking*
Life-threatening conditions while migrating (by boat, train, trucks, on foot)	*Separation from family members and support networks*
Post-migration risk factors	
Uncertainty about the asylum application	*Asylum seekers who have been in a host country for longer are more likely to have a number of mental health issues, including symptoms of PTSD, depression and anxiety, compared with those who have arrived more recently*

Detention	*The damaging effects of detention include PTSD, anxiety, depression and suicidal ideation, as well as suicide.*
Reduced social integration and economic hardships	*In refugees resettled for more than 5 years in a country, a poor post migratory socioeconomic situation was associated with a higher likelihood of depression. While unemployment is in itself a risk factor for mental disorders, it may also hinder full integration into the new environment.*

1.3 Preventive psychosocial interventions

Interventions to treat mental health problems exist, and there is a growing body of research proving effectiveness of such interventions for the RAS population.[19 22] This body of research has been summarised in evidence-based guidelines and packages developed to assist professionals and policy makers working in the field of mental health and in emergencies. The international WHO mental health Gap Action Programme (mhGAP) is an example of scientific initiative that translated research results into evidence-based integrated packages for treating mental, neurological, and substance abuse disorders in Low- and Middle-Income Countries (LMICs).[23] However, the focus of mhGAP is on treatment strategies for those who already developed a mental disorder in LMICs, while preventive interventions for those who are at risk of developing mental health problems were not addressed and mhGAP does not focus on high-income settings. Although there are possible exceptions,[24] preventive psychosocial interventions in HIC are often neither evidence-based nor of high quality nor very suitable for RAS.

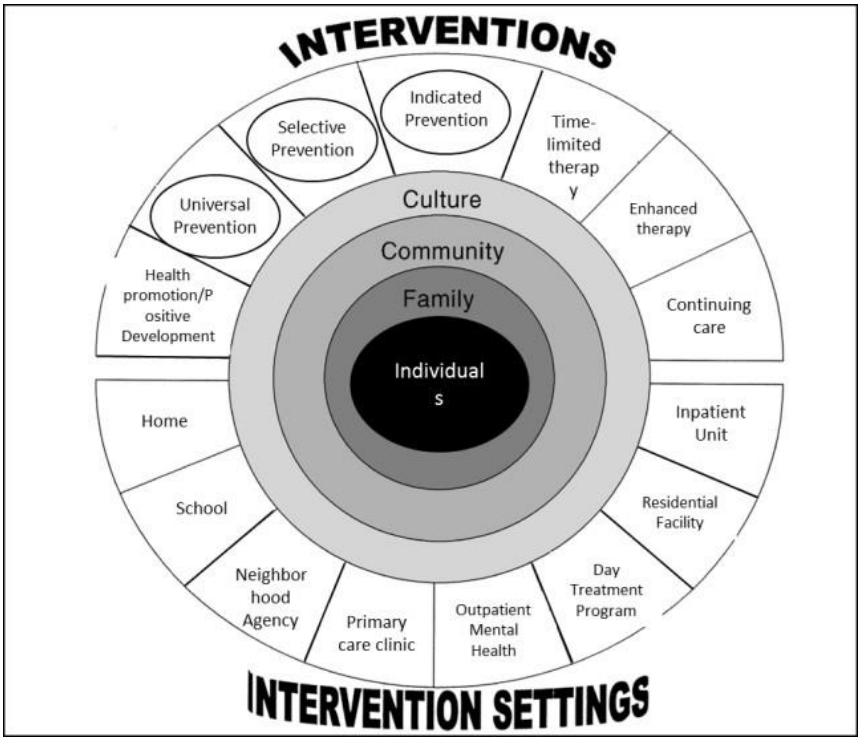
Services for RAS in European mental healthcare systems vary in capacity. This is in part due to the lack of available professionals, which limits the availability of specialised mental health services available for RAS. In some cases, such services may be delivered by highly trained professionals, involving anti-depressants, Cognitive Behavioural Therapy (CBT) and Interpersonal Psychotherapy (IPT) for depression, or CBT, Narrative Exposure Therapy or Eye Movement Desensitization and Reprocessing (EMDR) for Post-Traumatic Stress Disorder (PTSD). However, even though effective:

1. these approaches rely on professionals, which are a scare resource;
2. these interventions have often been developed according to the needs of Western populations, and intervention protocols usually need to be culturally adapted;[25]
3. These interventions are aimed at treating mental disorders but are not focused on preventing mental health conditions in distressed RAS exposed to a constellation of stressors.

According to a public mental health approach, preventive interventions may be categorised as follows (Figure 3):

- universal prevention: targeting the general public or a whole population group;
- selective prevention: targeting individuals or specific subgroups of the population whose risk of developing a mental disorder is significantly higher than that of the rest of the population;
- indicated prevention: targeting smaller groups of the population at high-risk of mental disorders (i.e., already presenting some symptoms of mental disorders).[26]

Figure 3. Mental health interventions and settings according to the public health approach.



In order to help large numbers of RAS, urgent transformations of health systems are required to adequately scale-up evidence-based preventive psychosocial interventions in ways that are feasible (i.e., practical and affordable), sustainable and cost-effective. This transformation has the potential of addressing individual quality of life and health of RAS, enhancing protective underlying mechanisms, and decreasing suffering. One important element of such a transformation is the inclusion of guided self-help approaches in routine care,[27] which have been shown

to be as effective as face to face psychological therapy in people with depression. This may have particular advantages for RAS, given the lack of services for these groups, the high level of need and that they can be delivered by non-professionals. Simultaneously, it would be beneficial for the scientific and clinical community as a whole, by reducing health costs and preventing an unprecedented social drift associated with mental health conditions.

Increasing the responsiveness of health systems for vulnerable populations in countries inside and outside Europe will meet the demands imposed by the current refugee crisis. However, it will additionally be of paramount relevance to human rights, health equity, and accessibility to high quality mental health services. Even though huge efforts have been made to address global inequities in health care for somatic conditions,[28] a similar effort for psychological distress and mental health conditions is still trailing behind. RAS populations are underrepresented in the mental health care systems and have been known to underutilize the care services because of barriers. Access to care is important for the promotion of mental well-being and for the prevention of mental illness. Starting from the premise that there can be "no health without mental health",[29] a health system cannot function properly if it is unable to protect and take care of the health rights and needs of the sick and vulnerable populations, including those who are mentally ill.

Worldwide, a large mental health treatment gap exists between the prevalence of mental health problems and the percentage of individuals receiving adequate preventive and treatment interventions.[23] It has been estimated that only one third of people suffering from mental conditions are treated in high-resource countries, and that as few as 2% of people with such conditions are treated in some middle-income countries.[30] There is now general consensus that improved access to mental health care is necessary for people suffering from these conditions. One of the reasons why mental healthcare interventions may not be accessed is that in many countries - including all too often European countries - the majority of services are offered in tertiary institutions such as psychiatric hospitals, whereas coverage would greatly increase if they were offered in decentralized locations, integrated in primary or community care.[31]

1.3.1 Evidence-based psychosocial interventions

Low-intensity interventions generally utilise fewer resources than more complex conventional psychosocial treatments, as they may be delivered by workers without a formal mental health professional training. They may use health technology, as video/audio tapes. Systematic and non-systematic reviews have shown that psychological interventions for PTSD, depression and/or anxiety are more effective than control conditions, suggesting that the use of psychological interventions is an effective strategy for treating people with an established diagnosis of common mental disorders (Table III).

REVIEW	TYPE OF REVIEW	TARGET GROUPS	FOCUS
Turrini et al. 2019	Systematic Review and Meta-analysis	Adult refugees or asylum	Evidence on psychosocial interventions
Thompson et al. 2018	Systematic Review and Meta-analysis	seekers resettled in high income countries	Evidence on psychosocial interventions
Crumlish & O' Rourke, 2010	Systematic Review	Adult and children refugees or asylum seekers resettled in low or high-income countries	Treatment for PTSD in refugees
McFarlane & Kaplan, 2012	A 30-year review 1980-2010	Adult survivors of torture and trauma	Evidence on psychosocial interventions
Nikerson et al. 2010	Systematic Review	Adult refugees resettled in low, middle and high-income countries	Evidence on trauma-focused and multimodal interventions for PTSD
Nosè et al., 2017	Systematic Review and Meta-analysis	Adult refugees or asylum seekers resettled in high income countries	Psychosocial interventions for PTSD
Palic & Elklit, 2010	Systematic Review	Adult refugees, low- and middle-income	Psychosocial treatment for PTSD
Patel et al., 2014	Systematic Review	Adult and children torture survivors	Psychological, social and welfare interventions

Robjant & Fazel, 2010	Review	Adult and children refugees or asylum seekers resettled in low, middle and high-income countries	Evidence for Narrative Exposure Therapy
Slobodin, 2015	Systematic review	Traumatized refugees Adult and children	Family intervention for the range of trauma-related problems
Sullivan, 2015	Systematic Review	Refugee and war-traumatized youth resettled in low, middle and high-income countries	School-based social- emotional interventions
Tyrer & Fazel, 2014	Systematic Review	Children RAS resettled in low, middle and high-income countries	Mental health interventions that had been evaluated in school or community-settings
Van Wyk & Schweitzer, 2014	Systematic Review	Adult refugees or asylum seekers resettled in high income countries	Naturalistic interventions

Table III. Summary of evidence on the effectiveness of psychological interventions for RAS with a diagnosis of a mental disorder.

Studies evaluating task-shifting interventions in mental health care have predominantly been carried out in LMICs, and show positive results in terms of reducing disability and improving overall and social functioning.[32] [33] A Randomized Controlled Trial (RCT) in Goa, India, showed that a collaborative care intervention led by lay counsellors was saving health costs.[34] A systematic review of task-shifting interventions for non-communicable diseases in LMICs showed that it is potentially effective for improving access for mental healthcare.[35] Challenges of task-shifting have also been described, such as the need for an intensive training and supervision system, lack of facilities in primary health care centers such as a private space, and attrition of lay-helpers. Other barriers that have been described include insufficient contextual adaptation of the methods, unfamiliarity with the materials, and practical difficulties in integrating new techniques within routine practice.[36] Finally, there have been limited attempts to

systematically disseminate and promote the use of the methods. Studies should systematically identify barriers for successful large-scale implementation and dissemination of task-shifting interventions.

1.4 Self Help Plus

Among other preventive psychosocial interventions, our research group focused on the Self Help Plus (SH+) programme, developed by WHO and that proved to be suitable as a preventive psychosocial intervention with promising beneficial (cost) effects.[37] The SH+ had never been formally tested before in RCTs with RAS populations in Europe and bordering countries (i.e., Turkey).

1.4.1 Description of the intervention

Evidence for the effectiveness of specific psychological interventions for populations exposed to adversities is mounting.[38] However, the largest evidence base exists for psychotherapeutic interventions delivered by specialized health care professionals (i.e., psychologists and psychiatrists) for the treatment of common mental disorders. Preventive psychosocial interventions for people who are at risk of developing mental health problems are much less studied. Scalable interventions to address the mental health needs of large groups of RAS, should be simple and of short duration, so that they can be carried out in the community or in primary care settings, ranging from supervised lay people with high school degrees (i.e., community workers) to people with bachelor degrees.[32] Also, the interventions should address a range of outcomes. This approach has been endorsed by leading health and refugee agencies, including the WHO, as the optimal framework to upscale affordable and sustainable health delivery to refugees.

SH+ programme was developed by WHO and collaborators working in the humanitarian field, with expertise in global mental health and psychosocial interventions. SH+ programme consists of a pre-recorded audio course, complemented with bibliotherapy. Thanks to this format, it does not require much time for its effective implementation. The potential of using a psychoeducational course to access hard-to-reach populations has been demonstrated previously.[24] Evidence for bibliotherapy is also promising.[22] SH+ was designed to be relevant for large segments of adversity-affected populations: it is intended to be

transdiagnostic, easily adaptable to different cultures and languages, and both meaningful and safe for people with and without mental disorders.

SH+ programme has two components: a pre-recorded course and a self-help book. Pre-recorded audio material (locally adapted) is delivered across five 2-hour sessions and in groups of 20 to 40 people. The audio material imparts key information about stress management and guides participants through individual exercises and small group discussions. A written facilitator guide helps briefly trained non-specialist facilitators to conduct the course using these audio materials. To augment the course materials, an illustrated self-help book reviews all essential content and concepts. The book contains more than 400 illustrations and conveys key points with minimal text. It was written to be useful both as a standalone product and as a key resource for those participating in the course.[37] The format of SH+ seeks to ensure that key intervention components are delivered as intended through the use of pre-recorded audio, without the burden of extensive training and supervision.

SH+ programme is based on acceptance and commitment therapy (ACT), a form of cognitive-behavioral therapy, with distinct features.[39] ACT is based on the concept that ongoing attempts to suppress unwanted thoughts and feelings can paradoxically make these problems worse. Instead, it emphasizes learning new ways to accommodate difficult thoughts and feelings – primarily through mindfulness approaches – without letting them dominate, while guiding people to take proactive steps towards living in a way that is consistent with their values. ACT has been shown to be useful for a range of mental health issues[40] and has been used successfully in a guided self-help format.[41]

To summarize, the essential core features of SH+ programme are the following:

1. SH+ is brief (5-sessions);
2. SH+ may be delivered by non-specialist community workers with the same cultural background as the client;
3. SH+ is transdiagnostic since it addresses symptoms of depression, anxiety, and PTSD, as well as stress and problems as defined by people themselves;
4. SH+ is culturally sensitive, that is a formal cultural translation and adaptation process can feasibly be performed. Part of the project of RE-

DEFINE is to culturally adapt the SH+ programme for individuals across different ethnicities. This cultural adaptation is based not only on language and cultural factors, but also on the evaluation of local resources, and health system contexts from which RAS originate;

5. SH+ is evidence-based. To prove its effectiveness, a large RCT was conducted in Uganda. The additional two RCTs that are part of RE-DEFINE study complemented the available evidence. After these two RCTs, we will perform meta-analysis and individual participant data (IPD) meta-analysis. If results are positive, WHO will adopt and disseminate the programme internationally.

1.4.2 SH+ integration in the health system

Due to the refugee crisis, the growing number of RAS is burdening existing health services, and it is estimated that mental health needs are largely unmet by regular health services in the upper and lower middle-income countries. Health care systems in these countries are overstretched and may lack responsiveness to the mental health needs of RAS population, leading to health inequity due to a lack of access to mental health care.

Health care systems in high-resource settings are generally more capable of adapting to the needs of a new condition or a new population than health systems in low-resource settings. Nevertheless, the sudden increase in demand for a specific type of support or type of care may exceed the resources available to respond to the increase in demand. The low-intensity SH+ programme has been specifically designed to address major gaps in existing mental health care systems. SH+ programme is based on cognitive-behavioural therapy, and in particular on guided acceptance and mindfullness-based behavioural therapies, which have shown promise in reducing symptoms as anxiety and depression.[37] Moreover, SH+ programme is designed to be relevant for large segments of hard-to-reach humanitarian and non-humanitarian populations, and thus reaching a considerable amount of RAS.

SH+ programme can be fully implemented with reasonably limited resources, and costs per person is expected be lower compared to existing more complex

interventions. SH+ programme is a brief, 5-session course delivered in a large-group workshop format, with up to 30 participants (there are no existing evidence-based interventions working in this way). It does not need to be facilitated by people with expertise in psychological interventions, nor it requires extensive training to be implemented. The course format is suitable for a range of different contexts and makes it possible for a group to be convened wherever there is a facilitator, a large space and an audio player.[37] These features make the intervention inexpensive compared to other preventive interventions, where there are usually fewer participants per session, more sessions, and which require more training and supervision for facilitators.

The SH+ programme has so far been tested in various studies coordinated by WHO aimed at investigating its feasibility and acceptability with South Sudanese refugees in Northern Uganda, Syria and South Turkey. In these studies, a generic English version of SH+ programme was translated into the relevant local languages (Juba Arabic for South Sudanese people and Arabic for Syrian people) and culturally adapted, following the comprehensive adaptation framework developed by WHO. A Northern Uganda open arm pilot study enrolled 65 South Sudanese refugees (33 women and 32 men) into a 5-week SH+ programme. Early results showed positive significant changes on a range of different validated instruments assessing health and disability, general functioning and wellbeing, depressive symptoms, and psychological distress. These promising results have been replicated in a small feasibility randomized controlled study with 47 South Sudanese refugees in Uganda. Despite these encouraging results, WHO will only release SH+ after two positive, fully powered RCTs. The intervention was tested in an adequately powered RCT (n=300) in Uganda with South Sudanese refugees.[42] RE-DEFINE will provide the second fully powered RCT with a different target group: all RAS in Europe and Turkey.

2. THE RE-DEFINE PROJECT

RE-DEFINE (Refugee Emergency: DEFining and Implementing Novel Evidence-based psychosocial interventions) aims to provide effective community-based health care implementation strategies to scale-up the delivery and uptake of psychosocial interventions for preventing the onset of mental disorders in RAS resettled in middle-income and in HICs. This goal will be reached by means of two twin RCTs that evaluated the effectiveness and cost-effectiveness of SH+ in asylum seekers and refugees with psychological distress resettled in Turkey and in six sites of five European countries (Italy, Austria, Germany, Finland, and two sites in the UK), as compared with treatment as usual (TAU). The primary objective is testing the effectiveness of SH+ in reducing the incidence of any mental disorders. Secondary objectives are the evaluation of mental health symptoms, psychological functioning, well-being, drop-out rates, and economic outcomes.

The RE-DEFINE project aims to generate a strong evidence-base for SH+, and to create a scientific framework to adapt and equip health care systems in countries inside and outside Europe with such low intensity intervention to provide sustainable and cost-effective preventive interventions to RAS. If the findings of this trial and of the aforementioned (see section 1.4.2) trial with South Sudanese refugees are both positive, then WHO will adopt SH+ programme as the low-intensity intervention approach to be globally implemented within community health care to distressed populations affected by adversity.

2.1 Objectives of RE-DEFINE

Objectives of the RE-DEFINE project are the following (Figure 4):

1. Translating and adapting SH+ for the recipients of care within specific health systems, and co-creating the necessary local conditions for implementation and up-scaling.

   Specific activities of objective 1 were:

   - A systematic assessment of migration flows and RAS population characteristics (i.e., types and sources of distress; risks and protective factors; population's needs and cultural characteristics),

in order to plan a translation/adaptation process of SH+ according to the specific populations in need of psychosocial interventions;

- Community engagement (to gain support and information from key stakeholders);
- Translation and adaptation of SH+ programme in three different languages, according to results of the systematic assessment. Translation and cultural adaptation were performed following a formal protocol already developed and tested by WHO; this includes activities such as feedback meetings and interviews with community representatives, health workers, and non-specialists to ensure that the material is understandable, culturally acceptable (i.e., non-offensive) and culturally relevant. After reaching agreement on the translation and adaptation, the multi-media package (pictorial self-help books; audio recording of course) was made available in the three different languages for testing.
- Training of facilitators that delivered the SH+ programme; data collection.

2. Testing SH+ in terms of health-system performance, effectiveness, affordability and sustainability, and identify barriers (including stigma and discrimination) and facilitators.

   Specific activities of objective 2 are:

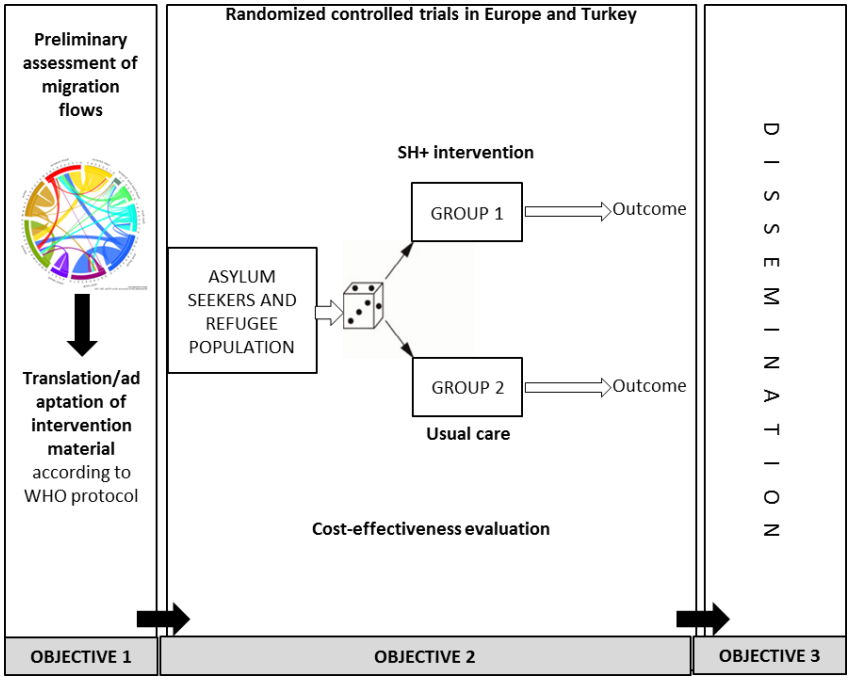
   - Formally evaluating the cost-effectiveness of SH+ by conducting two large, pragmatic, RCTs comparing delivery of SH+ versus usual care conditions in RAS populations: one RCT in Turkey, and one RCT in the following European countries: Italy, Germany, Finland, Austria, and the UK;
   - To determine and quantify the invested cost and effort (cost-effectiveness analysis) in terms of organizational, resource and political-economic requirements relative to the reduction of economic burden of the large-scale implementation of the SH+ programme into the health systems in different contexts.

3. Disseminating the SH+ programme inside and outside Europe, and assuring the highest dissemination and exploitation of the programme. Implementation of the SH+ programme can be carried out by non- specialist (lay) workers across primary and community health care settings, with supposed limited costs for training and supervision. This will enable the rapid building of cost-effective capacity across different settings. Moreover, it will allow the limited amount of more specialised staff and resources to assess and manage those RAS experiencing formally diagnosed mental disorders and requiring more structured pathways of care within the local public health systems.

   Specific activities of objective 3 are:

   - Disseminating the SH+ programme and the whole project results according to a specific dissemination plan. The dissemination plan includes scientific structured activities such as performing an IPD meta-analysis collecting data from available RCTs, to identify specific predictors of intervention's effects;
   - Maintaining long-term sustainability of the programme, and engage with new stakeholders and health systems to further scaling up SH+ programme across Europe and beyond. This is done through publishing SH+ materials on WHO's website, organization of a dissemination event at the European Society of Traumatic Stress Studies's annual meeting and journal articles;
   - Development of a dissemination guide for SH+ that covers: (a) systems issues such as identification of participants and referral of people for whom SH+ is not suitable, or for whom SH+ is not enough; (b) training and supervision of SH+ facilitators; (c) assessment of competencies of SH+ facilitators; (d) routine monitoring and evaluation of routine SH+ implementation.

Figure 4. Graphical summary of the RE-DEFINE methodology.



2.2 Specific objectives of this thesis

This thesis is focused on the object number 2 descripted in the previous paragraph, i.e. to report on the multicentre parallel-group RCT that evaluated the effectiveness and cost-effectiveness of SH+ in asylum seekers and refugees with psychological distress resettled at six sites in five European countries (Italy, Austria, Germany, Finland, and two sites in the UK), as compared with treatment as usual (TAU). The primary objective was testing the effectiveness of SH+ in reducing the incidence of any mental disorders. Secondary objectives were the evaluation of mental health symptoms, psychological functioning, well-being, drop-out rates, and economic outcomes. This project aims to generate a strong evidence-base for SH+, a low-intensity indicated preventive psychosocial intervention, and to create a scientific framework to adapt and equip health care systems in countries inside and outside Europe with such low intensity intervention to provide sustainable and cost-effective preventive interventions to RAS.

3. METHODS

3.1 Study design

The European trial of the RE-DEFINE project consists in a rater-blind, parallel group, multinational, pragmatic RCT, performed at six sites in five European countries (Table IV).

The trial protocol was published previously and registered in clinicaltrials.gov (NCT03571347). No changes were made to the study design after the trial started.

The project was approved by the Ethics Committee of the University of Verona (UNIVR), Italy (coordinating centre), by the WHO Research Ethics Review Committee, and by the Ethics Committees of all participating sites. In accordance with the Declaration of Helsinki, participants' confidentiality was preserved and the contents of the assessments were not disclosed to any third party.

Participant recruitment occurred from September 1, 2018 to November 30, 2019. Project coordinators from each site approached local organizations providing social, health, and/or legal support to refugees and asylum seekers to identify potentially eligible participants. Based on a situational analysis of international migration flows, we identified refugees and asylum seekers from Syria, Afghanistan, Pakistan, Iraq, and Nigeria as potential target groups. In each site, the recruitment strategy was pragmatic and involved local governmental organizations and/or local non-governmental organizations (NGOs), that implement projects for asylum seekers and refugees. These organizations may undertake integrated reception interventions that include food, housing, legal and social guidance and support, and the development of programmes to promote socioeconomic inclusion and integration, following the EU directive for the reception conditions of applicants for international protection in EU countries. They may also be organizations offering similar services, such as legal or welfare support, social/psychosocial support or other community activities for RAS and potentially wider migrant communities. In each recruiting site, local organizations that implement reception or similar projects were contacted and the RE-DEFINE project was presented as a possibility to screen asylum seekers and refugees for psychological problems. However, participating in the study did not create expectations in participants about future residence in the EU or the determination

of their refugee status by any national authorities and this was addressed in the consent process. Participant recruitment occurred in cooperation with one or more of these organizations, depending on local context aspects. Asylum seekers and refugees of specific language groups (Table IV) were consecutively approached and invited to participate by members of the research team, in agreement with local service staff who facilitate contacts. The choice of asylum seekers' and refugees' country of origin has been made in accordance to migration flows towards European countries and feasibility issues.[3] Research team members were trained on how to conduct the interviews. The training on how to conduct interviews and collect data was centralized and coordinated by UNIVR. Where required, due to language differences, contacts with asylum seekers and refugees involved cultural mediators - a refugee or migrant background or from the same/similar culture - and are conducted in comfortable and private locations which are convenient for the participant and safe for the staff and participants involved.

3.2 Participants

In accordance with migration flows towards European countries, and for feasibility reasons, the following population groups were the target population in each site.

EU country involved in the trial	Population group (Country of origin of participants)	Language for intervention and assessments
ITALY	Pakistan, Nigeria	Urdu, Pidgin English
AUSTRIA	Afghanistan, Iran	Dari
FINLAND	Iraq	Arabic
GERMANY	Syria, Afghanistan	Arabic, Dari
UK (LIVERPOOL)	Syria, Iraq, Afghanistan	Arabic, Dari
UK (YORK)	Syria, Iraq, Afghanistan	Arabic, Dari

Table IV. List of recruiting sites and target population

3.3 Informed consent for screening and trial

Informed consent followed a two-step procedure: first, potentially eligible asylum seekers and refugees were approached by a member of the research team for oral and written informed consent for screening. When necessary, a cultural mediator

translated information into the participant's language and assured full understanding of the research, including its practical aspects. If the asylum seeker or refugee screened positive, she/he was invited member of the research team to participate in the RCT and was provided with full trial informed consent. Illiterate participants were asked witnessed oral consent and a thumbprint in lieu of a signature, in line with recommendations from WHO.[43] The witness could not be a member of the research team.

A member of the research team assessed whether or not the prospective participant has the capacity to reach this decision for himself. The member of the research team judged the quality of that decision and considered whether the participant had agreed or refused to participate on the basis of freedom of choice and absence of coercion and having general understanding of the research and its intentions.

Before being enrolled in the trial, oral and written information about the study and its purpose were provided by a member of the research team - who was trained on how to deliver information on the study. When necessary, a cultural mediator translated information into the participant's language and assured full understanding of the research, including its practical aspects. A written informed consent document that includes both information about the study and the consent form was given to participants. After reading the informed consent document, time was given to make a decision about participation, emphasizing that the decision would not influence housing, resettlement, relocation or status determination procedures. Asylum seekers and refugees who decided to participate were asked to complete a written consent form. The participant's consent was confirmed by the personally dated signature of the participant and by the personally dated signature of the person conducting the informed consent discussion. At post-intervention, and at 6- and 12-months follow-up, the member of the research team that performed the assessments verbally reaffirms that no benefits related to housing, resettlement, relocation or status determination procedures are associated with the participation in this study.

Eligible asylum seekers or refugees giving oral and written consent to participate were asked to complete a baseline assessment (see below) and were subsequently randomly allocated to SH+ or TAU.

3.4 Screening phase

Asylum seekers and refugees that were in contact with local organizations for receiving legal, social, or other types of support/facilities were invited to participate. Participants giving oral and written consent to participate were initially assessed using an "Inclusion-Exclusion Criteria Form" and the General Health Questionnaire-12 in order to select a population with clinically significant psychological distress (GHQ-12 ≥ 3). As a second step, those with a GHQ-12 ≥ 3 were assessed for the presence of a mental disorder by means of the MINI International Neuropsychiatric Interview (M.I.N.I.).[44] Only asylum seekers and refugees with psychological distress, but without a mental disorder, were invited to participate to the trial and randomly allocated in a 1:1 ratio to the experimental and control condition (Table V).

Inclusion criteria	**Age 18** or above
	Able to **speak** and understand one of the target languages: Arabic, and/or Urdu, and/or Dari, and/or Pidgin English
	Asylum seeker or refugee defined in accordance to the table I reported above
	Presence of psychological distress, as shown by a score of 3 or more at the 12 item General Health Questionnaire (**GHQ-12 ≥ 3**)
	Both oral and written informed **consent** to enter the study
Exclusion criteria	Presence of any **mental disorders** according to DSM-V and ICD-10, as shown by a positive M.I.N.I.
	Acute **medical conditions** contraindicating study participation, based on clinical judgment of the health care professional with a clinical background who performs the screening
	Clinical evidence of imminent **suicide risk** or suicide risk scored as "moderate or high" (or a positive suicidality behaviour disorder) by the M.I.N.I. (section SUICIDALITY)
	Clinical evidence that the **decision-making** capacity is **impaired**

Table V. Eligibility criteria for RE-DEFINE study.

Following the screening phase, asylum seekers and refugees eligible for the trial were informed about further details and procedures of the study and were invited to

participate in the trial phase. For asylum seekers and refugees who did not meet the eligibility criteria, reasons for study ineligibility were verbally explained to them. Asylum seekers and refugees that were excluded because of a diagnosis of a mental disorder were advised to seek professional treatment, and contacts with local mental health care services were facilitated to provide them with adequate care, particularly in the presence of acute symptom or risk of suicide. In each European site, local mental health care services that have the capacity to assist RAS with a psychiatric diagnosis were contacted. Based on the specific clinical needs of asylum seekers and refugees, the pathway of care includes:

- pharmacological treatment;
- psychological support and/or psychotherapy;
- psychosocial rehabilitation.

These interventions (that may include hospitalization) were delivered to RAS by multidisciplinary teams within the mental health departments in each European site. Psychiatric care costs were covered in accordance with the local healthcare systems, in accordance with European and local rules. Each site defined in detail how the referral to mental health care services had to be conducted.

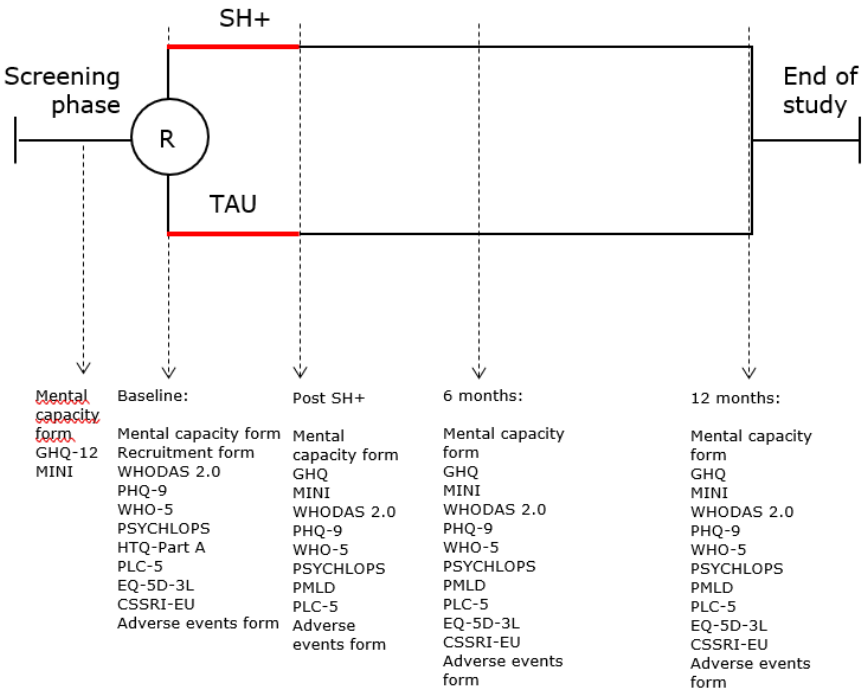
3.5 Pilot phase

Before starting the study, we conducted a preliminary randomized pilot trial with 4 participants for each site. This phase allowed testing different aspects related to the delivery of the intervention and assessments, feasibility, and time, prior to the performance of the full trial. Participants of the pilot study were not included in the final sample size. However, they did receive the experimental or control condition, and a close monitoring of their psychological status through two psychological assessments (one at baseline, and one at the end of the intervention). These assessments were composed of the same instruments that were used in the fully-powered trial.

3.6 Trial phase assessment

Assessments took place at screening, at baseline (before random allocation), post-intervention (0-1 week after intervention), and at 6- and 12-months after randomization (Figure 5). The assessments at 6- and 12-months were performed in person or by telephone/skype, to ensure the required rates of follow up. Methods of assessment were recorded and, if necessary, accounted for in the analyses.

Figure 5. Study flow chart



At baseline, socio-demographic data including sex, age, country of origin, education, religion, marital status and work status were collected using an *ad-hoc* form developed specifically for RE-DEFINE. Information on the adverse life events and environmental stressors were collected using the Harvard Trauma Questionnaire Part A (HTQ)[45] and the Post-Migration Living Difficulties (PMLD) and the Recovery Environment.[46] We administered the HTQ Part A, in which respondents were asked whether they have experienced each of the events, and a 17-item PMLD Checklist.

In addition, the following assessment scales were administered (Table VI):

- baseline: ad-hoc recruitment form, WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, HTQ Part A, PCL-5, EQ-5D-3L, and CSSRI-EU (adapted);
- post-intervention: GHQ-12, M.I.N.I., WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, PMLD, and PCL-5;
- 6-months follow-up: GHQ-12, M.I.N.I., WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, PMLD, PCL-5, EQ-5D-3L, and CSSRI-EU (adapted);
- 12-month follow up: GHQ-12, M.I.N.I., WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, PMLD, PCL-5, EQ-5D-3L, and CSSRI-EU (adapted).

Concept	**Screening**	**Baseline**	**Post-intervention**	**6-month follow-up**	**12-month follow-up**
Mental Capacity	Mental capacity form	Mental capacity form	Mental capacity form	Mental capacity form	Mental capacity form
Psychological distress	GHQ-12		GHQ-12	GHQ-12	GHQ-12
Psychiatric diagnosis	M.I.N.I.		M.I.N.I.	M.I.N.I.	M.I.N.I.
Socio-demographic and migration data		Recruitment form			
Functioning		WHODAS 2.0 – interviewer administered	WHODAS 2.0 – interviewer administered	WHODAS 2.0 – interviewer administered	WHODAS 2.0 – interviewer administered
Depressive symptoms		PHQ-9	PHQ-9	PHQ-9	PHQ-9
Subjective wellbeing		WHO-5 Wellbeing index	WHO-5 Wellbeing index	WHO-5 Wellbeing index	WHO-5 Wellbeing index

Self-defined psychosocial goals		PSYCHLOPS	PSYCHLOPS	PSYCHLOPS	PSYCHLOPS
Traumatic/ Adverse life events		HTQ –Part A/1			
Daily and Environmental Stressors			PMLD	PMLD	PMLD
Symptoms of PTSD		PCL-5	PCL-5	PCL-5	PCL-5
Health-related quality of life		EQ-5D-3L		EQ-5D-3L	EQ-5D-3L
Cost-effectiveness		CSSRI-EU		CSSRI-EU	CSSRI-EU
Adverse Events		Adverse events form	Adverse events form	Adverse events form	Adverse events form

Table VI. Overview of measures that were administered during the study

3.7 Primary outcome

The primary outcome was the number of participants with a current psychiatric diagnosis at six-month follow-up, as measured by the M.I.N.I..

Psychiatric diagnosis at six-month follow-up

The M.I.N.I. was designed as a brief structured interview for the major psychiatric disorders (i.e., major depressive disorder, suicide behavior disorder, post-traumatic stress disorder, social anxiety disorder, etc.) in DSM-5 and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the Structured Clinical Interview for DSM (Patient Edition)[47] and the Composite International Diagnostic Interview.[48] The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time

(mean 18.7 ± 11.6 min., median 15 min) than the above-referenced instruments. It can be used by health care professionals with a clinical background, after a brief training session. Lay interviewers require more extensive training.[49]

The M.I.N.I. is divided into modules identified by letters, each corresponding to a diagnostic category. At the beginning of each module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a gray box. At the end of each module, diagnostic box(es) permit(s) the health care professional to indicate whether the diagnostic criteria are met.

3.8 Secondary outcomes

Secondary outcomes of RE-DEFINE study were: psychological distress (GHQ-12); number of participants with a psychiatric diagnosis at post-intervention and at 12-month follow-up (M.I.N.I.), functioning (WHODAS 2.0), depressive symptoms (PHQ-9), subjective wellbeing (WHO-5 Wellbeing Index), self-defined psychosocial goals (PSYCHLOPS), health related quality of life (EQ-5D-3L), symptoms of PTSD (PCL-5), drop-out rates due to any reason, cost-effectiveness (CSSRI-EU adapted). Cost-effectiveness and participant assessment at 12- month follow-up will be reported elsewhere.

Psychological distress

Measured through the General Health Questionnaire-12 (GHQ-12).[50] The GHQ-12 is a measure of current mental health developed by David Goldberg in the 1970s, and it has been extensively used in different settings and cultures.[51] [52] The questionnaire asks whether the respondent has experienced a particular symptom or behaviour recently. Each item is rated on a four-point Likert scale (less than usual, no more than usual, rather more than usual, or much more than usual); and gives a total score of 36 or 12 based on the GHQ version and on the selected scoring methods. The most common scoring methods are bi-modal (0-0-1-1) for screening and Likert scoring styles (0-1-2-3) for outcome evaluation.

Psychiatric diagnosis at post-intervention and at 12-month follow-up

The M.I.N.I. interview was administered also at post-intervention and at 12-month follow-up, to evaluate the presence of any mental disorders.

Functioning

Assessed using the WHO Disability Assessment Schedule 2.0 (WHODAS) interviewer-administered version.[53] The WHODAS is a generic assessment instrument assessing health and disability.[53] It is used across all diseases, including mental, neurological and substance use disorders. It is simple to administer and applicable across cultures. WHODAS covers six domains (cognition, mobility, self-care, getting along, life activities, and participation). It assesses difficulties people have across these domains during the last 30 days. Difficulties are scored as none, mild, moderate, severe, or extreme. We used the 12-item interviewer-administered version. Data on socio-demographic information (sex, age, education, marital status and work status) was collected through questions A1-A5 of the WHO-DAS, which was administered first.[53]

Depressive symptoms

Assessed using the Patient Health Questionnaire-9 (PHQ – 9).[54] The PHQ-9 is a 9-item instrument measuring the presence and severity of depression. Major depression is diagnosed if five or more of the nine depressive symptom criteria have been present at least "more than half the days" in the past two weeks, and one of the symptoms includes depressed mood or anhedonia. Other types of depression are diagnosed if two, three, or four depressive symptoms have been present at least "more than half the days" in the past two weeks, and one of the symptoms includes depressed mood or anhedonia. As a severity measure, the PHQ-9 score may range from 0 to 27, since each of the nine items can be scored from 0 (not at all) to 3 (nearly every day).[54] The PHQ has been validated for a wide range of cultural groups.

Subjective well-being

Measured through the WHO-5 - Wellbeing Index.[55] The WHO-5 Wellbeing Index is a 5-item questionnaire measuring current psychological wellbeing and quality of

life, rather than psychopathology. Scores range from 0 to 25. The scale has demonstrated sensitivity to change in wellbeing and is available in numerous languages.

Self-defined psychosocial goals

To assess this dimension, we used the Psychological Outcome Profiles instrument (PSYCHLOPS).[56] The PSYCHLOPS consists of four questions. It contains three domains: problems (2 questions), function (1 question) and wellbeing (1 question). Participants are asked to give free text responses to the problem and function domains. Responses are scored on an ordinal six-point scale ranging from zero to five, producing a maximum score of 20. The pre- and post-therapy versions of PSYCHLOPS consist of the same four questions but the post-therapy version adds an overall evaluation question (determining self-rated outcome ranging from "much better" to "much worse"). PSYCHLOPS has been validated in primary care populations across several countries. It has been used in WHO mental health studies in Pakistan, Kenya, Lebanon and Uganda (Protocol IDs: RPC627; RPC656; RPC705).

Symptoms of PTSD

We used the PTSD Checklist for DSM-5 (PCL-5).[57] The PCL-5 is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. It takes approximately 5-10 minutes to complete. The PCL-5 can be scored in different ways: (a) a total symptom severity score (range - 0-80) can be obtained by summing the scores for each of the 20 items; (b) DSM-5 symptom cluster severity scores can be obtained by summing the scores for the items within a given cluster, i.e., cluster B (items 1-5), cluster C (items 6-7), cluster D (items 8-14), and cluster E (items 15-20); (c) a provisional PTSD diagnosis can be made by treating each item rated as 2 = "moderately" or higher as a symptom endorsed, then following the DSM-5diagnostic rule which requires at least: 1 B item (questions 1-5), 1 C item (questions 6-7), 2 D items (questions 8-14), 2 E items (questions 15-20); We used an adapted version making reference to the past week instead of the past month, for sensitivity reasons.

Generic measure of health for clinical and economic appraisal

In order to assess this dimension, we used the EuroQol-5Dimension-3 level version (EQ-5D-3L).[58] The EQ-5D-3L is applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The 3-level version of EQ-5D (EQ-5D-3L) was introduced in 1990 by the EuroQol Group. The EQ-5D-3L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results into a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

Proportion of participants leaving the study early (dropouts)

We measured the number of people leaving the study prematurely at any times, and reasons for discontinuation.

When possible, this information is collected in person or by telephone/skype (two attempts are made to reach participants). Unreachability of participants is also recorded as a dropout.

Cost-effectiveness measures

Measured through the Client Service Receipt Inventory, European version (CSSRI-EU): Client sociodemographic and service receipt inventory (adapted version with other socio-demographic characteristics).[59] The CSSRI is a research tool developed

for collecting information that describes in detail the types and level of services that comprise the care package of each study member. These data are important as they can inform decisions about planning, commissioning and providing services to meet the needs of particular populations. However, the schedule is designed so that service use data are recorded in a standardized way that best facilitates the estimation of the component and total costs of support for each client. Just as needs or outcome data are collected at the individual level, in an economic evaluation it is important to measure the costs of the resources used to generate those outcomes for each client. The CSSRI is a questionnaire which takes approximately 20 minutes to complete and collects retrospective information about the interviewee's use of health and social care services, accommodation and living situations, income, employment and benefits. The CSSRI-EU is a European version of the CSRI. The CSSRI-EU was developed within the framework of the EPSILON (European Psychiatric Services: Inputs Linked to Outcome Domains and Needs) project. The instrument is applicable for use in interview with patients and/or key staff. For the purposes of RE-DEFINE, the European version of the CSSRI was adapted to be used in asylum seekers and refugees, by means of interviews with asylum seekers and refugees and staff members from health and social care facilities providing services for asylum seekers and refugees. Expert interviews with representatives from relevant governmental and nongovernmental health and social care institutions (e.g. health insurance, health administration, immigration authority, refugee aid organizations) were conducted to assess the organizational as well as the time and other resource requirements of implementing SH+ in the participating countries. The results from these assessments will be presented elsewhere.

Traumatic life events and adverse events

Traumatic/adverse life events and daily and environmental stressors were collected by administering the Harvard Trauma Questionnaire - Part A and the 17-item Checklist for Post-Migration Living Difficulties (PMLD).

The Harvard Trauma Questionnaire, developed by Mollica and colleagues is a self-report questionnaire with 4 parts.[45] The purpose of part 1/A, the one we used for this study, is to measure traumatic life events. It consists in a list of possible

traumatic events connected to migration (i.e. Lack of food or water, serious injury, being close to death, forced separation from family members, …) and the respondents are asked to state if they experienced or witnessed each event.

The PMLD checklist (see Annex 14) was used to assess the levels of stress due to typical postmigration stressors developed from discussions with immigrant and refugee communities in Sydney. The checklist asks respondents to rate their experience of the problems, during the last 12 months, on a five-point scale ('was not a problem' to 'a very serious problem'). A high cumulative score indicates a high degree of post-migration stressors.[46]

Serious adverse events and other adverse events occurring within the trial are collected using an adapted form. The relationship with the study intervention, the action taken regarding intervention and the outcome of the adverse event are collected.

3.9 Randomization

Randomization occurred at individual level and was stratified by recruiting center. Randomization was centralized and coordinated by the WHO Collaborating Centre (CC) of the University of Verona. Eligible participants were randomly assigned to one of the two groups with an equal probability of assignment to each group (allocation ratio 1:1). The randomization schedule was generated using the web-based software Castor Electronic Data Capture. This electronic tool employs a variable block randomization method, in order to allocate groups randomly permuted in blocks of unequal size. The site investigators did not know the block size. Members of the research team involved in the recruitment were able to access the web-based software to randomize each new enrolled participant, but were not able to access the randomization list. In addition, the web-based software allowed random allocation only after the main information on the enrolled participant was entered, upon verification of the inclusion criteria. After random allocation, the software produced a unique identification number (ID) for each participant. Recruiting members of the research team could access the web-based software to randomize each new enrolled participant and were immediately informed about the

allocation arm, but they were not able to access the randomization list. The randomization list was accessible only to the data manager.

There is a theoretical possibility of contamination by recruiting asylum seekers and refugees who might interact with each other and therefore divulgate intervention's components from people in the experimental arm to those in the control condition. In order to minimize the possibility of any form of contamination, both the experimental and the control group were asked to refrain from sharing study-related information and materials during the study. At all possible times during the trial, steps were taken to organize the delivery of the intervention in a way that prevents potential contamination.

3.10 Masking

Masking participants and facilitators about the intervention status was impossible, due to the characteristics of the intervention. However, investigators evaluating primary and secondary outcomes at post-intervention and at 6- and 12-months follow-up, and the statistician performing all analyses, were masked to the allocation status of the participants. Masking was safeguarded, as health care professionals and cultural mediators involved in the assessments were instructed on how follow-up assessments should have been conducted in order to preserve effective masking. Similarly, the statistician analysing data was allowed only to access encrypted data, where the nature of the intervention was concealed.

In addition, to preserve masking, we asked the members of the research team to avoid interactions with study participants outside the study setting; we also checked that NGOs provide appropriate private spaces for intervention's delivery and for the assessments.

3.11 Characteristics of the control intervention: Treatment as Usual (TAU)

Control arm participants received routine social support and/or care according to ordinary practice and following local regulations. Additionally, they received baseline and follow-up assessments according to the study schedule, and information about freely available mental health services. The follow-up assessments consisted of interviews with members of the research team, and imply

the creation of a supportive environment and a clinical relationship. Asylum seekers and refugees that were excluded because of a diagnosis of a mental disorder were advised to seek professional treatment and contacts with local mental health care services were facilitated (as reported above).

3.12 Statistical analysis

We predicted an incidence rate of mental disorders of 25% at six months in this population group. We hypothesized that the provision of the Self-Help programme would show a clinically significant advantage by producing a between groups absolute difference of 10%.[60] With these figures, in order to achieve at least 80% power for a 0.05 level of significance in a Chi-square test for equality of proportions of people diagnosed with mental disorders at six months, a sample size of 500 participants (250 in each group) would have been needed.

Descriptive statistics (mean and standard deviation for continuous variables, absolute numbers and percentages for categorical variables) were calculated on socio-demographic, pre-migration, migration and post-migration variables at baseline. Balance between treatment groups was checked calculating standardized mean differences (SMDs). SMD values of 0.1 and -0.1 were used as thresholds for imbalance.[61 62]

We followed an intention-to-treat (ITT) approach for the analysis of primary and secondary outcomes. The ITT population consisted of all participants who were randomly assigned to the competing intervention strategies, and with data on the baseline assessment available, irrespective of the number of SH+ sessions received. In order to check the robustness of results, the primary outcome was additionally analysed using a per protocol (PP) approach, by including only those participants who completed at least three SH+ sessions. The analysis of the PP population was used for confirmatory purposes only.

The primary outcome was compared between the two groups through a chi-square test (primary analysis); Cramer's V was also calculated, together with a risk ratio (RR) and its 95% confidence interval (95% CI). Additionally, a multivariate analysis (secondary analysis) was performed through a Poisson regression model, with a robust error variance, to estimate RRs directly, and to explore the potential

confounding effect of prognostic factors, and the interactions with treatment, controlling for variables showing imbalance at baseline.

A mixed analysis of covariance (ANCOVA) was performed for each rating scale used to measure secondary outcomes, using the values at post-intervention, and at six-month follow-up, respectively, controlling for the value at baseline; standardized coefficients, together with their standard errors, were also calculated. For six-month follow-up, a last observation carried forward (LOCF) approach was used: ratings were carried forward from the last available assessment to the six-month follow-up assessment. The null hypothesis that the experimental intervention had no effect on GHQ-12, WHODAS 2.0, PHQ-9, WHO-5 Wellbeing index, PSYCHLOPS, PCL-5 scores was finally tested by performing seemingly unrelated regression (SUR),[63] in its modification to allow for unbalanced data proposed by Baum and Schaffer[64] through the Stata "suregub" command. In particular, SUR was performed for each time point, controlling for baseline values. For each questionnaire, in case of missing items, we used the Corrected Item Mean Substitution method (i.e. the item mean across participants weighted by the subject's mean of completed items,[65] using information from subjects belonging to the same treatment arm for the same follow-up time, through the Stata "hotvalue" command.[66] The substitution was only performed if resulting in admissible values in all cases, and only for observations having less than 50% of missing items. As a sensitivity analysis, we re-ran our models without any data imputation.

Possible interactions between treatment and specific variables (recruiting centre country of origin, gender, age, years of education, length of stay in the hosting country) were evaluated. In particular, in the case of continuous outcomes, SUR for unbalanced data on all outcomes was performed, with their value at baseline, treatment status, all potential moderators, and their interactions with treatment status, as predictors. A global test on all interaction terms was implemented and, in case of statistical significance, the same test was performed for each scale. Finally, for scales meeting the statistical significance threshold, single regressions were considered.

As for binary outcomes, to avoid the issue of poor performance of the model in case of solutions near the boundary described by Zhou et al. (2018),[67] Poisson regression

models with robust standard errors having the variable intervention allocation, each variable separately, and its interaction with treatment as regressors, were performed, using the Bonferroni correction to take multiple testing into account. Originally, further analyses stratifying by method of assessment (face-to-face versus telephone or secure online audio/video communication) were planned. However, due to the Sars-CoV2 pandemic, these analyses were not performed, as most follow-up assessments were conducted remotely.

Multivariate analyses were performed for each secondary outcome to take confounding factors into account, again including the baseline value as a covariate. Finally, lost-to-follow-up were compared between the two groups using a Chi-square or a Fisher exact test, as appropriate. All analyses were performed using Stata/SE, Release 15.1.[68] A statistical analysis plan was developed and signed before data analysis.

3.13 Ethical aspects

It was essential to conduct this research because rigorous evidence needed to be collected on the effectiveness of this intervention, which has been specifically developed for vulnerable population groups. Additionally, it provided valuable information about optimal adaptation strategies and aspects to consider when scaling up in another context.

The trial was conducted according to globally accepted standards of good clinical practice (as defined in the ICH E6 Guideline for Good Clinical Practice, 1 May 1996), in agreement with the Declaration of Helsinki and in keeping with local regulations.

The following key ethical issues were carefully taken into consideration by each site conducting the study:

- Ongoing monitoring of decision-making capacity to consent to participate in the study. The decision-making capacity was evaluated using a specific form developed in accordance to the British Psychological Society guidelines for conducting research with people not having the capacity to consent to their participation. The form was administered during the screening phase, at baseline, and at each follow-up assessment.

- Importance of robust referral mechanisms for mental health services.
- Monitoring of participants expectations from their involvement in the study (e.g. expecting this to affect their status determination). Moreover, members of the research team clearly reaffirmed that the participation in this study would have not provided asylum seekers and refugees with any benefits in terms of housing, resettlement, relocation or status determination procedures.
- Safety of members of the research team involved in the study, including, if required, gender matching and awareness of socio-demographic differences to participants and impact this may have on the research encounter.
- Intervention delivery: importance of gender matching.
- Facilitator training and supervision to ensure their competency to practice and protect against burnout / additional stress due to being exposed to participants experiences.

The participation in the study was on a voluntary basis. During the informed consent procedures for screening and for the study this was explicitly stated in written (in the informed consent form) and with oral communication by the health care professional and the cultural mediator.

An international EAB supervises all the ethical issues related to the trial. The EAB helped the consortium keep high ethical standards which ultimately enhance the quality of research, increase its likely social impact, promote integrity and a better alignment of RE-DEFINE with social needs and expectations. The EAB made sure that relevant steps were undertaken to minimize risks or provide solutions in case relevant psychological problems are detected during screening or during the course of the study. The EAB indirectly supervised three main aspects: (1) recruitment, inclusion and exclusion criteria, and informed consent procedures; (2) data management (protection and privacy); (3) vulnerability of the population.

3.14 Data management

All study data were managed with the electronic, web-based tool Castor Electronic Data Capture (EDC). This tool allowed to manage the entire study flow, including the collection of baseline assessments, the subsequent random allocation phase, the

collection of socio-demographic and clinical data (including rating scales) and their storage in a dataset, that was used for statistical analysis.

A study administrator, based at the WHO CC of the University of Verona, ensured the correct functioning of this electronic tool throughout the entire study course. The study administrator was not involved in determining participants' eligibility, administering treatments, assessing outcome, or analysing data. The correctness and consistency of the data entered in the system were ensured by an upstream validation of data entered, which provides an immediate feedback to the user entering data.

Castor EDC complied with all the most relevant national and international regulations to reliably and accurately design, conduct, monitor, record, analyse and report data of clinical trials, including Good Clinical Practice (GCP), 21 Code of Federal Regulation (CFR) Part 11, EU Annex 11, and the European Data Protection Directive. In detail, this electronic tool fulfilled all the following GCP data management requirements:

- An appropriate and consistent use of the system was ensured by a set of SOPs.
- In order to ensure the confidentiality of records and safeguard the identity of participants, an unambiguous, anonymous and unalterable identification code was automatically generated for each participant at the time of enrolment.
- In order to address the possibility of human errors altering the quality and consistency of the dataset, all entered data and all changes were automatically saved throughout the study (audit trail, data trail and edit trail).
- A security system was in place to prevent unauthorized access to data. Each researcher involved in the study was allowed to access and use the web-based tool only to the extent that is related to their specific role (e.g. participants' recruitment, outcome assessment, data analysis, etc.). The study administrator, based in the WHO CC in Verona, provided each researcher with specific rights for the use of the tool, preventing him/her to intentionally or unintentionally alter study data. The authorization to access

data was allowed only to those directly involved in the process of data analysis, for limited time periods.

- A list of all individuals authorized to make data changes was kept. All alterations of user rights throughout the course of the study were automatically recorded.
- All collected data were automatically backed up and archived, so they can be easily retrieved at any time. As all data changes were recorded, the status of a particular record at a particular moment in time can always be retrieved.
- The concealment of allocation was safeguarded, as only users with randomization rights randomize participants, without knowing in advance which group the participant ends up in. Also, the masking was safeguarded, as outcome assessors are authorized only to collect and insert data in the system, but participant allocation to treatments is concealed. Similarly, the statistician analysing data was allowed only to access data with an encrypted information on the treatment allocation.
- The web-based system complied with the FAIR Principles (Findable, Accessible, Interoperable, Reusable). In synthesis, collected data were: (a) findable, as data are organized and indexed in a searchable resource, and described with rich metadata. Further, data and metadata were assigned a unique and unchangeable identifier; (b) accessible, as a standardized communications protocol was produced to allow retrieving data and metadata; (c) interoperable, as a formal, accessible, shared, and broadly applicable language for knowledge representation is employed to name data and metadata; (d) reusable, as data and metadata were identified by a plurality of accurate and relevant attributes.

In accordance with the Declaration of Helsinki,[69] the participants' confidentiality was preserved at all times and the contents of the recruitment and follow-up forms were not disclosed to any third party.

Trial investigators ensured that the trial was adequately monitored in order to ascertain the accuracy, completeness, and appropriateness of procedures employed to collect and register study data. Recruiting centres allowed the coordinating centre, at its discretion, to monitor and audit the conduct of any procedure related

to the study. That includes the right to inspect any facility being used for the study and to examine any relevant procedure and record.

A Data Protection Officer (DPO) supervised and regularly reported that all data collection and processing were carried out according to EU and national legislations. The DPO ensured compliance with requirements, regularly monitors performance with the aim of addressing potential issues proactively. The DPO kept all the data-relevant authorizations available and produced periodic reports to accompany the periodic project reporting.

A Data Management Plan (DMP) including detailed information on the procedures that were implemented for data collection, storage, protection, retention, merging, reuse and/or destruction was drafted following the guidance issued by the European Commission. It was drafted using a template (Version: 26 July 2016) provided by the European Commission and is updated over the course of the project whenever significant changes arise. The implementation of the DMP is monitored by the EAB and the DPO.

According to the Guidance note on research on refugees and asylum seekers,[70] a SOP for helping participants in case of incidental findings (human rights violations, human and sexual trafficking, domestic violence, forced marriage, female genital mutilation, trading in human organs, child pornography) was drafted in order to ensure that the responsible national authorities, NGOs or other agencies with relevant expertise are informed following local legislation.

3.15 Adverse events reporting

All adverse events (AE) reported spontaneously by the participants or observed by research or intervention staff were recorded in a form specifically developed for AE reporting. An event was considered a potential adverse reaction if it were an undesirable experience occurring to a participant during the study, whether or not considered related to the research procedure. This definition includes all aspects of mental health and psychological functioning, but also any undesirable experiences. The chair or a nominated person from the EAB reviews spontaneously reported serious adverse reactions (i.e., suicide attempts) within 48h, deciding if it is likely related or unrelated to the intervention. General adverse reactions are reviewed by

the EAB in regular bi-monthly meetings. In both instances, the EAB determines if any appropriate action in respect of ongoing trial conduct is necessary and specify what action this would be (i.e. referral to specialized care). The site Principal Investigator is responsible for ensuring that required actions are implemented. The site Principal Investigator also informs trial participants and those bodies providing ethical oversight if anything occurs on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen. SOPs were prepared and followed for adverse events reporting.

3.16 Implementation phase

This phase aimed at defining and implementing communication and dissemination strategies about all actions to be performed in all the phases and the results achieved during the project lifetime. It ensured that all knowledge on implementation of the low-intensity SH+ programme was made available to all stakeholders and facilitators.

RAS, policy makers and the scientific community were included as recipients, and also to facilitate distribution and dissemination of the SH+ programme to Italy, Germany, the UK, Finland, Austria, and Turkey, but also to any other country. This phase engaged with policy makers, financial donors NGOs, national and international scientists, professionals and para-professionals. An in-depth monitoring and analysis of the scientific and technical outputs of the project was performed and ensured an effective dissemination plan. The dissemination and exploitation approach was further refined and defined at the early stages of the project implementation with key actors (stakeholders and facilitators). Furthermore, these dissemination actions were continuously monitored and adjusted according to emerging needs and changing conditions during the project implementation.

RE-DEFINE included also the development of a dedicated, easily navigable website which is kept regularly updated by the consortium (http://re-defineproject.eu/).

Specific dissemination strategies included:

- Dissemination strategy for national and international scientists: a) publication of research results in international peer-reviewed journals with

high Impact Factor; b) presentation of research results in international conferences (i.e., annual Cochrane Colloquia; Centres for Global Mental Health events and conferences); c) presentation of research results in academic seminars and journal clubs (UNIVR has a strong tradition in academic educational activities); d) presentation of the project methodology and results in the dedicated website; e) considering that we gathered data within the understudied RAS population currently scattered around different locations inside and outside Europe, we created a large database of unprecedented size that will provide us with the unique opportunity to reliably identify predictors for the effects of the low-intensity intervention to reduce symptoms of psychological distress. Partner in the project Pim Cuijpers and Corrado Barbui are experts in performing advanced IPDs, to identify mediators and moderators of intervention effects. Pim Cuijpers will collect IPD from our RCTs, and he will integrate this amount of data with the data coming from the RCT conducted in Uganda.[42]

- Dissemination strategy for health care professionals and para-professionals: a) ad-hoc newsletters (for international professionals and para-professionals): we developed a network (advised by WHO) to draw together a mailing list of key people to receive materials and information about the project); b) presentation of the project at national and international workshops (i.e., Cochrane Colloquia; Cochrane mid-year meetings; international conferences on mental health); c) presentation of the project in the dedicated website.
- Dissemination strategy for RAS, public institutions and NGOs: a) materials introducing SH+ freely available on the project website; b) development of a policy brief (of around 10 pages) summarising research project, methodology and main results. The policy brief was produced in English and translated in 3 languages (French, Spanish; German). It was structured in introduction, recommendations, actions, results and conclusion c) presentation of the project in the dedicated website.

- Development of implementation tools including: a) training and supervision tools; b) competency assessment of facilitators; c) tools for monitoring and evaluation of SH+ in routine care.

4. RESULTS

After screening 1,475 potentially eligible participants, 1,016 were excluded. A total of 505 participants were excluded because the level of distress was lower than the established cut-off, 461 participants were excluded because of a positive M.I.N.I., and 50 participants were excluded for other reasons, including plans of living the study site shortly. As shown in Figure 6, This left 459 individuals who met the inclusion criteria and were allocated to either SH+ (230) or TAU (229). We could not assess 112 individuals at post-intervention with the M.I.N.I., and 156 individuals at 6-month follow-up. Participants were lost to follow-up because they refused to participate (69), were not reachable and/or moved to other locations (40), or were not available due to other personal priorities (i.e., working, housing, other) (47). The distribution of participants lost to follow-up was similar between the study groups (Table VIII). Selected socio-demographic characteristics of the included participants are shown in Table VII (the full list of socio-demographic variables is presented in appendix, table A). Mean participant age was 33 years (SD 11) in the SH+ group and 32 years (SD 10) in TAU group. The majority of participants were male, with a mean of 10 years of education. For about 40%, primary school was the highest received level of education, while 20% received academic education. About 28% of participants came from Syria, 25% from Nigeria, 18% from Iraq, followed by Afghanistan, Pakistan, and other bordering countries. The travel route was through the Balkans for 28% of participants in the SH+ group and 34% in TAU group, followed by the African route, the Eastern, and other travel routes. About 30% of participants experienced detention during their transition to Europe.

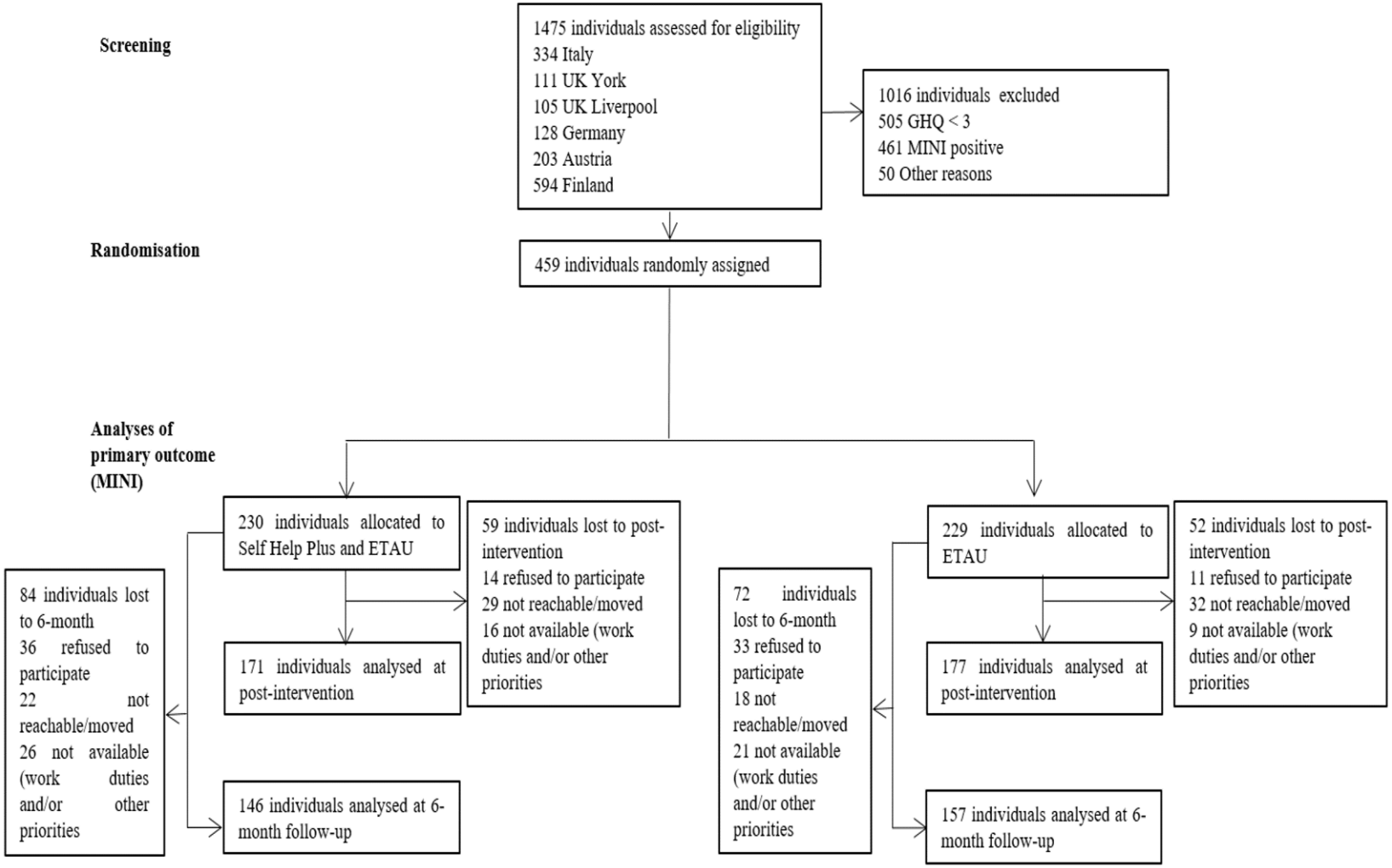


Figure 6. Study flow diagram

VARIABLES	**TAU**	**SH+**	**Difference (Standard Error)**	**SMD**
Age, mean years (SD)	31.537 (9.505)	32.961 (10.779)	1.424 (0.949)	0.099
Female gender	30.13% (69/229)	28.26% (65/230)	-0.019 (0.043)	-0.029
Education, mean years (SD)	10.157 (5.451)	10.452 (4.890)	0.295 (0.497)	0.040
Type of education				
Illiterate	11.50% (26/226)	5.73% (13/227)	**-0.058 (0.026)**	**-0.146***
Primary school	40.71% (92/226)	44.93% (102/227)	0.042 (0.047)	0.060
High school	27.88% (63/226)	27.75% (63/227)	-0.001 (0.042)	-0.002
University	19.91% (45/226)	20.70% (47/227)	0.008 (0.038)	0.014

n. of relatives, mean (SD)	1.655 (2.413)	1.409 (1.978)	-0.246 (0.206)	-0.079
n. of children, mean (SD)	1.369 (2.426)	1.348 (1.798)	-0.021 (0.200)	-0.007
Country of origin				
Afghanistan	14.41% (33/229)	14.35% (33/230)	-0.001 (0.033)	-0.001
Iraq	18.78% (43/229)	17.39% (40/230)	-0.014 (0.036)	-0.025
Nigeria	24.02% (55/229)	25.65% (59/230)	0.016 (0.040)	0.027
Pakistan	9.61% (22/229)	8.26% (19/230)	-0.013 (0.027)	-0.033
Syria	28.38% (65/229)	28.26% (65/230)	-0.001 (0.042)	-0.002
Other country	4.80% (11/229)	6.09% (14/230)	0.013 (0.021)	0.040
Travel route				

Balkan	34.50% (79/229)	28.26% (65/230)	-0.062 (0.043)	-0.095
Eastern	19.65% (45/229)	22.17% (51/230)	0.025 (0.038)	0.044
African	26.64% (61/229)	27.83% (64/230)	0.012 (0.042)	0.019
Other route	18.34% (42/229)	20.43% (47/230)	0.021 (0.037)	0.037
Detention during transition	29.46% (66/224)	31.70% (71/224)	0.022 (0.044)	0.034

Table VII: Demographic characteristics

SMD= Standardized Mean Difference, SD= standard deviation. Values in bold highlight imbalance at baseline.

The two groups were similar with regard to most socio-demographic characteristics and baseline scores on outcomes, with the exception of the following variables: literacy, having distant relatives in the country of origin, detention duration, legal status conditions (humanitarian protection, political asylum), and number of siblings. We added these variables in planned regression analyses accounting for imbalance between groups, without identifying relevant differences with respect to our main analyses on both primary and secondary outcomes (appendix, table D). Assessment of more than 10% of SH+ sessions showed near-perfect fidelity. We only identified small mistakes consisting of a delay of 10-15 minutes in restarting the audio and taking more time for group discussion than allotted in the manual. Based on information collected at each site, the total supervision time required for

all five sessions of a SH+ group was two hours on average.

Differences between study conditions on primary and secondary outcome measures are reported in Table VIII. SH+ led to a statistically significant reduction in the incidence of any mental disorders as measured with the M.I.N.I. at post-intervention (Cramer's V 0.135, p= 0.012, RR 0.499, 95% CI 0.285 to 0.873), but not at six-month follow-up (Cramer's V 0.007, p= 0.902, RR 0.962 CI 0.521 to 1.778) (primary outcome).

PRIMARY OUTCOME - MINI	**TAU**	**SH+**	**Cramer's V**	**p-value***	**RR (CI)**
Post-intervention	33/176 (18.75%)	16/171 (9.36%)	0.135	**0.012**	0.499 (0.285-0.873)
6 months	19/157 (12.10%)	17/146 (11.64%)	0.007	0.902	0.962 (0.521-1.778)
SECONDARY BINARY OUTCOME					
Lost to FU – post-intervention	53/229 (23.14%)	59/230 (25.65%)	0.029	0.532	1.108 (0.803-1.530)
Lost to FU - 6 months	72/229 (31.44%)	84/230 (36.52%)	0.054	0.251	1.162 (0.899-

					1.501)
SECONDARY CONTINUOUS OUTCOMES			**Coefficient**	**p-value***	**Std.coef. (SE)**
GHQ score (0-12)					
Screening (N=459)	5.507 (2.447)	5.619 (2.185)	-	-	-
post-intervention (N=344)	4.154 (3.383)	3.07 1 (2.991)	-1.014	**0.002**	-0.157 (0.051)
6 months (N=368)	3.123 (3.201)	2.983 (3.103)	-0.103	0.747	-0.016 (0.051)
PCL5 score (0-80)					
Baseline (N=459)	22.765 (16.239)	24.692 (16.352)	-	-	-
post-intervention (N=341)	20.930 (16.966)	19.223 (15.820)	-2.556	0.108	-0.078 (0.048)
6 months (N=365)	18.053 (15.496)	17.533 (15.959)	-1.503	0.297	-0.048 (0.046)
PHQ9 score (0-27)					

Baseline (N=459)	8.384 (5.546)	8.478 (5.816)	-	-	-
post-intervention (N=342)	7.595 (5.817)	6.098 (5.408)	-1.418	**0.013**	-0.125 (0.050)
6 months (N=365)	6.925 (5.779)	6.124 (5.710)	-0.761	0.184	-0.066 (0.050)
WHO-5 (0-100)					
Baseline (N=459)	47.354 (24.984)	46.723 (23.625)	-		-
post-intervention (N=343)	47.977 (25.315)	56.357 (24.977)	8.882	**0.001**	0.175 (0.051)
6 months (N=365)	48.834 (26.251)	57.855 (25.146)	9.526	**≤ 0.001**	0.183 (0.050)
WHODAS (0-1)					
Baseline (N=459)	0.152 (0.144)	0.148 (0.141)	-	-	-
post-intervention (N=337)	0.113 (0.145)	0.115 (0.149)	0.001	0.939	0.004 (0.049)
6 months (N=364)	0.101	0.093	-0.009	0.452	-0.036

	(0.133)	(0.110)			(0.047)
PSYCHLOPS score (0-20)					
Baseline (N=432)	13.925 (4.396)	14.097 (4.013)	-	-	-
post-intervention (N=325)	12.882 (4.903)	11.128 (5.412)	-1.771	**0.001**	-0.172 (0.052)
6 months (N=353)	11.312 (5.122)	10.853 (5.253)	-0.577	0.274	-0.056 (0.051)
PMLD (0-68)					
Baseline	-	-	-	-	-
post-intervention (N=342)	25.589 (12.846)	24.174 (12.199)	-	-	-
6 months (N=289)	20.490 (11.510)	20.607 (11.747)	0.470	0.660	0.020 (0.046)
EQ-5D					
Baseline (N=455)	0.716 (0.280)	0.716 (0.280)	-	-	-

post-intervention	-	-	-	-	-
6 months (N=287)	0.751 (0.296)	0.767 (0.274)	0.037	0.219	0.067 (0.054)

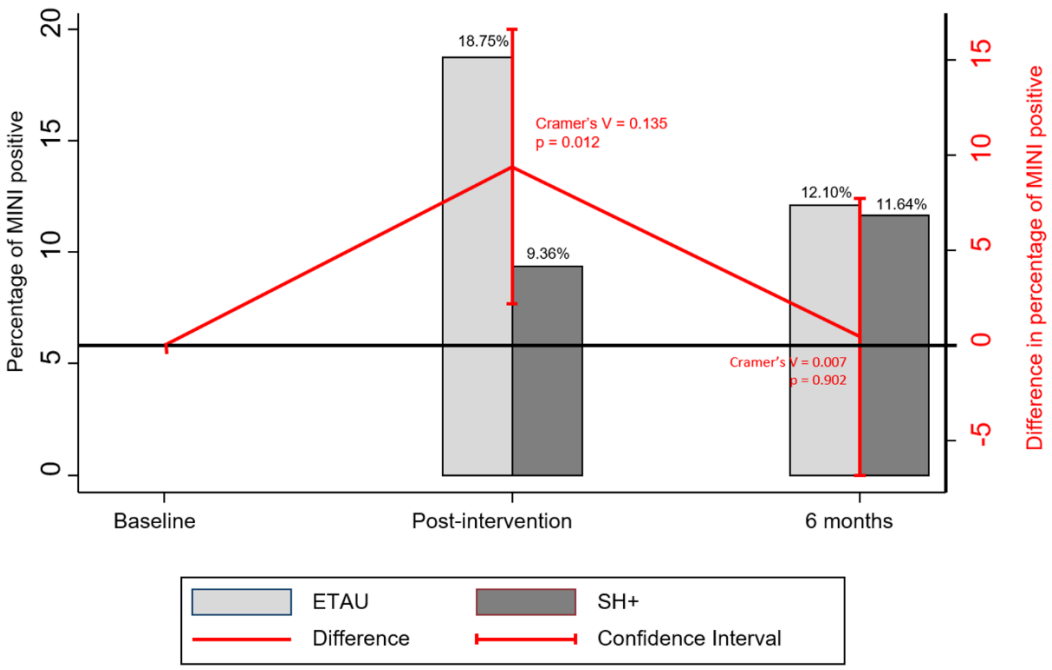
Table VIII: Summary statistics of results for primary and secondary outcomes at each timepoint

CI= confidence interval, TAU= treatment as usual, FU= follow-up, RR= risk ratio, SE= standard error. Values in bold highlight statistically significant differences

Figure 7 is a graphical representation of the trend over time in the incidence of mental disorders in each of the two groups, and of their difference.

SH+, compared with TAU, was also associated with larger improvements at post-intervention for the secondary outcomes of psychological distress as measured with the GHQ-12 (Standardized Coefficient (Std Coef) -0.157, Standard Error (SE) 0.051, p=0.002), depression symptoms as measured with the PHQ-9 (Std Coef -0.125, SE 0.050, p=0.013), wellbeing as measured with the WHO-5 (Std Coef 0.175, SE 0.051, p=0.001), and perceived problems as measured with PSYCHLOPS (Std Coef -0.172, SE 0.052, p=0.001). Such results were confirmed by global statistical significance of the intervention on all outcomes by performing SUR (p-value = 0.001). At 6-month follow-up, we detected a statistically significant difference in favour of SH+ on WHO-5 (Std Coef 0.187, SE 0.050, $p \leq 0.001$), while the other secondary outcomes differences did not reach statistical significance. Results from SUR showed evidence of a global effect of treatment on secondary outcomes (p-value 0.005) at 6-month follow-up as well.

Figure 7: Trend in the incidence of any mental disorders over time.



The histograms represent the proportion of participants with mental disorders at post-intervention and at six months of follow-up, while the red line represents the difference in the proportion of participants with mental disorders at post-intervention and at six months of follow-up.

The ITT analysis results were confirmed in the PP analysis (appendix, table B). Secondary analyses of continuous outcomes conducted without any imputations of missing values did not identify any relevant difference with respect to the main analyses (appendix, table C).

None of the interactions reached the statistical significance threshold for binary outcomes. By performing SUR on post-intervention secondary outcomes, a global test on all interactions of the variable intervention allocation, with centre and the potential moderators on all regressions, turned out to be not statistically significant (p-value 0.581). The same test performed at six-month follow-up revealed interactions to be statistically significant (p-value 0.025). We then conducted single regressions, and found global statistical significance of all interactions only in the regression having WHODAS as an outcome (p-value < 0.001). Thus, we finally performed simple models controlling for WHODAS at baseline with the variable "group allocation", each separate variable, and their interaction, as regressors. Only length of stay in the hosting country (p-value 0.022) and years of education (p-value

0.042) emerged as statistically significant moderators. As shown in appendix (statistical appendix: Figure 8), a significant protective effect of SH+ on the WHODAS score at six-months emerged for people resettled in the host country for six years or more. With regard to safety considerations, the EAB responded to eight adverse events, and none were evaluated to be related to the study/intervention participation.

5. DISCUSSION

This thesis presents the first prevention trial in in asylum seekers and refugees, being the largest study ever conducted in this population group in HICs. To the best of our knowledge, no evidence from RCTs was available on the effectiveness of any psychosocial interventions in preventing the onset of mental disorders in this vulnerable population. We failed to show any preventative effect of SH+ at six months of follow-up, which was our primary endpoint, however we were able to show a statistically significant and clinically relevant difference in favour of SH+ in reducing the incidence of mental disorders at post-intervention.

Compared to TAU, SH+ halved the incidence of any mental disorders, which is a remarkable and promising finding, as it provides for the first time experimental evidence that it is possible to prevent the incidence of mental disorders in asylum seekers and refugees resettled in HICs. In line with this finding, we additionally identified a beneficial effect of SH+ in reducing psychological distress, depression symptoms, perceived problems, and in increasing wellbeing at post-intervention, while a beneficial effect on secondary outcomes was found at six months of follow-up for well-being only.

The beneficial effects of SH+ may be related to its main core components. The intervention - based on the Acceptance and Commitment Therapy[71 72] - aims to enhance psychological flexibility and improve coping strategies for dealing with adversity, and was culturally adapted to the target backgrounds and languages of the target population groups. SH+ may have encouraged participants to better adapt to fluctuating situational demands, to shift perspective, balancing competing desires, needs, and life domains, through the range of skills covered in the course. Participants may have also learned to accommodate difficult thoughts and feelings, through the

use of mindfulness techniques. Additionally, the opportunity to have guided discussions with peers using their native language could have strengthened participants' sense of community and resilience. The use of native languages may be a key aspect, as qualitative and quantitative evidence exists suggesting that poor command of the receiving country language is a central factor limiting communication and optimal uptake of psychological and psychosocial interventions.[73 74] Moreover, the sense of belonging and social connectedness that SH+ promotes are well-established protective factors for mental health, providing a buffering effect against psychological distress, particularly for individuals who have experienced adverse life events.[75 76] Further research should include measures of constructs such as perceived social support, and/or social capital and a qualitative process evaluation in order to corroborate the inferences that can be made about potential mechanisms of change.

These factors have likely exerted a positive and preventative effect at post-intervention, but this effect was not maintained over the time, with the exception of wellbeing. Several reasons may explain these findings, in particular the short duration of the intervention, which is composed of five sessions delivered weekly, and a reduction of practise or application of the techniques after the groups had ended. Interestingly, a decreased intervention effect over time was similarly observed in the SH+ trial conducted in Uganda; smaller effect sizes for psychological distress, PTSD symptoms, depression symptoms and other outcomes were observed at follow-up as compared to immediate post-intervention.[42] More generally, evidence on the effectiveness of psychosocial interventions in vulnerable population groups found that the beneficial effects of interventions on PTSD, depression, and anxiety symptoms, were reduced at follow-up.[77-79] A recent systematic review of 17 RCTs involving 1,108 adult refugees confirmed a strong beneficial effect of psychological interventions in reducing PTSD and depression at immediate post-intervention, that was reduced, but still statistically significant, at follow-up.[80] Length of follow-up was up to six months in the majority of the included studies, with no information on longer-term assessments.[80] In addition, there was high heterogeneity across included studies, related for example to major differences in the support refugees and asylum seekers receive - especially in countries where asylum seeking people are not allowed

to work - or in the type of accommodation provided (e.g., flat, hostel, refugee camp, reception centre), hence indicating that there are moderators and mediators that need to be investigated in further analyses.[81] Finally, meta-analyses from the available systematic reviews included very small studies either at post-intervention and follow-up (e.g., six or less participants per arm), raising concerns on methodological standards and quality.[82 83]

Little knowledge exists on whether these drops in the effect sizes are due to intervention-related processes (e.g., a return to previous emotional/behavioural patterns), or context-related variables (e.g., new or continued adversities experienced in the host countries, associated with renewed psychological distress) or the impact that increased adversity may have on the effect of interventions. For SH+, it will be important to explore whether booster sessions, after the delivery of the group intervention, might assist in maintaining its benefits over the time. Notably, booster sessions for SH+ are already possible, given the publication of the SH+ illustrated book - "Doing what matters in time of stress".[84] This can potentially be delivered as guided self-help over the telephone, in groups or - with further development - as an individual online intervention, using the illustrated book as the core session content, with trained helpers motivating and encouraging ongoing use. This approach may be studied either as a strategy to reinforce the effects of the standard SH+, within stepped-care models composed of different intensity interventions, or as a stand-alone intervention. It does not require face-to-face interactions, which could be an important added value during the SARS-CoV2 or similar pandemic periods requiring physical distancing and isolation measures.

We note several limitations of our study. First, although this is the largest study in this population in HICs, we were able to get close, but did not reach, the planned sample size. Several potential factors may have contributed to the smaller sample size. As the included participants did not have a mental disorder, they may not have perceived their psychological wellbeing as a priority. Reported priorities included uncertainty about refugee application status, housing, unstable working conditions, management of visa issues, the safety of family members, a fear of being returned to home country, and plans to move to another country as often the study site was not their final destination. These factors limited engagement and availability to

participate. Moreover, we identified a relatively large proportion of individuals with a psychiatric diagnosis, that were advised to seek appropriate care according to a pre-defined protocol, and were excluded from participation. We note, however, that the systematic exclusion of participants with a mental disorder at baseline is a key strength of our study, as compared with previous studies evaluating psychological interventions as prevention strategies in other population groups. These studies did not exclude participants with mental disorders at baseline, making it impossible to calculate the true incidence of mental disorders at follow-up.[85-87] Despite these challenges in reaching the target sample size, we were able to detect a statistically and clinically significant difference at post-treatment, thus indicating sufficient statistical power. The lack of difference at six months is unlikely related to poor statistical power, as shown by a reverse fragility index of 11.[88] This means that, in order to get a significant positive result, among the 17 participants in the SH+ arm who were M.I.N.I.-positive, more than half (9) would need to become M.I.N.I. negative.

Second, the SARS-CoV2 pandemic impacted the study procedures, because in all the recruiting sites follow-up assessments were conducted using online tools instead of face-to-face meetings. Although this switch influenced both arms equally and did not influence the total number of evaluations, it is unknown whether this may have impacted the responses of participants to the instruments.

A third limitation is related to the heterogeneity of the included population groups, coming from Pakistan, Afghanistan, Syria, Iraq, Nigeria, and other countries, and having different histories and lengths of time being in the study countries. The choice of involving people from multiple backgrounds was justified by the need to generate an evidence-base for a promising psychological intervention that has the potential of large-scale uptake across migrant populations. However, it is possible that some population groups were more responsive than others to the intervention, and that other factors such as age, gender, travel routes, time already spent in the new country, and types or number of traumatic events may act as moderators of intervention effect. Secondary analyses of SH+ studies have already been planned to shed light on these important issues.

Finally, as expected in view of the population characteristics, a substantial proportion of participants was lost to follow-up. We note, however, that the number of people

lost to follow-up is in line with the expectations listed in the study protocol,[60] and similar to those reported in other psychological intervention studies.[89]

6. CONCLUSION

Given the characteristics of SH+ - delivery by briefly trained non-specialist peers, ease of implementation, large group format, its short-term efficacy in preventing mental disorders, its efficacy in ameliorating psychological status in different populations, and the lack of adverse effects associated with its delivery, we suggest it may be considered as a public health strategy for national and international healthcare agencies and non-governmental organizations implementing migrant reception programs. Results from our study suggest that SH+ may be offered as an indicated prevention strategy aiming to prevent mental disorders in RAS resettled in HICs.

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STATISTICAL APPENDIX

Table A: Balance of full list of collected socio-demographic variables at baseline

Variable	TAU	SH+	Difference (Standard Error)	Difference Standardized
Age in years	31.537	32.961	1.424	0.099
	(9.505)	(10.779)	(0.949)	
Female gender	30.13%	28.26%	-0.019	-0.029
	(69/229)	(65/230)	(0.043)	
Country of origin				
Afghanistan	14.41%	14.35%	-0.001	-0.001
	(33/229)	(33/230)	(0.033)	
Iraq	18.78%	17.39%	-0.014	-0.025
	(43/229)	(40/230)	(0.036)	
Nigeria	24.02%	25.65%	0.016	0.027
	(55/229)	(59/230)	(0.040)	
Other country	4.80%	6.09%	0.013	0.040
	(11/229)	(14/230)	(0.021)	
Pakistan	9.61%	8.26%	-0.013	-0.033
	(22/229)	(19/230)	(0.027)	
Syria	28.38%	28.26%	-0.001	-0.002
	(65/229)	(65/230)	(0.042)	
Single	42.29%	46.96%	0.047	0.066
	(96/227)	(108/230)	(0.047)	
Married/Cohabitant	49.78%	46.96%	-0.028	-0.040
	(113/227)	(108/230)	(0.047)	
Divorced/widowed	7.49%	6.09%	-0.014	-0.039
	(17/227)	(14/230)	(0.024)	
N of relatives	1.655	1.409	-0.246	-0.079
	(2.413)	(1.978)	(0.206)	
N of children	1.369	1.348	-0.021	-0.007
	(2.426)	(1.798)	(0.200)	
Years of education	10.157	10.452	0.295	0.040
	(5.451)	(4.890)	(0.497)	
Illiterate	11.50%	5.73%	-0.058	-0.146
	(26/226)	(13/227)	(0.026)	
Primary	40.71%	44.93%	0.042	0.060
	(92/226)	(102/227)	(0.047)	
High School	27.88%	27.75%	-0.001	-0.002
	(63/226)	(63/227)	(0.042)	
University	19.91%	20.70%	0.008	0.014
	(45/226)	(47/227)	(0.038)	
N of siblings	4.382	4.923	0.541	0.119

	(3.189)	(3.230)	(0.309)	
Religion				
Christian	28.70%	26.55%	-0.022	-0.034
	(64/223)	(60/226)	(0.042)	
Muslim	66.37%	66.37%	0.000	0.000
	(148/223)	(150/226)	(0.045)	
Other religion	4.93%	7.08%	0.021	0.064
	(11/223)	(16/226)	(0.022)	
Single pre migration	42.29%	46.96%	0.047	0.066
	(96/227)	(108/230)	(0.047)	
Married Cohabitant_ pre migration	49.78%	46.96%	-0.028	-0.040
	(113/227)	(108/230)	(0.047)	
Divorced/widowed pre migration	7.49%	6.09%	-0.014	-0.039
	(17/227)	(14/230)	(0.024)	
Observations	229	230	459	
Unemployed pre migration	11.95%	7.89%	-0.041	-0.096
	(27/226)	(18/228)	(0.028)	
Employed pre migration	56.19%	58.33%	0.021	0.031
	(127/226)	(133/228)	(0.047)	
Self-employed pre migration	13.27%	15.35%	0.021	0.042
	(30/226)	(35/228)	(0.033)	
Student pre migration	9.29%	9.65%	0.004	0.009
	(21/226)	(22/228)	(0.028)	
Alone pre migration	7.96%	7.86%	-0.001	-0.003
	(18/226)	(18/229)	(0.025)	
Spouse/Cohabitant pre migration	40.27%	38.86%	-0.014	-0.020
	(91/226)	(89/229)	(0.046)	
Parents pre migration	43.81%	46.29%	0.025	0.035
	(99/226)	(106/229)	(0.047)	
Other relatives pre migration	5.75%	4.37%	-0.014	-0.045
	(13/226)	(10/229)	(0.021)	

Living with others pre migration	2.21%	2.62%	0.004	0.019
	(5/226)	(6/229)	(0.014)	
Age at departure in years	27.710	28.767	1.057	0.075
	(9.430)	(10.414)	(0.944)	
Departure agreement	75.46%	75.56%	0.001	0.002
	(163/216)	(170/225)	(0.041)	
Balkan route	34.50%	28.26%	-0.062	-0.095
	(79/229)	(65/230)	(0.043)	
Eastern route	19.65%	22.17%	0.025	0.044
	(45/229)	(51/230)	(0.038)	
African route	26.64%	27.83%	0.012	0.019
	(61/229)	(64/230)	(0.042)	
Other route	18.34%	20.43%	0.021	0.037
	(42/229)	(47/230)	(0.037)	
Travel duration	10.290	10.634	0.343	0.012
	(17.336)	(23.587)	(2.096)	
Present country is the final destination	90.79%	91.70%	0.009	0.023
	(207/228)	(210/229)	(0.026)	
Detention during travel	29.46%	31.70%	0.022	0.034
	(66/224)	(71/224)	(0.044)	
Detention duration in months	0.688	1.206	0.518	0.128
	(1.887)	(3.599)	(0.268)	
Travel alone	19.21%	22.17%	0.030	0.052
	(44/229)	(51/230)	(0.038)	
Travel with relatives	44.98%	43.48%	-0.015	-0.021
	(103/229)	(100/230)	(0.046)	
Migrants travel	34.93%	32.17%	-0.028	-0.041
	(80/229)	(74/230)	(0.044)	
Relatives in the country of origin	88.11%	90.35%	0.022	0.051
	200/227	206/228	0.029	
Sons/daughters	9.61%	13.91%	0.043	0.095
	(22/229)	(32/230)	(0.030)	
Partner: husband/wife	8.73%	12.61%	0.039	0.089
	(20/229)	(29/230)	(0.029)	
Parents	52.40%	52.61%	0.002	0.003
	(120/229)	(121/230)	(0.047)	
Other relatives	64.63%	72.61%	0.080	0.122

	(148/229)	(167/230)	(0.043)	
Friends	20.96%	24.78%	0.038	0.064
	(48/229)	(57/230)	(0.039)	
Asylum seeker	53.71%	52.17%	-0.015	-0.022
	(123/229)	(120/230)	(0.047)	
Humanitarian protection	17.47%	12.17%	-0.053	-0.105
	(40/229)	(28/230)	(0.033)	
Subsidiary protection	3.93%	5.65%	0.017	0.057
	(9/229)	(13/230)	(0.020)	
Political asylum	18.78%	25.22%	0.064	0.110
	(43/229)	(58/230)	(0.039)	
Other legal status	5.68%	4.78%	-0.009	-0.028
	(13/229)	(11/230)	(0.021)	
Length of stay in host country in months	33.944	35.240	1.295	0.036
	(22.809)	(28.457)	(2.444)	
Living alone post migration	20.00%	20.61%	0.006	0.011
	(45/225)	(47/228)	(0.038)	
Living with partner post migration	32.89%	32.46%	-0.004	-0.007
	(74/225)	(74/228)	(0.044)	
Living with parents post migration	4.44%	4.82%	0.004	0.013
	(10/225)	(11/228)	(0.020)	
Living with other relatives post migration	3.56%	2.19%	-0.014	-0.058
	(8/225)	(5/228)	(0.016)	
Living with others post migration	39.11%	39.91%	0.008	0.012
	(88/225)	(91/228)	(0.046)	
Living in a Refugee center post migration	34.50%	39.30%	0.048	0.070
	(79/229)	(90/229)	(0.045)	
Rented apartment post migration	50.66%	49.34%	-0.013	-0.018
	(116/229)	(113/229)	(0.047)	
Other accommodation post migration	13.10%	10.04%	-0.031	-0.067
	(30/229)	(23/229)	(0.030)	
Accomodation found through government	49.33%	55.07%	0.057	0.081
	(111/225)	(125/227)	(0.047)	

Accomodation found through private association	27.11%	25.11%	-0.020	0.032
	(61/225)	(57/227)	(0.041)	
Accomodation found through voluntary association	2.22%	2.20%	-0.000	-0.001
	(5/225)	(5/227)	(0.014)	
Accomodation found through facilitation of hosting country	13.78%	13.22%	-0.006	-0.012
	(31/225)	(30/227)	(0.032)	
Accomodation found through another way	7.56%	4.41%	-0.032	-0.094
	(17/225)	(10/227)	(0.022)	
Unemployed post migration	47.16%	49.78%	0.026	0.037
	(108/229)	(114/229)	(0.047)	
Employed post migration	20.09%	17.47%	-0.026	-0.047
	(46/229)	(40/229)	(0.037)	
Student post migration	17.47%	17.47%	0.000	0.000
	(40/229)	(40/229)	(0.036)	
Home maker post migration	4.80%	5.24%	0.004	0.014
	(11/229)	(12/229)	(0.020)	
Vocational training	6.11%	4.37%	-0.017	-0.051
	(14/229)	(10/229)	(0.021)	
Other occupation post migration	4.37%	5.68%	0.013	0.042
	(10/229)	(13/229)	(0.020)	
Observations	229	230	459	

Table B: Per-protocol analysis

Variable	TAU (229)	SH+ (117)	Cramer's V	Risk Ratio(CI)
PRIMARY OUTCOME - MINI				
Post-intervention	33/176(18.75%)	9/111(8.11%)	0.147 (0.013)	0.432(0.215-0.869)
6 months	19/157(12.10%)	10/89(11.24%)	0.013 (0.840)	0.928(0.452-1.908)
6 months with LOCF	28/190(14.74%)	13/112(11.61%)	0.044 (0.443)	0.788(0.426-1.457)
Variable			**Coef(p)**	**Std.coef.(SE)**
SECONDARY OUTCOMES				
GHQ				
Screening(N=346)	5.507(2.447)	5.427(2.147)	-	-
Post-intervention(N=284)	4.154(3.383)	2.706(2.920)	-1.135 (< 0.001)	-0.201(0.055)
6 months non-LOCF(N=235)	2.887(3.097)	2.631(2.916)	-0.196 (0.623)	-0.031(0.063)
6 months LOCF(N=298)	3.123(3.201)	2.622(3.033)	-0.442 (0.225)	-0.068(0.055)
PCL5				
Baseline(N=346)	22.765(16.239)	24.744(16.242)	-	-
Post-intervention(N=282)	20.930(16.966)	17.204(14.669)	-4.400 (0.011)	-0.132(0.052)
6 months non-LOCF(N=235)	16.794(15.298)	18.210(16.847)	-0.149 (0.936)	-0.005(0.057)
6 months LOCF(N=296)	18.053(15.496)	17.719(16.075)	-1.036 (0.511)	-0.032(0.048)
PHQ9				
Baseline(N=346)	8.384(5.546)	8.077(5.8887)	-	-
Post-intervention(N=283)	7.595(5.817)	5.403(4.953)	-1.928 (0.001)	-0.168(0.051)

6 months non-LOCF(N=236)	6.493(5.747)	6.194(5.687)	-0.222 (0.761)	-0.019(0.062)
6 months LOCF(N=296)	6.925(5.779)	6.002(5.636)	-0.663 (0.302)	-0.056(0.054)
WHO5				
Baseline(N=346)	47.354(24.984)	45.750(23.478)	-	-
Post-intervention(N=284)	47.977(25.315)	60.661(24.206)	13.055 (< 0.001)	0.248(0.055)
6 months non-LOCF(N=236)	50.693(26.401)	58.093(26.967)	7.711 (0.027)	0.139(0.062)
6 months(N=296)	48.834(26.251)	59.309(25.373)	10.859 (≤ 0.001)	0.199(0.055)
WHODAS				
Baseline(N=346)	0.152(0.144)	0.157(0.131)	-	-
Post-intervention(N=279)	0.113(0.145)	0.106(0.131)	-0.008 (0.583)	-0.028(0.051)
6 months non-LOCF(N=239)	0.093(0.127)	0.103(0.121)	0.011 (0.443)	0.043(0.055)
6 months(N=296)	0.101(0.133)	0.101(0.117)	-0.002 (0.885)	-0.007(0.049)
PSYCHLOPS				
Baseline(N=323)	13.925(4.396)	14.200(3.468)	-	-
Post-intervention(N=267)	12.882(4.903)	10.702(5.417)	-2.173 (<0.001)	-0.206(0.056)
6 months non-LOCF(N=225)	11.005(4.981)	11.235(4.801)	0.000 (1.000)	0.000(0.066)
6 months(N=285)	11.312(5.122)	10.574(5.181)	-0.817 (0.177)	-0.078(0.058)
PMLD				
Baseline	-	-	-	-
Post-intervention(N=283)	25.587(12.846)	23.805(12.082)	-	-
6 months(N=236)	20.490(11.510)	20.861(11.366)	0.607 (0.608)	0.026(0.051)
EQ-5D				

Baseline(N=345)	0.706(0.276)	0.696(0.281)	-	-
Post-intervention	-	-	-	-
6 months(N=235)	0.751(0.296)	0.749(0.274)	0.008 (0.821)	0.013(0.057)

Table C: Analysis with no imputation

Variable	TAU	SH+	Coef (p)	Std.coef. (SE)
GHQ				
Screening (N=458)	5.507 (2.447)	5.616 (2.189)	-	-
Post-intervention (N=343)	4.154 (3.383)	3.089 (2.991)	-0.997 (0.003)	-0.154 (0.051)
6 months (N=289)	2.888 (3.097)	2.913 (3.036)	0.061 (0.865)	0.010 (0.059)
PCL5				
Baseline (N=450)	22.712 (16.286)	24.598 (16.464)	-	-
Post-intervention (N=334)	20.759 (16.673)	18.988 (15.668)	-2.701 (0.091)	-0.083 (0.049)
6 months (N=283)	16.678 (15.261)	16.810 (16.073)	-1.977 (0.240)	-0.063 (0.054)
PHQ9				
Baseline (N=458)	8.390 (5.557)	8.478 (5.816)	-	-
Post-intervention (N=338)	7.561 (5.816)	6.103 (5.429)	-1.403 (0.015)	-0.124 (0.051)
6 months (N=287)	6.493 (5.747)	5.978(5.567)	-0.625 (0.333)	-0.055 (0.057)
WHO5				
Baseline (N=457)	47.354 (24.984)	46.544 (23.649)	-	-
Post-intervention (N=342)	48.253 (25.123)	56.357 (24.977)	8.490(0.001)	0.167(0.052)
6 months (N=290)	50.693 (26.401)	57.229 (25.949)	6.930 (0.021)	0.132 (0.057)
WHODAS				
Baseline (N=452)	0.149 (0.142)	0.147 (0.141)	-	-
Post-intervention (N=330)	0.110 (0.142)	0.115 (0.150)	0.006 (0.674)	0.021 (0.050)
6 months (N=292)	0.092 (0.125)	0.094(0.112)	0.001 (0.950)	0.003 (0.054)
PSYCHLOPS				
Baseline (N=418)	13.957 (4.409)	14.257 (3.946)	-	-
Post-	12.924	11.151	-1.800	-0.172

intervention (N=309)	(4.913)	(5.475)	(0.001)	(0.053)
6 months (N=271)	11.014 (5.006)	11.229 (5.079)	-0.152 (0.799)	-0.015 (0.060)
PMLD				
Baseline	-	-	-	-
Post-intervention (N=326)	25.198 (12.856)	24.069 (12.337)	-	-
6 months (N=281)	20.514 (11.526)	20.741 (11.863)	0.196 (0.860)	0.013 (0.047)

Table D: Results controlling for imbalances at baseline

Variable	N (regr)	Coef (p)	Std.coef. (SE)
PRIMARY OUTCOME			
MINI Post-intervention	322	-0.704 (0.018)	-0.353 (0.149)
6 months	283	-0.068 (0.828)	-0.034 (0.157)
SECONDARY OUTCOMES			
LTFU Post-intervention	432	-0.023 (0.886)	-0.011 (0.080)
6 months	432	0.080 (0.551)	0.040 (0.067)
GHQ Post-intervention	319	-0.996 (0.005)	-0.154 (0.055)
6 months	342	-0.122 (0.723)	-0.019 (0.054)
PCL5 Post-intervention	317	-1.788 (0.287)	-0.055 (0.052)
6 months	340	-1.000 (0.507)	-0.032 (0.048)
PHQ9 Post-intervention	318	-1.232 (0.042)	-0.109 (0.054)
6 months	340	-0.745 (0.211)	-0.065 (0.052)
WHO5 Post-intervention	319	7.451(0.007)	0.148 (0.055)
6 months	341	9.186(0.001)	0.180 (0.053)
WHODAS Post-intervention	312	0.014 (0.375)	0.047 (0.052)
6 months	339	-0.002 (0.880)	-0.008 (0.050)
PSYCHLOPS Post-intervention	300	-1.564 (0.006)	-0.151 (0.054)
6 months	322	-0.329 (0.559)	-0.032 (0.054)
PMLD 6 months	247	0.605 (0.581)	0.027 (0.049)

EQ-5D 6 months	265	0.031 (0.324)	0.056 (0.056)

Test of interactions

In simple regression models considering as outcome variables the M.I.N.I. and being lost to follow-up (LTFU), the variable intervention allocation, the variables related to gender, education in years, age, length of stay in the host country, country of origin, and recruiting center, considered separately, and their interaction with intervention allocation, as regressors, none of the interactions reached the conventional statistical threshold either at post-intervention or at six months. By performing seemingly unrelated regression on post- intervention secondary outcomes, a global test on all interactions of intervention status turned out not to be statistically significant (p-value 0.581). The same test performed at six-month follow-up found instead interactions to be statistically significant (p-value 0.025). We then proceeded to test single regressions, and found global statistical significance of all interactions only in the regression having WHODAS at outcome (p-value < 0.001). Thus, we finally performed simple models controlling for WHODAS at baseline and with intervention allocation, each variable considered separately, and their interaction with intervention allocation, as regressors. This analysis found that only length of stay in the host country (p-value 0.022) and years of education (p-value 0.042) emerged as statistically significant moderators. In particular, as shown in Figure 7 and Figure 8, a statistically significant protective effect of SH+ on WHODAS score at 6-months emerged for people in the country from five years or more, while for none of the observed values of years of education a statistically significant effect of SH+ was found.

Figure 8: Estimated effect of SH+ on WHODAS at 6 months per length of stay in the hosting country

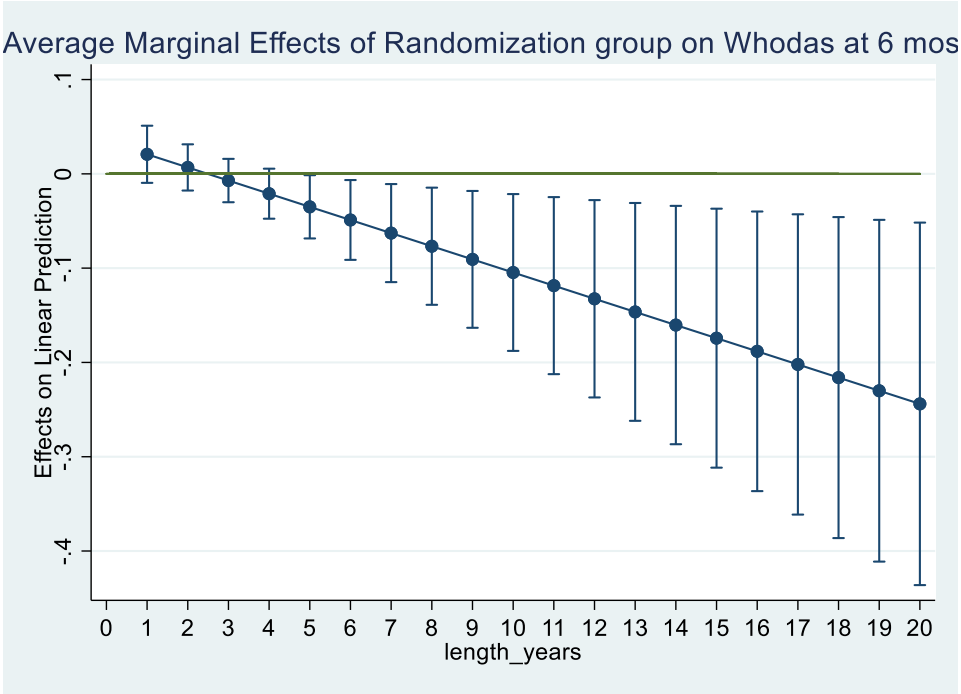

Figure 9: Estimated effect of SH+ on WHODAS at 6 months per length of stay in the hosting country