Review title

A network meta-analysis of complex interventions to prevent mental-ill-health in children and young people: evaluation of effective and cost-effective intervention components

Review question(s)

The overall aim of this project is to identify the most effective and cost-effective intervention component(s), or combination of components, for universal and targeted (indicated and selected) prevention of common mental health problems in children and young people. This will be achieved by:

1. Identification of health and social outcomes of interest for *(i)* children and young people, *(ii)* parents and *(iii)* public health practitioners and commissioners to inform taxonomy development, systematic review and cost-effectiveness analysis model;

2. Systematic review of school and community-based *(i)* universal and *(ii)* targeted prevention interventions for mental ill-health that have been evaluated in randomised controlled trials;

3. Development of a classification scheme, or taxonomy, of preventative mental health intervention components;

4. Identification of health and social outcomes of interest for *(i)* children and young people and *(ii)* public health practitioners and commissioners To inform the systematic review and cost-effectiveness analysis model;

5. Identification and evaluation of effective components of mental health interventions using a meta-regression based extension to network meta-analysis. This will be completed *(i)* across mental ill-health conditions and also *(ii)* for specific mental health conditions;

6. Economic evaluation to determine the most cost-effective component, or combinations of components of;

    6.1. targeted interventions for *(i)* primary aged children with conduct disorders, anxiety, or depression *(ii)* secondary-aged children/ young people with conduct disorders, anxiety or depression; and (iii) university-aged young people with anxiety or depression and

    6.2. universal interventions for *(i)* primary aged children, *(ii)* secondary aged children and *(iii)* university aged young people. We will also assess whether universal interventions are more cost-effective when delivered in primary compared with secondary school settings.

Searches

Databases to be searched for this project are Medline, CINAHL, EMBASE, Cochrane, PSYCINFO, ERIC, SOCIAL SCIENCE CITATION INDEX, ASSIA, Trials Register of Public Health Interventions, Database of Public Health Effectiveness Reviews, C2 SPECTR and PSITRI. Search terms will be adapted from existing systematic reviews [1][2]. There will be no language or publication date restrictions. We will also manually search the reference lists of relevant research articles and previous reviews. Citation searches will be conducted to locate companion papers, in particular intervention manuals, process evaluations and study protocols which could provide additional information on intervention content and delivery.

Condition or domain being studied

Common mental health problems include depression, anxiety, obsessive-compulsive disorder, phobia, post-traumatic stress, panic disorder and conduct disorder. We will accept the trialists' definitions of participants' illness status. Sub-clinical mental ill-health may be defined in reference to diagnostic criteria such as ICD-10 or DSM IV categorised disorders (e.g. oppositional-defiant disorder, dysthymia, depression, anxiety, OCD) or 'in research' via use of disorder specific screening instruments e.g. Children's depression inventory or SDQ. Young people with co-

morbid mental health diagnoses will also be included; however, we will exclude psychiatric conditions which can be defined as psychotic, neuro-developmental or neuro-behavioral e.g. ADHD, schizophrenia or an autistic spectrum disorder.

Participants/population

Young people aged 5 to 25. For the targeted review those at risk of mental ill-health will be included. Examples of 'at risk' populations include those with familial history of mental illness, those engaging in substance mis-use, children with deprived home environments or those scoring highly on scales assessing externalising or internalising behaviours. Populations 'at risk' from self-harming behaviours will also be included in the reviews.

Intervention(s), exposure(s)

All interventions focussed on mental ill-health prevention are eligible for inclusion; they may address generic mental health and well-being, a specific mental health condition or a combination of conditions. Interventions of interest are broadly defined and include:

- Universal, indicated or selected interventions at the individual, family or group level
- Psychological, psychosocial, educational and physical (eg. exercise, occupational therapy) interventions to prevent/reduce depression, anxiety, panic, stress, self-harm, suicidal ideation and behaviour, and conduct problems (including aggression & violence).
- Psychological and psychosocial, educational and physical interventions to reduce general mental ill-health and/or increase emotional well-being.

We will not restrict inclusion by mode of intervention delivery. Examples of eligible delivery include interventions delivered by peer-educators (both with and without experience of personal mental health issues), teachers, youth workers, clinicians, health visitors, school nurses and school counsellors. Digital and social media interventions are also eligible for inclusion if they are delivered in the education setting, or are a component of a wider programme delivered in the school/ educational setting.

We will not exclude interventions based on geography or language of publication. We will include interventions designed and implemented in lower, middle and high income countries.

Unless the objective of the intervention is to prevent mental ill-health, interventions designed to primarily target behaviours considered to be on the causal pathway to a mental disorder (e.g. substance abuse) will be excluded.

Comparator(s)/control

All relevant control interventions will be included, for example:

- Treatment as usual/ usual care
- Waiting list
- No treatment
- Attention 'placebo' interventions
- Other interventions for preventing mental health problems

Types of study to be included

Study designs to be included are both parallel group and cluster RCTs. Where necessary we will adjust for clustering, if trial authors have not done so, using the approach suggested by the Cochrane Collaboration. Crossover trials are unlikely in this area but if found only the first period will be eligible for inclusion in the review. We will include quasi-randomised studies (i.e. where allocation to intervention is on the basis of a pseudo-random sequence). Multi-arm trials will be included.

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Context

- School-based, including primary, secondary and tertiary education settings
- School-affiliated youth and community groups e.g. after school and holiday clubs, church groups, youth clubs and student unions.

We will exclude clinical inpatient treatment settings. Due to concerns regarding the transitivity assumption, interventions set in young offender institutions and for looked after children in residential care will be excluded

Primary outcome(s)

We are conducting PPI and stakeholder consultations to identify outcomes of interest to young people and public health professionals. Using an established methodology, these outcomes will be mapped to those reported in the trials and systematic reviews on which our reviews are based [3]. Where there is discordance and/or gaps with the published literature this will be highlighted. Primary outcomes include:

- Illness-specific symptom measurement scale e.g. Depression (Moods and Feelings, Children's Depression Inventory) and anxiety (Childhood Anxiety Related Emotional Disorders)
- Well-being (self-report scales, e.g. Warwick-Edinburgh)
- Suicidal ideation and behaviour; self-harm
- Inequalities

Intervention follow-up is likely to vary across the studies; consequently our primary endpoint for the NMA will be immediately post-intervention. However, sustainability of intervention effect is important and so we will also assess intervention effect at the longest timepoint recorded by each study.

Secondary outcomes

- Acceptability of intervention to young people,
- Teacher/parent/ observer defined outcomes e.g. depression, problem behaviour
- Self-reported problem behaviour,
- Involvement in violence or aggressive behaviour
- Stigma
- Academic expectations/ achievement/ attainment
- Substance use

Data extraction (selection and coding)

Data extraction will be carried out by one investigator and checked by a second. Information will be collected on:

- study design - randomisation, description of allocation concealment and blinding;
- study participants - inclusion and exclusion criteria, country, region, population studied, and baseline characteristics such as age, ethnicity, sex, socio-economic indicators;
- intervention and comparison groups - intervention name/ branded, condition specific or general, if intervention is theory based, description of intervention theory, intervention components (see below), duration, mode of delivery, whether intervention in manualised and fidelity to intervention;
- outcomes of interest, losses to follow up and study sponsor.

This information will be entered on to data extraction spreadsheets. Following Melendez-Torres [4] intervention components will be categorised at the level of;

i) 'meaningful units', theory or therapeutic mechanism of the intervention; and
ii) grouping by intervention activity and modality e.g. cognitive, or educational & teacher delivered or peer-delivered

Here a 'meaningful unit' will be defined as the type of intervention delivered e.g. interpersonal therapy, assertiveness training, or cognitive behavioural therapy (CBT) and NMAs have been successfully conducted using these categorisations. However, even within a 'meaningful units' analysis there can be intervention differences which contribute to heterogeneity . Further dismantling of interventions by component activity and modality will use a pragmatic approach called Intervention Component Analysis (ICA) [5]. ICA takes an inductive and iterative approach to categorise intervention components and uses qualitative analysis techniques similar to those used in a thematic or realistic evidence synthesis.

Risk of bias (quality) assessment procedure

The Cochrane tool for assessing risk of bias will be used to determine whether there is high, low or unclear risk of bias in the following domains: random sequence generation, allocation concealment, blinding or participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias [6]. Two investigators will independently assess the risk of bias in each of the trials. Disagreements will be resolved via discussion with a third colleague.

Strategy for data synthesis

We will analyse each of the primary outcomes using network meta-analysis. NMA is an extension of a standard meta-analysis which enables the simultaneous comparison of multiple interventions in a single model, whilst retaining the distinct identity of each intervention analysed. It also enables the ranking of treatments according to the probability that each is the best, or worst, for a given outcome. In its simplest form, NMA is the combination of direct and indirect estimates of relative intervention effect, where indirect evidence refers to evidence on intervention C relative to B obtained from A vs. B and A vs. C studies. If both direct and indirect estimates are available, they can be pooled in NMA to produce an internally coherent set of effect estimates of each intervention relative to every other whether or not they have been compared in head-to-head trials.

The NMA will be conducted using the components-based approach developed by Welton for complex interventions. We will evaluate four models: a single-effect model (akin to standard meta-analysis), an additive main effects model, a two-way interaction model (allowing pairs of components to have either a bigger or smaller effect than would be expected from the sum of their effects alone) and a full interaction model. We anticipate population heterogeneity and will incorporate this using a random effects model, assuming a homogeneous between-study variability across studies. We will assess the goodness of fit of each model to the data by calculating the posterior mean residual deviance. This is defined as the difference between the deviance for the fitted model and the saturated model, where the deviance measures the fit of the model using the likelihood function. The Deviance Information Criterion (DIC), which is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters P_D, will be used as a basis for model comparison. The DIC penalises the posterior mean residual deviance (a measure of model fit) by the effective number of parameters in the model (as measure of complexity) and can therefore be viewed as a trade-off between the fit and complexity of the model. All statistical analyses will be conducted in a Bayesian framework using OpenBUGS software.

Analysis of subgroups or subsets

The validity of a NMA depends on the assumption of transitivity; that there is no effect modification of the intervention effects by treatment comparison or, that the prevalence of effect modifiers is similar in the different studies. An epidemiological judgement of the plausibility of this assumption requires assessment of the inclusion/exclusion criteria of every trial in the network, to assess whether the participants, trial protocols, intervention administration etc. are similar in ways that might modify treatment effect. We will compile a table of important trial and patient characteristics and visually inspect the 'similarity' of factors we consider likely to modify treatment effect. These include age, mental illness targeted, intensity of intervention and mode of delivery. The statistical manifestation of transitivity is known as consistency and is analogous to an additional layer of heterogeneity that occurs in networks of evidence when there is a discrepancy between a direct and indirect estimate of treatment effect. We will use model fit and selection statistics to assess whether discrepancies between direct and indirect evidence are evident.

Conflicts of interest

None known

References

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