Association between mental disorders and somatic conditions: protocol for an umbrella review

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ABSTRACT

Introduction Although several systematic reviews (SRs)/meta-analyses (MAs) on the association between specific mental disorders and specific somatic conditions are available, an overarching evidence synthesis across mental disorders and somatic conditions is currently lacking. We will conduct an umbrella review of SRs/MAs to test: 1) the strength of the association between individual mental disorders and individual somatic conditions in children/adolescents and adults; 2) to which extent associations are specific to individual mental and somatic conditions .

Methods and analysis We will search a broad set of electronic databases and contact study authors. We will include SRs with MA or SRs reporting the effect size from individual studies on the association between a number of somatic and mental conditions (as per the International Classification of Diseases, 11th Revision). We will follow an algorithm to select only one SR or MA when more than one are available on the same association. We will rate the quality of included SRs/MAs using the AMSTAR-2 tool. We will assess to which extent mental disorders are selectively associated with specific somatic conditions or if there are transdiagnostic, across-spectra or diagnostic spectrum-specific associations between mental disorders and somatic conditions based on the Transparent, Reporting, Appraising, Numerating, Showing (TRANSD) recommendations.

Discussion The present umbrella review will shed light on the association between mental health disorders and somatic conditions, providing useful data for the care of patients with mental health disorders, in particular for early detection and intervention. This work might also add insight to the pathophysiology of mental health conditions, and contribute to the current debate on the value of a transdiagnostic approach in psychiatry.

INTRODUCTION

Over the past years, there have been increasing awareness and evidence that many conditions classically characterised as disorders of the brain are associated also with alterations in organs/systems in other parts of the body.[1]

The pathways underpinning the comorbidity of mental disorders and somatic conditions are complex and potentially bidirectional. On the one hand, somatic conditions may contribute to mental disorders (eg, sleep apnoea increasing the risk of attention deficit hyperactivity disorder (ADHD)).[2] On the other hand, negative outcomes associated with mental disorders may increase the risk for medical conditions (eg, increased risk of sexually transmitted infections in bipolar disorder).[3] It is also possible that mental and somatic disorders share common risk factors, which have been found to include early trauma and chronic stress, inflammation, as well as socioeconomic factors (eg, low income and poor educational attainment).[4] For instance, for the association between ADHD and obesity, a number of non-mutually exclusive factors, including a common genetic vulnerability, a disruption of immunological pathways, and behavioural factors (eg, impulsivity leading to overeating and obesity) have been hypothesised.[5] In another example, the links between depression and chronic medical disorders have been summarised in complex models focused on the interaction between increased risk of health habits (such as smoking, diet, overeating and sedentary life style), the negative impact of depressive symptoms on the adherence to medical treatment regimens, and the direct effects of physiological alterations (such as decreased heart rate variability, increased adhesiveness of platelets, and pro-inflammatory state).[6]

While there have been a number of individual studies (eg, on the relationship between depression and non-food allergies[7]) and systematic reviews/meta-analyses (eg, on the alink between schizophrenia and lung cancer[8]) on the association between specific mental disorders and specific somatic conditions, an overarching synthesis of the literature across mental disorders and somatic conditions is currently lacking.

To fill this gap, we will conduct a transdiagnostic hypothesis-generating umbrella review[9] of systematic reviews (SRs) and/or meta-analyses (MAs) aimed at addressing the following questions:

1. What is the strength (credibility) of the association between individual mental disorders and individual somatic conditions?
2. With reference to the Transparent, Reporting, Appraising, Numerating, Showing (TRANSD) recommendations proposed by Fusar-Poli *et al*,[10 11] are specific mental disorders selectively associated with specific somatic conditions or are there transdiagnostic, across-spectra or diagnostic spectrum-specific associations between mental disorders and somatic conditions?

The project is referred to as Association between Mental And Somatic conditions: an Umbrella review (AMASU) and includes a section focused

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on adults (AMASU-A) and another one on children/adolescents (AMASU-PED).

METHODS AND ANALYSIS

Methods, including the search strategy, have been developed based on recent guidance for the conduct of umbrella reviews.[9 12] The protocol has been developed according to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols items,[13] when applicable.

Searches

The search strategy has been designed with the support of a librarian from the University of Southampton, UK. We will search the following electronic databases: PubMed (including MEDLINE), Ovid databases (PsycInfo, EMBASE+EMBASE Classic (which include grey literature), Ovid Medline) and Web of Knowledge (Web of Science Core Collection, Biological Abstracts, BIOSIS Citation Index, Current Contents Connect, Data Citation Index, Derwent, Innovations Index, FSTA—the food science resource, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, SciELO Citation Index). We will not apply any restrictions in terms of date/language/type of document (ie, reports published as full text, conference proceedings or other format). Corresponding authors of reports published as conference proceedings only or other forms of grey literature will be contacted to inquire about the publication status of their SR/MA and their willingness to share unpublished data if a published full text is not available. We will also hand search the references of SRs/MAs retained in the umbrella review to detect any relevant SR/MA not retrieved with the electronic search. The full search strategy, search terms and syntax are reported in online supplementary appendix 1.

Types of studies to be included

We will include SRs with or without MA. In line with the recent proposal by Martinic *et al*,[14] regardless of the definition provided by the authors in the title, abstract or text, a paper will be considered a 'systematic review' if it includes all of the following: 1) specific research question(s); 2) sources that were searched, with a reproducible search strategy (naming of databases, naming of search platforms/engines, search date and complete search strategy); 3) inclusion and exclusion criteria; 4) selection (screening) methods; 5) list of studies included in the SR (and, optionally, a list of studies excluded from the SR after reading the full text, with reasons for exclusion). To be included, MAs will need to provide a quantitative synthesis based on an SR and information about data analysis and synthesis that allows the reproducibility of the results. We will mainly include SRs and MAs with a quality appraisal of the included studies. Only for associations (between a mental disorder and somatic condition) for which no SR or MA is available that provided a quality assessment, we will rate the quality of individual studies included in SR or MA not presenting such rating using the Newcastle Ottawa Scale (NOS).[15]

If there are more than one SR or MA for each specific association (eg, association between social anxiety disorder and asthma), we will select the SR/MA to be included in our umbrella review using the following algorithm:

1. We will include preferably MAs. We will include SRs only when there are no MAs for a specific association and when the SRs report the effect size (ES) (with corresponding 95% CI), sample size and design for the majority of individual studies retained in the SR.
2. We will also check if there is any study, included in the SRs that we will not retain, that is not included in the MAs (that we will retain), and that would meet the criteria for inclusion based on the definition of conditions and participants highlighted in the present protocol; if so, we will re-run the MA including these missing studies.
3. If there are two or more MAs or SRs with effect size data on the same association, we will include the largest (ie, the one including the largest number of studies) and we will check if any study included into each further smaller MA (or SR with effect size data) was not included in the largest MA (or SR); if this is the case, we will re-run the MA including studies from the largest MA (or SR) and any additional relevant study detected from the smaller one(s) that would meet the criteria for inclusion based on the definition of conditions and participants highlighted in the present protocol.

In terms of diagnosis of mental health conditions, we will retain SRs/MAs including studies with a diagnosis of the mental disorders based on (semi)structured interviews according to standardised criteria (eg, Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD)), codes in electronic records, clinical diagnosis in medical files, or self-reported diagnosis or studies where the presence a mental health condition was based on a score above a threshold on a scale/questionnaire, without a formal diagnosis. We will explore the feasibility of conducting subgroup analyses limited to specific ways to define the mental conditions. Any subtype/presentation of the mental health disorder (eg, ADHD inattentive or hyperactive impulsive subtype) will be eligible for inclusion.

We will retain SRs/MAs including cross-sectional, and/or cohort, and/or case-control studies. For MAs pooling data from prospective/retrospective studies, we will check that data have been extracted relative to the first time point available. If not, we will extract data at first time point and pool them with other cross-sectional data. We will assess the feasibility of conducting subgroup analyses focusing on systematic reviews including cross-sectional, cohort, or case-control studies only, respectively.

Condition or domain being studied

While it is clearly unfeasible to include all known somatic conditions, we will focus on a number of conditions based on the list included in the study by Correll *et al*,[16] expanded by additional conditions which have been defined with the input of two internist doctors who were asked to list the most relevant conditions for each body system (see online supplementary appendix 2).

We will accept any way to define these disorders (eg, self-reported, reported in medical files, etc) as per the inclusion criteria of the included SRs/MAs. We will explore the feasibility of conducting subgroup analyses limited to specific ways to define the somatic conditions.

Likewise, while it would not be feasible to include all the mental health disorders, we will focus on mental conditions defined in the ICD-11 (online supplementary appendix 3).

Participants/Population

We will include SRs/MAs focusing on adults and elderly (aged >18 years) in AMASU-A and children/adolescents (≤18 years) in AMASU-PED. In the case of SRs/MAs including both studies in children/adolescents and in adults, we will use data to meta-analyse the individual studies in adults and children/adolescents only, respectively. Studies in which the first time

point occurred before or at the age of 18 and the second after the age of 18, will be considered for AMASU-PED.

Intervention(s), exposure(s)

This is an umbrella review of SRs/MAs assessing associations. No interventions will be considered.

Comparator(s)/Control

Comparisons: participants without any of the mental disorders reported above, as defined in the individual SRs and MAs.

Context

Studies including participants from any settings (ie, both from the general population, and clinical settings) will be considered.

Main outcome(s)

Any effect size (eg, OR, HR, risk ratio, incident rate ratio) expressing the association between mental health disorders and somatic conditions will be considered. As the primary outcome, we will consider the unadjusted effect size.

Additional outcome(s)

We will consider the feasibility of performing a sensitivity analysis focused on adjusted effect sizes. We are indeed aware of meta-analyses[17 18] pooling the adjusted ORs from studies where these were available. The factors adjusted for will inevitably vary in each of the studies included in the individual MA.

Data extraction (selection and coding)

SRs/MAs identified with electronic and manual searches will be listed with citation, titles and abstracts in Endnote[19]; duplicates will be excluded using the Endnote function 'remove duplicates'.

The eligibility process will be conducted in three separate stages:

1. Two authors will independently screen title and abstracts of all non-duplicated papers and will exclude those not pertinent. A final list will be agreed on with discrepancies resolved by consensus between the two authors. When consensus is not reached, a third, senior author will act as arbitrator. If any doubt about inclusion exists, the article will proceed to the next stage.
2. The full-text version of the articles passing stage 1 screening will be downloaded and assessed for eligibility by two authors, independently. Discrepancies will be resolved by consensus between the two authors and, if needed, a third senior author will act as arbitrator.

Where required, we will contact the corresponding author to inquire on study eligibility. We will report excluded articles from this stage along reasons for exclusion.

3. A matrix containing all eligible studies for each available combination of somatic and psychiatric disorder will be created. Two authors will indicate the selection of the study for each combination of somatic and psychiatric disorder following the criteria previously outlined. Discrepancies will be resolved by consensus between the two authors and, if needed, a third senior author will act as arbitrator.

Data extraction

Two researchers will perform independently the data extraction; any discrepancy will be resolved by consensus between the two authors. If this is not possible, another senior author from the review team will make a judgement on the data entered and act as an arbitrator.

For each pertinent SR/MA, the following variables will be extracted:

1. First author surname;
2. Year of publication;
3. Inclusion and exclusion criteria in relation to the type of studies and participants included. This will include details regarding the type and definition of the mental health and somatic conditions, study design (case-control, cross-sectional, cohort,) and type of association (cross-sectional, longitudinal);
4. Electronic databases searched by the authors;
5. Inclusion of unpublished data;
6. Number and type of studies included;
7. Presence of sensitivity or subgroup analyses focusing on: setting (population-base or clinical), continent/country, age, sex, treatment status;
8. Type of effect size and numerical values for available effect sizes, with 95% CI;
9. Measures of heterogeneity (eg, Cochran χ^2 test, I^2);
10. Publication bias/small study effect test (ie, Egger's test);
11. Critical appraisal of the included studies and, if so, which tool was used and the rating/judgement for each included study;
12. Time point for each relevant study outcome;
13. Modality to assess outcome (reported concurrently, reported retrospectively or directly measured).

As mentioned above, we might need to re-run the MA including data from individual studies. In this case, we will need to extract the following data from each individual study:

1. First author surname;
2. Year of publication;
3. Inclusion and exclusion criteria in relation to type and definition of the mental health and somatic conditions;
4. Study design (cross-sectional, case-control, cohort);
5. Type of effect size and numerical values for available effect sizes, with 95% CI.

Risk of bias (quality) assessment

We will use the AMSTAR-2 tool,[20] based on which the overall confidence in the results of each SR/MA will be rated as: high, moderate, low or critically low. To rate the quality of individual studies, we will use NOS,[15] with a global score equal to or higher than seven defining 'high-quality' reviews.

Strategy for data synthesis

When pooled effect sizes need to be calculated based on data extracted from each individual study included in the MA or systematic review, before pooling them, we will convert, if needed, effect size across studies to a common effect size (OR), as suggested by Fusar-Poli and Radua.[12] When needed, we will pool effect sizes using the random-effects model.

The meta-analyses and meta-analytic regressions (see below) will be weighted by the reciprocal of the variance of the effect size, which gives greater weight to larger studies. We will use the I^2 index to assess the heterogeneity of effect sizes. The I^2 index estimates the percentage of variation among effect sizes that can be attributed to true heterogeneity. Q will also be calculated as a measure of heterogeneity. We will use Egger's test to assess publication (or small study) bias. Analyses will be performed using Comprehensive Meta-Analysis 3.[21]

Assessment of possible transdiagnostic/trans-spectra associations

We will assess to which extent the associations between mental health disorders and somatic conditions are disorder-specific,

universally transdiagnostic, diagnostic spectrum-specific or across-spectra (even if not universal)-specific. Spectra will be defined according to the ICD-11 diagnostic blocks. Specifically, TRANSD recommendations will be applied.[11] TRANSD recommendations are strict criteria recently proposed to introduce a rigorous and replicable approach to define a construct as 'transdiagnostic'.[10] These criteria set the bar for a high-quality threshold for projects testing transiagnostic approaches, and include the need for Transparent definition of disorders (namely focusing on studies defining disorders according to gold standard definitions only (ICD, DSM, other), specific diagnostic types, official codes, primary vs secondary diagnoses, diagnostic assessment interviews), for clear Reporting of the primary outcome of the study, as well as the study design and the definition of the transdiagnostic construct in the abstract and main text, for explicitly Appraising the conceptual framework/approach of the transdiagnostic approach (ie, across-diagnoses, beyond-diagnoses, others to be explained), for Numerating the diagnostic categories, spectra and non-clinical samples in which the transdiagnostic construct is being tested and then validated, for Showing the degree of improvement or non-inferiority of the transdiagnostic approach against the specific diagnostic approach through specific comparative analyses (subgroup analyses among studies including one psychiatric diagnostic group only each and a larger group including all diagnoses significantly associated with the medical condition) and for Demonstrating the generalisability of the transdiagnostic construct through external validation studies (namely associations confirmed in more than one study in eligible meta-analyses).

Analysis of subgroups or subsets

As mentioned, we will explore the feasibility of conducting the following subgroup analyses:

1. Focused on systematic reviews/meta-analyses including cross-sectional or longitudinal studies only;
2. Based on different ways to define somatic disorders;
3. Focused on pharmacologically treated or non-treated/first episode/treatment-naïve participants.

We will also explore the feasibility of conducting the following sensitivity analyses:

1. Removing SRs/MAs where not all studies were required to use DSM or ICD criteria to define psychiatric disorders;
2. Excluding SR/MA rated at low quality (score <7) on the AMSTAR-2;
3. Focused only on adjusted effect size, as opposed to unadjusted effect size used for the primary analysis.

We will also explore the feasibility of conducting meta-regression analyses, including continent/country, study setting, publication year, age, per cent males in the study populations, per cent of white patients, per cent of patients on psychotropic medications in general or on specific medication classes (eg, antipsychotics, mood stabilisers, antidepressants), number of psychiatric disorders, illness duration, study follow-up duration and mean quality of the meta-analysed studies (NOS score) as effect size moderators.

We will stratify the credibility of available evidence using the approach proposed by Fusar-Poli and Radua,[12] as follows:

- *Convincing* (class I) when number of cases is >1000, $p<10^{-6}$, I^2 <50%, 95% prediction interval excluding the null, no small-study effects and no excess significance bias;
- *Highly suggestive* (class II) when number of cases is >1000, $p<10^{-6}$, largest study with a statistically significant effect and class I criteria not met;
- *Suggestive* (class III) when number of cases is >1000, $p<10^{-3}$ and class I–II criteria not met;
- *Weak* (class IV) when p is <0.05 and class I–III criteria not met;
- *Non-significant* when p is >0.05.

DISCUSSION

To our knowledge, this will be the first umbrella review of systematic reviews/meta-analyses addressing the association between a large number of mental disorders and somatic conditions.

From a clinical standpoint, gaining insight into the association between mental health disorders and somatic conditions is of relevance because it may inform a comprehensive management of the patient, taking into account both the psychiatric and the physical conditions (eg, screening for and treatment of comorbid ADHD in patients with obesity, which has been reported to improve the outcome of obesity itself via a reduction of impulsivity and improvement of executive functions [17]). Our umbrella review may also contribute by shedding light on the overlapping pathophysiology of mental and physical health conditions, suggesting possible therapeutic avenues (eg, immunotherapy in patients for whom alterations of the immune or inflammatory system may lead both to psychiatric and somatic symptoms).

From a research/methodological point of view, while current guidance from Cochrane[22] does not specify how to select papers for an umbrella review when more than one systematic reviews/meta-analyses on the same topics are available, we believe that our algorithm could be implemented in future umbrella reviews. Our umbrella review will also highlight research gaps in the field, pointing to associations that have not yet been explored.

Overall, this umbrella review will contribute to the current debate on the value of a transdiagnostic approach in psychiatry.[10]

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Contributors SC drafted the protocol. SC, MS, AC, PF-P and CC elaborated the algorithm. SC, MS, GA, AC, HL, PF-P and CC critically revised the first draft of the protocol.

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