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Prognostic models for predicting relapse or recurrence of depression (Protocol)

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[Prognosis Protocol]

Prognostic models for predicting relapse or recurrence of depression

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ABSTRACT

This is a protocol for a Cochrane Review (Prognosis). The objectives are as follows:

Primary objective

To summarise the predictive performance of prognostic models developed to predict the risk of relapse, recurrence, sustained remission or recovery in adults with depression who meet criteria for remission.

Secondary objectives

- To describe the characteristics of models identified, including predictors and method of derivation (e.g. regression, machine learning, neural networks etc.).
- To review the net benefit of identified models, where this has been reported.
- To summarise the value of updating or modifying an existing prognostic model or identify whether the development of a novel prognostic model to predict relapse and recurrence in depression is required. We will make this decision through discussion involving the whole team and will be guided by risk of bias assessment and applicability of methods as well as predictive performance.

Investigation of sources of heterogeneity between studies

We anticipate between-study heterogeneity in model performance. Sources of heterogeneity in this case are likely to relate to population/case mix (e.g. age of participants and multimorbidity), study setting of models (e.g. differences between models developed in primary and secondary care settings), study design (e.g. follow-up time, source of data, outcome definition and sample size). All of these could prove to be significant sources of heterogeneity in this review and we will take them into account in the event that a meta-analysis is undertaken.

BACKGROUND

Description of the condition

Depression is the leading cause of disability worldwide (WHO 2018). After treatment of the first episode of depression, approximately half of patients will relapse, and this risk increases for every subsequent episode (to 70% after a second episode and 90% after a third episode) (Ali 2017). A recent study showed that of those who relapse, the majority (79%) do so within the first six months (Ali 2017).

Relapse in the context of depression has been defined as the re-emergence of depressive symptoms following some level of remission but preceding recovery and is distinguished in the literature from recurrence (the onset of a new episode of depression following an extended period of remission) (Beshai 2011). Remission and recovery are similarly differentiated, with remission meaning asymptomatic but still 'in episode' and recovery being defined as resolution of the underlying episode (usually after 6 to 12 months) (Bockting 2015). 'Response' is often used to describe some improvement but not fully well (i.e. not yet achieving remission).

Description of the prognostic models

Prognosis refers to future outcomes given a particular baseline condition or disease. The **Prog**nosis **Res**earch **S**trategy (PROGRESS) framework was developed in 2013 (PROGRESS 2013), and described four main categories of prognosis research: overall prognosis; prognostic factor research; prognostic model research; and predictors of treatment effect. This review will focus on prognostic model research (Riley 2019). A prognostic factor is a variable that is associated with an increased risk of a future outcome. A multivariable prognostic model is a way (usually a mathematical equation) of combining information about multiple prognostic factors (hence multivariable) to produce an estimate of an individual's risk of developing a particular outcome in the future (Riley 2019).

We will review the predictive performance, format, included predictors and net benefit of all existing prognostic models developed to predict relapse or recurrence of depression. Sustained remission can be thought of as the inverse, or opposite, of relapse; and recovery as the inverse of recurrence. Both of these hold potentially valuable prognostic information pertinent to relapse risk prediction models. We are interested, therefore, in multivariable prognostic models that have been developed to predict an individual's risk of relapse, recurrence, sustained remission or recovery in depression. The starting point for prognostication is when a patient with depression has responded to treatment and meets criteria for remission. The included models must have been developed with the intention of providing individualised risk predictions and we will exclude papers reporting multivariable models not intended for this purpose.

Health outcomes

Relapse or recurrence of depression, and sustained remission or recovery from depression, all as defined by authors of individual studies.

Why it is important to do this review

There is evidence to suggest that the severity of depression and resistance to treatment increases with each successive episode (Kendler 2000), so there are potential benefits of intervening to prevent relapse. Reliable prediction of individuals' risk of relapse and recurrence would enable more efficient allocation, in practice, of interventions to prevent relapse. The strongest prognostic factors associated with increased risk of relapse and recurrence of depression are childhood maltreatment, history of recurrent depression and presence of residual symptoms. Comorbid anxiety, rumination, neuroticism and age of onset have also been associated with increased risk of relapse or recurrence (Buckman 2018).

While a single prognostic factor can give an estimate of overall prognosis, combining several prognostic factors within the same model usually results in better individualised risk predictions. A systematic review of existing prognostic models for the intended population, outcome and setting and their performance is a recommended first step in the development of a novel prognostic model. If an existing model performs satisfactorily, adjusting this for the intended population and externally validating the model is likely to be a better use of resources than developing a model from the beginning (Riley 2019).

The predictive performance of a prognostic model can be measured in several ways which include: overall measures of model fit (for example R^2, which measures explained variation for models with continuous outcomes, or generalizations of R^2 for models with binary or time-to-event outcomes); calibration (which measures the extent to which risk predictions and observed outcomes are in agreement); and discrimination (the model's ability to separate patients who develop the outcome of interest and those who do not, usually measured using the Concordance (C-) statistic or area under the curve (AUC). A C-statistic of 1 indicates that a model has perfect discrimination while a C-statistic of 0.5 means that the model performs no better than chance) (Riley 2019).

There have been some attempts to derive and validate prognostic models to predict depression-related outcomes. Existing prognostic models for depression outcomes include a model (the Depression Outcomes Calculator-Six Items, (DOC-6©)) to predict remission (C-statistic (AUC) of 0.62 (95% CI 0.57 to 0.66)) or persistent depressive symptoms (C-statistic (AUC) of 0.67 (95% CI 0.61 to 0.72)) at 6 months' post-diagnosis (Angstman 2017); to predict persistent symptoms at 6 months (C-statistic not reported; R^2 of 0.40 in development sample and 0.27 in validation sample) (Rubenstein 2007); and to predict onset of depression in non-depressed general practice attendees (C-statistic of 0.79 (95% CI 0.77 to 0.81)) (King 2010). In a scoping review, only one model was identified to predict risk of recurrence of depression over three years (C-statistic of 0.72 on external validation) (Wang 2014). There has been no systematic review to identify all such models.

OBJECTIVES

Primary objective

To summarise the predictive performance of prognostic models developed to predict the risk of relapse, recurrence, sustained remission or recovery in adults with depression who meet criteria for remission.

Secondary objectives

- To describe the characteristics of models identified, including predictors and method of derivation (e.g. regression, machine learning, neural networks etc.).
- To review the net benefit of identified models, where this has been reported.
- To summarise the value of updating or modifying an existing prognostic model or identify whether the development of a novel prognostic model to predict relapse and recurrence in depression is required. We will make this decision through discussion involving the whole team and will be guided by risk of bias assessment and applicability of methods as well as predictive performance.

Investigation of sources of heterogeneity between studies

We anticipate between-study heterogeneity in model performance. Sources of heterogeneity in this case are likely to relate to population/case mix (e.g. age of participants and multimorbidity), study setting of models (e.g. differences between models developed in primary and secondary care settings), study design (e.g. follow-up time, source of data, outcome definition and sample size). All of these could prove to be significant sources of heterogeneity in this review and we will take them into account in the event that a meta-analysis is undertaken.

METHODS

Criteria for considering studies for this review

The eligibility criteria required for studies to be included in the review will be informed by the following PICOTS criteria.

- Population — adult patients (18 years and over) diagnosed with depression and meeting criteria for remission.
- Index model — all prognostic models predicting relapse, recurrence, sustained remission or recovery in patients with depression.
- Comparator — there is no comparator in this review.
- Outcome(s) — relapse, recurrence, sustained remission or recovery in depression. We will accept and clearly document any definition.
- Timing — our pre-specified start-point is the point at which a patient has responded to treatment and is identified as meeting criteria for remission. The end-points are those described under 'Outcome(s)' over any time period.
- Setting — any setting (primary, secondary or community care). We will include models developed for participants from high-, medium- or low-income countries.

Types of studies

We will include all model development and validation (internal and external) studies, including those that update existing models. If a sufficient number of external validation studies exist for a particular model, we will perform a meta-analysis to provide a quantitative summary of that model's predictive performance. We will report a qualitative description of the rationale, methods and outcome of studies that aimed to update an existing model and we will treat updated models as separate models for the purposes of meta-analysis. We expect the majority of studies to be cohort studies (both prospective and retrospective; and most likely to include prognosis studies based on registries and on cohorts from randomised controlled trial data). We will include other types of studies if they meet the other inclusion criteria. Reports of impact assessments of prognostic models (e.g. in randomised trials) will not be included in this review, as these studies require different methodology.

Targeted population

Adult patients (18 years and over) who have been diagnosed with (by validated diagnostic tool or diagnostic interview) and treated for depression and now meeting criteria for remission. We will exclude models developed in populations with co-morbid severe mental illness (for example, schizophrenia and bipolar affective disorder) as these patients will typically receive more intensive psychiatric input and results would be less generalizable. Children with depressive disorders are treated in very different settings with different practitioners and follow-up schedules and may have meaningfully different predictors than independent adult patients. We will include older adults, although we will be mindful that multimorbidity may impact on depression outcomes in this population more so than in a general adult population.

Types of prognostic models

All multivariable prognostic models developed to predict the risk of relapse, recurrence, sustained remission or recovery in individuals with depression who have entered remission. We will not include models that predict sustained depressive symptoms as these models require a different population (i.e. those who have been diagnosed as depressed rather than those with depression who have subsequently entered remission). We are interested in all multivariate models, whether they were developed to guide therapeutic decision-making or for any other purpose. They must have been developed with this intention of providing individual risk predictions, and not for other purposes (e.g. to quantify the adjusted effect of a prognostic factor). Metrics for discrimination or calibration (or both) should be reported.

Types of outcomes to be predicted

Relapse, recurrence, sustained remission or recovery in depression over any time period. We will accept all definitions.

Search methods for identification of studies

Electronic searches

An Information Specialist will conduct searches on the following bibliographic databases using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource. The search strategies will be designed to identify prognostic models developed to predict the risk of relapse, recurrence, sustained remission or recovery in adults with (unipolar) depression who have entered remission.

- Ovid MEDLINE (1946 onwards) (Appendix 1);
- Ovid Embase (1980 onwards);
- Ovid PsycINFO (1806 onwards);
- Cochrane Library (current issue);
- Web of Science (1900 onwards).

We will not request any restrictions on date, language or publication status be applied to the searches. We will screen the

results of the MEDLINE search in the first instance to help increase the precision of the search for the target population. We will also consider the sensitivity and specificity of the prognostic models filter at this point.

The Information Specialist will search for retraction statements and errata once we have selected the included studies and will rerun all searches close to publication if the initial search date is greater than 12 months.

Searching other resources

The Information Specialist will search the following sources of grey literature (primarily for dissertations and theses).

- Open Grey (www.opengrey.eu);
- ProQuest Dissertations & Theses Global (www.proquest.com/products-services/pqdtglobal.html);
- DART-Europe E-theses Portal (www.dart-europe.eu);
- EThOS - the British Libraries e-theses online service (ethos.bl.uk);
- Open Access Theses and Dissertations (oatd.org).

Reference lists

We will check the reference lists of all relevant study reports and the Information Specialist will conduct a forward citation search on the Web of Science and Google Scholar, to identify additional studies missed from the original electronic searches (e.g. unpublished or in-press citations).

Personal communication

We will contact authors and subject experts for information on unpublished or ongoing studies, or to request additional data.

Data collection

Selection of studies

Two independent reviewers will review the titles and abstracts of studies identified by the search strategy and full texts obtained for studies potentially meeting the inclusion criteria. The two reviewers will resolve uncertainty or disagreement through discussion or, if necessary, by referral to a third researcher.

Data extraction and management

Two independent reviewers will conduct the data extraction (ASM and NM). The **Ch**ecklist for Critical **A**ppraisal and Data Extraction for Systematic **R**eviews of Prediction **M**odelling **S**tudies (CHARMS) has been developed to guide data extraction in systematic reviews of prognostic models and we will use it for this review. Data to be extracted are:

- method of depression diagnosis;
- year of patient recruitment and follow-up;
- setting;
- source of data;
- participants' characteristics;
- study design;
- definition of relapse and recurrence;
- information on number and type of candidate predictors;
- sample size;
- number of events;
- missing data;
- model development (e.g. logistic regression, Cox regression, machine learning, neural network) and any adjustment for model overfitting (e.g. using penalisation or shrinkage techniques);
- model performance (calibration, discrimination and classification measures), including optimism-adjusted estimates in the development data;
- model evaluation (method used, whether internal and external validation was done, model updating in case of poor validation); and
- results: interpretation and discussion of generalizability, strengths and weaknesses

We will also collect information on how the model was presented (risk chart, nomogram, full regression formula) and whether it is possible to use a model based on the information presented in the article. Where measures of predictive performance are not available directly, we will extract these with reference to recent guidance (Debray 2018).

Assessment of risk of bias in included studies

Two independent reviewers will assess risk of bias using the **P**rediction model **r**isk**o**f **b**ias **as**sessment **t**ool (PROBAST), which assesses risk of bias over four domains, as well as applicability (Riley 2019; Wolff 2019).

- Participants: appropriate data sources and inclusion/exclusion criteria.
- Predictors: which should be defined and assessed in a similar way for all participants, assessed without knowledge of outcomes and available at the time at which the model is intended for use.
- Outcomes: determined appropriately, pre-specified, predictors should be excluded from outcome definition, defined and determined in a similar way for all participants, determined without knowledge of predictors, and appropriate time interval between predictor assessment and outcome determination.
- Analysis: reasonable number of participants with the outcome, appropriate handling of continuous and categorical predictors, all enrolled participants should be included in the analysis, missing data handled appropriately, relevant model performance measures handled appropriately, overfitting and optimism in performance accounted for and predictors and assigned weights in the final model should correspond to results from multivariable analysis.

Measures of association or predictive performance measures to be extracted

We will extract information about the models' predictive performance, in terms of discrimination (C-statistic, area under the curve) and calibration (calibration slope, OE ratio, calibration plots), and net benefit measures.

Dealing with missing data

When performance measures (such as C-statistic, OE ratio) are not reported in the paper, we will contact authors. If we are unable to obtain the required data, we will use standard methods and formulae described by Debray and colleagues to estimate the O:E

ratio and C-statistic and associated standard errors (Debray 2017). If this is not possible due to limited data, we will explore the impact of missing data in a sensitivity analysis.

Assessment of heterogeneity

Reviews of prognostic studies often have to deal with a substantial amount of heterogeneity. We will assess the impact of heterogeneity in predictive performance across validation studies, by calculating prediction intervals which provide a range for the potential performance of a model in a new validation study (Debray 2017). We will also calculate I^2 and Tau^2 statistics. We will extract performance in subgroups if reported.

If there are sufficient data (a minimum of 10 studies), we will investigate potential sources of heterogeneity using meta-regression with the transformed summary estimate of model performance (e.g. logit C-statistic or log O:E ratio) as a dependent variable and study-level covariates (population/case-mix (age of participants and multimorbidity), study setting of models (primary and secondary care settings) and study design (follow-up time, source of data, outcome definition and sample size) as explanatory variables.

Data synthesis

Data synthesis and meta-analysis approaches

We will initially complete a narrative data synthesis, reporting the performance of individual prognostic models. Data are likely to be highly heterogeneous; therefore, if we identify a sufficient number of high-quality studies externally validating the same model, a random-effects meta-analysis will be performed, aiming to summarise the performance of that model. If possible we will pool information about each model's discrimination (using C-statistic or equivalent), calibration (using calibration slope, calibration-in-the-large; and ratio of observed (O) to expected (E) events (O:E ratio)) and equivalents from time-to-event models (e.g. Harrell's C-statistic, calibration slope, D statistic, O:E at each time point). For each performance measure separately, we will use a random-effects meta-analysis model with transformed performance measures (logit C-statistic and log O:E ratio) to produce a summary result (with 95% confidence intervals (CIs)) that quantifies the average performance across studies. To better account for the uncertainty in the estimated between-study heterogeneity, we will use the restricted maximum likelihood (REML) estimation, with 95% CIs for the summary (average) performance of a model, derived using the Hartung-Knapp-Sidik-Jonkmann method, as recommended by Debray 2017 and Langan 2018.

Subgroup analysis and investigation of heterogeneity

We will investigate for potential sources of heterogeneity using meta-regression with the transformed summary estimate of model performance (e.g. logit C-statistic or log O:E ratio) as a dependent variable and study level characteristics as explanatory variables (see above). This will only be possible if there are a sufficient number of studies (usually 10 or more). We will evaluate the impact of risk of bias by doing analyses only of those studies assessed to be low risk of bias.

Sensitivity analysis

To explore the differences in model performance between primary and secondary care patients we will perform sensitivity analysis, looking at the impact of excluding secondary care patients on model performance. We will also examine effects of missing data and multimorbidity here if applicable.

Conclusions and summary of findings

We will use the summary of findings to highlight the better performing models and next steps for their comparison, extension or implementation. We will consider the benefits of updating and/or externally validating an existing model with sufficiently reasonable performance, low risk of bias and acceptable applicability or we will develop a novel model for validation and impact assessment in a primary care cohort.

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APPENDICES

Appendix 1. Database searches

Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 onwards>
Search Strategy:

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1 DEPRESSION/ (110341)
2 DEPRESSIVE DISORDER/ (70786)
3 DEPRESSIVE DISORDER, MAJOR/ (28163)

4 DEPRESSION, POSTPARTUM/ (5084)
5 DEPRESSIVE DISORDER, TREATMENT-RESISTANT/ (1064)
6 (depress* adj3 (acute or clinical* or diagnos* or disorder* or major or unipolar or illness or scale* or score* or adult* or patient* or participant* or people or inpatient* or in-patient* or outpatient* or out-patient*)).ti,ab,kf. (151900)
7 (depress* and (Beck* or BDI* or DSM* or (Statistical Manual adj2 Mental Disorders) or Hamilton or HAM-D or HAMD or MADRS or (International Classification adj2 Disease?) or ICD-10 or ICD10 or ICD-9 or ICD9 or PHQ-9 or PHQ9 or patient health questionnaire or GDS or EPDS)).ab. (47514)
8 "with depressi*".ab. (24930)
9 (depressi* or depressed).ti. (136381)
10 (depress* adj3 (postnatal* or post-natal* or postpartum* or post-partum* or pregnan*)).ti,ab,kf. (7938)
11 (depress* adj3 (refractor* or resistan* or chronic* or persist*)).ti,ab,kf. (11607)
12 (depress* and ((antidepress* or anti-depress* or SSRI* or SNRI* or serotonin or medication* or psychotropic or treatment*) adj2 (fail* or no* respon* or nonrespon* or non-respon* or unrespon* or un-respon*))).ti,ab,kf. (1516)
13 or/1-12 (293144)
14 (recurr* or relaps* or remiss* or remitt*).ti,ab,kf,hw. (885726)
15 13 and 14 (20248)
16 ((recurr* or reoccur* or re-occur* or new episode or another episode or relaps* or re-emerg* or resurg* or re-surg* or reappear* or re-appear* or flare-up) adj5 depress*).ti,ab,kf. (5741)
17 ((remiss* or remitt* or recover*) adj5 depress*).ti,ab,kf. (6268)
18 or/15-17 (23629)
19 (Prognosis/ or Decision Support Techniques/) and (Algorithms/ or Logistic Models/ or Risk Assessment/) (44253)
20 ((prognos* or predict* or decision*) and (algorithm? or model* or rule? or risk? or outcome?)).ti,kf,hw. (400284)
21 ((prognos* or predict* or decision*) adj3 (algorith? or model* or rule? or risk? or outcome?)).ab. (244497)
22 clinical prediction.mp. (2467)
23 ((prognos* or predict* or decision*) and (history or variable* or criteria or scor* or characteristic* or finding* or factor*)).ti,kf,hw. (316814)
24 ((prognos* or predict* or decision*) adj3 (history or variable* or criteria or scor* or characteristic* or finding* or factor*)).ab. (230941)
25 or/19-24 (818040)
26 18 and 25 (2404)
27 (exp animals/ or exp models, animal/) not humans.sh. (4602276)
28 (mice or mouse or murine or rat or rats or rodent* or animal model*).ti. (1408830)
29 26 not (27 or 28) (2399)
30 (comment or letter or editorial or news).sh. (1925773)
31 29 not 30 (2388)

CONTRIBUTIONS OF AUTHORS

ASM: lead author of the protocol. Contributed to the conception of the review. Wrote the first draft of the protocol and response to peer review.
NM: commented on the background and contributed to the methodology of the protocol.
SG: contributed to the conception of the review and the background and methodology of the protocol.
CCG: contributed to the conception of the review and the background and methodology of the protocol.
RC: commented on the background and contributed to the methodology of the protocol.
SA: contributed to the conception of the review and the background and methodology of the protocol.
RSP: commented on the background and contributed to the methodology of the protocol.
RDR: contributed to the methodology of the protocol.
DM: contributed to the conception of the review and the background and methodology of the protocol.

DECLARATIONS OF INTEREST

ASM: no conflicts of interest
NM: no conflicts of interest
SG: no conflicts of interest
CCG: no conflicts of interest
RC: leads and has responsibility for Cochrane Common Mental Disorders, which has supported parts of the review process and is largely funded by a grant from the National Institute for Health Research (NIHR) in the UK.
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