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**Protocol**

# Predicting antipsychotic-induced weight gain in first episode psychosis- a protocol for a field-wide systematic review of prognostic factor studies

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## ABSTRACT

**Background:** One significant complexity associated with management of antipsychotic-induced weight gain (AIWG) is extensive interindividual variability amongst patients in initial susceptibility to AIWG, time to plateau of weight gain, and resultant final amount of weight gained. Prior to antipsychotic commencement, risk-stratified information highlighting those at increased risk of experiencing significant AIWG would allow tailored weight monitoring and subsequent management protocols to be developed.
**Methods:** This protocol is for a planned systematic review to identify the current utility of baseline clinical, sociodemographic, and biological prognostic factors in predicting the likelihood of significant AIWG occurring prior to antipsychotic commencement. The cohort assessed will be antipsychotic-naïve adults with a first episode of psychosis. Searches for both randomised and prospective non-randomised studies will be undertaken by searching four electronic databases and two trial registers, followed by reference searching, forward citation searching and liaison with content experts. A meta-analysis of study results will be undertaken where study quality and homogeneity allow. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework modified for prognostic research will be used to assess evidence certainty. This protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Protocols guideline and latest guidance from the Prognosis Methods Group of the Cochrane Collaboration.
**Results:** This review will establish the current quantity, quality and clinical utility of evidence addressing the prognostic association of clinical, biological, and sociodemographic factors in prospectively identifying those more likely to experience significant AIWG.
**Registration details:** PROSPERO registration number CRD42021258148.

**Keywords:** Antipsychotic-induced weight gain, Metabolic side effects, Antipsychotics, Risk factors, Prediction, Psychosis

## INTRODUCTION

Obesity prevalence is 2-3-fold higher amongst those with schizophrenia compared to the general population.[1] Antipsychotic-induced weight gain (AIWG), particularly that induced by use of second-generation antipsychotics, is undoubtedly a significant contributor to such high obesity rates.[2] Managing AIWG is complex and challenging for patients, clinicians and policy makers alike. This is partly due to extensive interindividual variability associated with this side effect, both in susceptibility to initial weight gain and in particular, the extent of total weight gained over time.[3] Whilst antipsychotic choice is an important differentiator of risk, evidence suggests that baseline genetic, clinical and sociodemographic risk profiles of individuals also contribute to personal susceptibility to AIWG.[1,4,5] In the case of clinical and sociodemographic risk factors, the extent of their impact is yet to be systematically elucidated.

The most effective way to manage AIWG is in its prevention and subsequent early intervention.[1] To date, interventions studied have included both non-pharmacological and/or pharmacological approaches.[6] In the case of non-pharmacological interventions, individualised lifestyle, dietary and exercise counselling have been shown to be one of the most effective interventions, and offer important advantages when compared to the current standard of delivery of such lifestyle advice as group sessions.[6] The widespread uptake of individualised lifestyle advice is however limited by their inherently resource-intensive nature. Time taken to reach a plateau of AIWG is in many cases unknown but has been cited as taking months to years to occur.[5,7] Thus, the provision of any management intervention will likely be needed for prolonged periods. In the case of pharmacological management of AIWG, polypharmacy is already a prominent issue in psychiatry.[8] Risk associated with addition of another medication is an important consideration when assessing potential merits of pharmacological AIWG management. Identifying those most at risk of experiencing significant AIWG and thus, where the largest absolute benefits from preventative and early interventions would be gained a priori, would be beneficial for all stakeholders involved in management.

### *Aims*

This is a protocol for a field-wide systematic review synthesizing available evidence on the prognostic value of baseline clinical, sociodemographic, and biological factors in predicting weight outcomes following antipsychotic commencement amongst antipsychotic-naïve adults experiencing a first episode of psychosis (FEP). A preliminary review of published literature identifies this as a growing area of research, evidenced by serial primary studies assessing the adjusted and unadjusted prognostic value of a range of clinical and sociodemographic prognostic factors.[1,5,7,9] A prognostic factor is defined as any variable that predicts or is associated with a risk of a subsequent health outcome occurring within a specific time in individuals with a certain health state or outcome.[10] Different values or categories of a prognostic factor are associated with a better or worse prognosis of future health outcomes. To the best of our knowledge, no effort to systematically summarize and critically appraise evidence on the entire prognostic factor landscape in this area has been undertaken.

Although genetics has been hypothesized to play an important role in AIWG susceptibility, the current cost of pharmacogenomic tests, lack of cost-effectiveness data, and rare application of pharmacogenomic in current psychiatric practice, represent clear barriers to the practical implementation of encouraging research results.[11,12] Furthermore results of the most recent and comprehensive systematic review and meta-analysis of pharmacogenomic associations of AIWG found that effect sizes of individual gene variants were too small to fulfil the promise of personalised medicine, and that future studies should explore the effects of combining multiple genetic markers and relevant clinical factors to improve clinical prediction.[11]

The research question we will address is as follows*:* Amongst antipsychotic-naïve adults with a first episode of psychosis, are there baseline clinical, sociodemographic and/or biological prognostic factors that serve as reliable predictors of weight outcomes following antipsychotic commencement?

This review will appraise prognostic factor studies (also known as risk factor or predictive factor studies) to identify which prognostic factors have been linked to alterations in average anthropometric outcomes following antipsychotic commencement.[9] Our objectives are as follows: 1) Identify what clinical, sociodemographic and/or biological prognostic factors have been reported as being predictors of a range of anthropometric outcomes following antipsychotic initiation, 2) Assess the current phase of investigation of identified prognostic factors, including whether such factors are in exploratory or confirmatory research phases and the quality of such research to inform its current clinical utility, 3) Suggest improvements that can be made to further developments in this area.

## METHODS

### *Protocol and registration*

This protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols (PRISMA-P) checklist criteria and the latest guidance from the prognosis methods group of the Cochrane collaboration.[13,14] A copy of the PRISMA-P checklist is included in the supporting

information appendix. This protocol was registered with PROSPERO (registration number CRD42021258148). Both PROSPERO and the Cochrane Database of Systematic Reviews were checked prior to protocol development and registration. No similar reviews were identified.

### *Eligibility criteria*

Modification of the traditional PICOTS system for use in systematic reviews of prognostic factor studies was used to develop study selection criteria. Population, Index prognostic factor, Comparator prognostic factors, Outcome, Timing and Setting are considered under the modified PICOTS acronym.[10] A summary of the modified approach applied to this review is summarized in Table 1.

Table 1 key items for framing review aims, associated search strategy, and study inclusion and exclusion criteria, following PICOTS guidance.[10]

**Table 1: PICOTs acronym applied to this systematic review.**

| Items | Definition |
|---|---|
| **Population** | Adult (participants diagnosed with a first episode of psychosis who are antipsychotic-naïve. For the purposes of this review, antipsychotic naïve participants are defined as having:<br>- ≤ 6 weeks' antipsychotic exposure in their lifetime<br>- 0-2 weeks exposure prior to trial enrolment<br>- Never received a long-acting injectable form of antipsychotic. |
| **Index prognostic factors** | Any clinical (e.g., positive/negative symptomology), sociodemographic (age, sex, socioeconomic status), or biological (e.g., baseline weight, blood markers) measured upon or immediately prior to antipsychotic initiation and examined prospectively for an association with change in a subsequent anthropometric outcome(s). |
| **Comparator prognostic factors** | Not applicable |
| **Outcomes** | *Primary outcomes:*<br>Relationship between one or more baseline clinical, sociodemographic, or biological prognostic factor(s) and mean change in weight (kg) following antipsychotic commencement<br>Relationship between one or more baseline clinical, sociodemographic, or biological prognostic factor(s) and mean change in body mass index (BMI) following antipsychotic commencement<br>Relationship between one or more baseline clinical, sociodemographic, or biological prognostic factor(s) and likelihood of experiencing clinically significant weight change following antipsychotic commencement, (≥7% of baseline body weight)<br>*Secondary outcomes:*<br>Relationship between one or more baseline clinical, sociodemographic, or biological prognostic factor(s) and mean change in waist circumference (cm) following antipsychotic commencement |
| **Timing** | Prognostic factors measured upon or immediately prior to antipsychotic initiation and assessing prognostic value over any time horizon and across all outcomes. |
| **Setting** | No restrictions on study setting |

### *Population*

We will include studies with adult participants (≥16 years of age) experiencing a first episode of psychosis, including a brief psychotic disorder, first episode schizophrenia and associated subtypes (including schizoaffective disorder), or delusional disorder. Diagnosis must be made in accordance with standardised clinical criteria e.g., DSM-V or ICD-10. We will only include studies where participants are antipsychotic-naïve and follow up begins from the point of antipsychotic prescribing. We will also accept studies where most participants (≥80%) meet this criteria, as applied in previous reviews.[15] We will exclude studies where participants are prescribed an antipsychotic for a condition other than psychosis, including in the context of an affective disorder, as in such cases, antipsychotics are frequently co-prescribed with other medications that commonly alter weight outcomes.[16] As in clinical practice, those with a psychotic illness not secondary to mood disorders may be prescribed other medications that have the potential to significantly influence weight. We will include studies where 20% or less are co-prescribed medications commonly associated with altered weight, including but not limited to sodium valproate, lithium, corticosteroids, mirtazapine, or tricyclic antidepressants.

### *Index prognostic factor*

As this review aims to appraise the entire body of evidence assessing the clinical utility of a potential range

of clinical, sociodemographic, and biological prognostic factors, rather than to compare the prognostic ability of one factor with others, we have not identified an index prognostic factor. We will accept studies assessing the predictive value of any clinical, sociodemographic, or biological prognostic factor on prespecified anthropometric outcomes. We will accept studies where the effect size related to the prognostic factor under examination has been adjusted for other prognostic factors, or where the effect estimate remains unadjusted, although conclusions drawn from analyses will give preference to the adjusted prognostic effect estimate.[11] Specific to the intervention applied, we will include studies where participants are prescribed any antipsychotic licensed in at least one country and where the median/mean dose is specified.

***Comparator prognostic factors***

Not applicable.

***Outcomes***

We expect that most studies will report the association between prognostic factors and anthropometric outcomes as continuous variables and in the case of clinically significant weight gain, as a dichotomous variable.

***Primary outcomes***

The primary outcomes will be the prognostic association of a potential range of baseline clinical, sociodemographic, or biological variables in explaining variation in (i) mean change in body weight (kg) and (ii) body mass index (BMI) following antipsychotic initiation. We will also include the prognostic association of baseline variables with the likelihood (odds or risk) of clinically significant weight gain occurring as a primary outcome. This has been most commonly defined in the literature as ≥ 7% increase in body weight, but we will accept studies where this outcome is defined as ≥5% increase. Studies that define this outcome similarly will be grouped together for analysis.

***Secondary outcomes***

The predictive power of a potential range of baseline clinical, sociodemographic, or biological variables in explaining variation in mean change in waist circumference (cm).

***Timing***

We will only include studies where the timing of antipsychotic initiation, measurement of a prognostic factor(s) and commencement of weight monitoring are synchronous. We will evaluate studies where the prognostic association of a factor(s) is assessed over any time point and across all outcomes. We will prioritise combining studies with the longest durations, as international recommendations for continuing antipsychotic treatment after resolution of symptoms in FEP range from 1-5 years.[18]

***Setting***

No limits will be applied to study setting.

***Study type***

This review will include both randomised controlled trials (RCTs) and non-randomised studies (NRS). In the case of NRS, we will include studies that are prospective, have a clear inception point i.e., identify new antipsychotic users only. We will also include nested case-control studies from which data were initially derived from a prospective cohort. Only studies available as full texts will be included. We will exclude NRS that are retrospective or cross-sectional in design to increase evidence certainty. Clinical information collected retrospectively is often incomplete and clinicopathological data may not have been collected in a standardised fashion.[10]

***Search strategy***

The search strategy was built using the peer review of electronic search strategies (PRESS) checklist as well as piloted with fifty references prior to the finalisation.[19]

***Electronic searches***

The following major databases will be searched from their inception to November 2021 using a combination of free text words and associated synonyms, alongside appropriate controlled vocabulary: PubMed, Embase, PsycINFO and Cochrane Central Register of Controlled Trials (CENTRAL).

A copy of the database search strategy is contained within the supporting information appendix. An example of the search strategy adapted for searching PubMed is contained within Table 2. Unpublished studies and ongoing studies will be identified via the searching of international trial registries, including following: Clinicatrials.gov, world health organisation (WHO) as well as the international clinical trials registry platform (ICTRP).

If completed studies are identified during clinical trial registry searches, but results not publically available, authors will be contacted to request study results. Our search was built to be intentionally inclusive due to the potentially broad range of prognostic factors under investigation, variation in study design, and lack of standardised terminology applied in prognostic factor research.[10] Our iteratively-developed search strategy was designed to align with recent methodological investigation in search methods for systematic reviews of prognostic factor studies to improve search sensitivity.[20]

No studies will be excluded based on sample size, follow-up duration or publication year. We will exclude non-English language studies and grey literature.

Table 2 example of applied search strategy using the PubMed database.

**Table 2: Search strategy example.**

| PubMed search strategy | |
|---|---|
| **Search number** | **Terms applied** |
| **1** | Predict*[tw] OR Risk*[tw] OR prognos*[tw] OR outcome*[tw] OR course[tw] |
| **2** | "Antipsychotic Agents"[MeSH] OR “First generation antipsychotic*”[tw] OR “First-generation antipsychotic*”[tw] OR “second generation antipsychotic*”[tw] OR “second-generation antipsychotic*”[tw] OR Antipsychotic*[tw] OR neuroleptic*[tw] |
| **3** | "Body Weight Changes/drug effects"[MeSH] OR “Weight gain”[tw] OR “metabolic side effect*” OR “metabolic side-effect*”[tw] OR “Antipsychotic induced weight gain”[tw] OR “Antipsychotic-induced weight gain”[tw] |
| **4** | Schizo*[tw] OR Psycho*[tw] OR delusion*[tw] OR “first episode psychosis” OR “first-episode psychosis” OR "Psychotic Disorders"[Mesh] |
| **5** | #1 AND #2 AND #3 AND #4 |
| **6** | (amisulpride OR aripiprazole OR asenapine OR cariprazine OR clozapine OR chlorpromazine OR fluphenazine OR flupenthixol OR haloperidol OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR sulpiride OR ziprasidone OR zuclopenthixol [tw]) |
| **7** | (#2 OR #6) AND "Metabolic Syndrome"[MeSH] |
| **8** | Prospective [tw] AND #3 AND (#2 OR #6) |
| **9** | #1 AND #3 AND (#2 OR #6) |
| **10** | "Overweight"[MeSH] |
| **11** | (#2 OR #6) AND #10 |
| **12** | correlat* [tw] |
| **13** | (#2 OR # 6) AND #3 AND #12 |
| **14** | "follow-up stud*"[tw] |
| **15** | (#2 OR # 6) AND #3 AND #14 |
| **Limits set to: English language** | |

***Searching other resources***

Hand searching of reference lists of included studies will be undertaken to identify additional studies. We will also contact content experts in the field to locate any other published or unpublished studies which our search has missed. Finally, Web of Science will be used to identify additional relevant studies through forward citation searching of studies already included.

***Data collection***

Screening at title and abstract level, as well as screening of full articles for eligibility, will be undertaken by two independent reviewers. Disagreements will be resolved via discussion and subsequent consultation with an independent third party, if needed. Where clarification is required regarding study conduct or design, study authors will be contacted.

***Data extraction***

Study data will be extracted using a modified version of the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies – Modified for Prognostic Factor Studies (CHARMS-PF).[10] Within this tool a range of signalling questions across eight domains are contained and includes source of data; participants; outcomes to be predicted; prognostic factors; sample size; missing data; analysis; results and; interpretation and discussion.[10] Signalling questions not of relevance to this review have been removed. A copy of the amended checklist can be found in the supporting information appendix. All data extraction forms will be piloted prior to commencement to ensure appropriateness and uniformity of data extraction. Two independent authors will extract all data. Any discrepancies between authors will be checked against original reports. If needed, recourse to a third independent author will be undertaken. Like data collection, study authors will be contacted for missing information or where queries regarding study properties, conduct or reporting exist.

***Risk of bias assessment***

The risk of bias tool that will be used is the quality in prognosis studies (QUIPS) tool.[21] This tool was developed for the purposes of assessing risk of bias at study level across prognostic factor studies. The QUIPS tool identifies study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other factors, and statistical analysis and reporting to be critically appraised when evaluating bias in prognostic factor studies: study participation, study attrition, prognostic factor measurement, confounding (covariate) measurement and account, outcome

measurements, and analysis and reporting. To grade each study, each of the six domains is judged as being as high, moderate, or low risk of bias. An overall rating of bias to a given study is not recommended when using QUIPS.[21] A risk of bias assessment with be carried out independently by two study authors. Discrepancies will be resolved through discussion and consensus, with recourse to a third independent author if necessary. Piloting of the tool by members of the review team will take place prior to review commencement to ensure uniformity of assessment. Where details pertinent to completing the assessment are missing from the study protocol or/are unclear, the study authors will be contacted.

***Data analysis***

We plan to extract all unadjusted and adjusted measures of association from included studies, along with the reported set of adjustment factors used. In the case of continuous outcome measures, we will synthesize regression coefficients and their standard errors (SE). In the case of binary outcome measures (e.g., clinically significant weight gain), we will synthesize odds ratios (OR) or risk ratios (RR) as reported in the publication, and their associated SE. We will appropriately transform individual study associations and their measures of variance to their natural logarithms to normalise their distribution. If these estimates are unavailable, we will attempt to recover these using alternative available information (e.g., standard deviations, confidence intervals (CI), 2×2 tables, p values etc.), to avoid possible selection bias. We will contact study authors for missing or unusable data, as necessary. If we cannot obtain OR values or regression coefficients from published papers or from study authors, we will report correlation coefficients or any other measures of association.

***Dealing with missing data***

Where possible, we will include studies that investigate the relationship between baseline prognostic factors and any anthropometric outcome, even if there is evidence of missing data or limited evidence is provided about the effect size.

***Assessment of heterogeneity***

Meta-analysis will be conducted if valid data are available assessing associations between a baseline prognostic factor and a prespecified anthropometric outcome in three or more studies that are deemed sufficiently homogenous. We will summarise clinical heterogeneity qualitatively according to population, measures of the prognostic factor and outcome measurement and consider the appropriateness of the proposed synthesis. Where possible a separate meta-analysis will be considered for subgroups of results defined by the following: 1) Adjusted (multivariable) associations and unadjusted (univariable) associations, 2) prognostic factor effects measured at different cut-offs or thresholds (or groups of similar cut-offs), 3) different methods of measurement (for factors and outcomes) and 4) different timepoints of outcome measurement.

Preference will be given to synthesizing adjusted results, as defined by the inclusion of a minimum set of adjustment factors in the studies analyses. This minimum set of adjustment factors aims to increase homogeneity of synthesized results. As this is a systematic review of field-wide prognostic factors and is the first of its kind in this area, there is no consensus on a predetermined set of prognostic factors considered essential to be adjusted for as a minimum when assessing the independent prognostic value of a new factor. We have therefore defined a minimum set of adjustment factors as listed below, based on existing evidence of association with weight outcomes in the general population, and known variance in weight outcomes depending on the antipsychotic prescribed amongst those with psychosis.[4,22] Age, sex, ethnicity (where mixed in the study population) and antipsychotic prescribed (where several antipsychotics are prescribed in the study population).

We will quantify statistical heterogeneity using the $I^2$ statistic (which provides the proportion of total variability that is due to between-study heterogeneity) and the estimated between-study variance ('tau-squared'). To reveal the impact of heterogeneity more clearly, we will also calculate a 95% prediction interval for the prognostic effect when applied in an individual setting (provided there are at least five studies). If it is not appropriate to combine results using meta-analysis (for example, if the heterogeneity would make results difficult to interpret meaningfully), results will be presented qualitatively.

***Data synthesis methods***

For each prognostic factor of interest, where appropriate, we will perform random-effects meta-analyses to allow for potential between-study heterogeneity in each prognostic effect (a common occurrence in prognostic factor studies).[23] If no between-study heterogeneity is found to exist, this model suitably reverts to a common-effect model. Restricted maximum likelihood (REML) estimation will be used to fit all meta-analyses, with 95% CIs derived using the Hartung-Knapp Sidik-Jonkman approach, to account for uncertainty in the estimated variances (e.g., tau-squared).[24]

All analyses will be conducted using STATA (StataCorp version 17) or RevMan (RevMan version 5.4, the Cochrane collaboration).

***Risk of publication bias***

We will examine publication bias for each meta-analysis, provided there are 10 or more studies, by visually examining asymmetry using contour-enhanced funnel plots and appropriate statistical tests.[25]

***Subgroup and sensitivity analysis***

We will use sensitivity analyses to explore the impact of study all-domain risk of bias, firstly restricting the analysis to studies rated as having low risk of bias, and if this is not feasible, restricting to low or moderate risk of bias. If there is heterogeneity, we will investigate it using the following pre-specified subgroup analyses, provided there are at least three studies per subgroup: 1) Antipsychotic subgroup prescribed, 2) country where the study was conducted.

This methods section was based on the exemplar Cochrane prognosis review protocol for prognostic factors.[26]

***Certainty of evidence***

Certainty of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for each prognostic factor and across all outcomes. We will apply a modified version of GRADE based on guidance previously published on its use in assessing prognostic factor studies.[27] This modified approach involves consideration of same eight domains that may affect evidence certainty (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and increase in certainty (large effect, dose response and plausible confounding).[27] Depending on the study design and issues relating to these domains, evidence quality is ultimately designated as high, moderate, low and very low. An overall rating will be provided for based on the lowest quality rating assigned across all domains and specific to the outcome under assessment. All assessments will be undertaken using the GRADEpro web application, and by two independent reviewers. Disagreements will be resolved via discussion amongst reviewers and with recourse to a third independent reviewer, if necessary.[28] As some degree of subjectivity in applying the process is inevitable, authors will document the rationale for any decisions regarding rating evidence quality up or down in GRADE summary of findings (SoF) tables.[27] SoF tables will be constructed for evidence addressing each prognostic factor and across all outcomes.

## DISCUSSION

Prognostic factors have the potential to play an important role in pathways towards improved health, including clinical practice, healthcare research, and the development, evaluation and targeting of interventions. There is need for initial evidence supporting the application of a prognostic factor to be shown as consistent in subsequent studies and thus, systematic reviews of prognostic factor studies are imperative in assessing the clinical application of prognostic factor research.[29] Whilst it is known that primary research exists assessing the relationship between certain clinical, sociodemographic, and biological prognostic factors and anthropometric outcomes amongst those initiating antipsychotic treatment, the breadth, quality and clinical utility of this research is unknown.[5,7,9] This includes whether any prognostic factor remains significant after adjustment for covariates, consideration of different contexts and over extended time periods. This review represents the first systematic aggregation of primary studies to begin to address these uncertainties. Strengths of this review lie in the inclusion of studies only where data was collected prospectively and the sole inclusion of an antipsychotic-naïve population. This ensures that outcomes occur after assessment of candidate prognostic factors and that measures of association are not complicated by previous, significant antipsychotic exposure. Potential application of review findings includes discovery and evaluation of factors that may be on the causal pathway of AIWG and thus potentially serve as modifiable factors for interventions to improve outcomes, and identification of prognostic factors that serve as building blocks for prognostic model development.[11,29]

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## APPENDIX

### *S1-Supporting information*

1. Completed PRISMA-P checklist
2. Copy of database search strategy
3. Copy of modified CHARMS-PF data collection tool

### *1. Completed PRISMA-P checklist*

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

| Section and topic | Item no. | Checklist item |
|---|---|---|
| **Administrative information** | | |
| Title: | | |
| Identification | 1a | Identify the report as a protocol of a systematic review - completed |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such – n/a |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number – completed |
| Authors: | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author – Completed as part of proposal upload for journal. Email address of first author provided in protocol. |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review - completed |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments – n/a |
| Support: | | |
| Sources | 5a | Indicate sources of financial or other support for the review - completed |
| Sponsor | 5b | Provide name for the review funder and/or sponsor – n/a |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol – n/a |
| **Introduction** | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known - completed |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) - completed |
| **Methods** | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review - completed |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage - completed |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated - completed |
| Study records: | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review - completed |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) - completed |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators - completed |

Continued.

| Section and topic | Item no. | Checklist item |
|---|---|---|
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications – completed, data collection form contained in supplementary appendix |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale - completed |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis - completed |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised - completed |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) – completed |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) – completed |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned - completed |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) – completed |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) - completed |

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

***2. Copy of database search strategy***

*Concept 1-Prognostic factors*

MeSH=Nil suitable identified

Keywords=Predict*[tw] OR Risk*[tw] OR prognos*[tw] OR course[tw]

*Concept 2-Antipsychotic*

MeSH= "Antipsychotic Agents"[Mesh]

Keywords="Antipsychotic Agents"[Mesh] OR "First generation antipsychotic*"[tw] OR "second generation antipsychotic*"[tw] "first-generation antipsychotic*"OR "second-generation antipsychotic*"[tw] OR Antipsychotic*[tw] OR neuroleptic*[tw]

Concept 3-Weight Gain

MeSH="Body Weight Changes/drug effects"[Mesh]

Keywords="Body Weight Changes/drug effects"[Mesh] OR "Weight gain"[tw] OR "metabolic side effect*" OR "metabolic side-effect*"[tw] OR "Antipsychotic induced weight gain"[tw] OR "Antipsychotic-Induced weight gain"[tw] OR "Antipsychotic-related weight gain" [tw] OR "weight increase"[tw]

Concept 4 – Adults with Psychosis

MeSH = "Psychotic Disorders"[Mesh]

Keywords = Schizo*[tw] OR Psycho*[tw] OR delusion*[tw] OR "first episode psycho*"[tw] OR "first-episode psycho*"[tw] OR "Psychotic Disorders"[Mesh]

**Database search strategy.**

| Search strategies | |
|---|---|
| **Search no.** | **Terms applied** |
| **PubMed search strategy** | |
| **1** | Predict*[tw] OR Risk*[tw] OR prognos*[tw] OR outcome*[tw] |
| **2** | "Antipsychotic Agents"[Mesh] OR “First generation antipsychotic*”[tw] OR “First-generation antipsychotic*”[tw] OR “second generation antipsychotic*”[tw] OR “second-generation antipsychotic*”[tw] OR Antipsychotic*[tw] OR neuroleptic*[tw] |
| **3** | "Body Weight Changes/drug effects"[Mesh] OR “Weight gain”[tw] OR “metabolic side effect*” OR “metabolic side-effect*”[tw] OR “Antipsychotic induced weight gain”[tw] OR “Antipsychotic-Induced weight gain”[tw] |
| **4** | Schizo*[tw] OR Psycho*[tw] OR delusion*[tw] OR “first episode psychosis” OR “first-episode psychosis” OR "Psychotic Disorders"[Mesh] |
| **5** | #1 AND #2 AND #3 AND #4 |
| **6** | (amisulpride OR aripiprazole OR asenapine OR cariprazine OR clozapine OR chlorpromazine OR fluphenazine OR flupenthixol OR haloperidol OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR sulpiride OR ziprasidone OR zuclopenthixol [tw]) |
| **7** | (#2 OR #6) AND "Metabolic Syndrome"[Mesh] |
| **8** | Prospective [tw] AND #3 AND (#2 OR #6) |
| **9** | #1 AND #3 AND (#2 OR #6) |
| **10** | "Overweight"[Mesh] |
| **11** | (#2 OR #6) AND #10 |
| **12** | correlate* [tw] |
| **13** | (#2 OR # 6) AND #3 AND #12 |
| **Embase search strategy** | |
| **1** | predict*:ti,ab,kw OR 'risk*or prognos*':ti,ab,kw OR 'risk factor':ti,ab,kw |
| **2** | 'first generation antipsychotic*':ti,ab,kw OR 'second generation antipsychotic*':ti,ab,kw OR antipsychotic*:ti,ab,kw OR neuroleptic*:ti,ab,kw OR 'atypical antipsychotic agent':ti,ab,kw OR 'typical antipsychotic':ti,ab,kw OR 'first-generation antipsychotic*':ti,ab,kw OR 'second-generation antipsychotic*':ti,ab,kw |
| **3** | 'body weight gain':ti,ab,kw OR ('weight gain':ti,ab,kw OR 'metabolic side effect*':ti,ab,kw OR 'antipsychotic induced weight gain':ti,ab,kw OR 'antipsychotic-induced weight gain':ti,ab,kw OR 'antipsychotic-related weight gain':ti,ab,kw) |
| **4** | 'psychosis'/exp AND (schizo*:ti,ab,kw OR psycho*:ti,ab,kw OR delusion*:ti,ab,kw) AND psychosis:ti,ab,kw |
| **5** | #1 AND #2 AND #3 AND #4 |
| **6** | amisulpride:ti,ab,kw OR asenapine:ti,ab,kw OR aripiprazole:ti,ab,kw OR cariprazine:ti,ab,kw OR chlorpromazine:ti,ab,kw OR clozapine:ti,ab,kw OR flupenthixol:ti,ab,kw OR fluphenazine:ti,ab,kw OR haloperidol:ti,ab,kw OR lurasidone:ti,ab,kw OR olanzapine:ti,ab,kw OR paliperidone:ti,ab,kw OR quetiapine:ti,ab,kw OR risperidone:ti,ab,kw OR sulpiride:ti,ab,kw OR ziprasidone:ti,ab,kw OR zuclopenthixol:ti,ab,kw |
| **7** | (#2 OR #6) AND 'metabolic syndrome x'/exp |
| **8** | prospective:ti,ab,kw AND #3 AND |
| **9** | #1 AND #3 AND (#2 OR #6) |
| **10** | ('obesity'/exp OR overweight) |
| **11** | (#2 OR #6) AND #10 |
| **12** | correlat* |
| **13** | (#2 OR #6) AND #3 AND #12 |
| **Central search strategy** | |
| **1** | Predict*:ti,ab,kw OR Risk*:ti,ab,kw OR prognos*:ti,ab,kw |
| **2** | [Antipsychotic Agents] explode all trees OR 'first generation antipsychotic*':ti,ab,kw OR 'first-generation antipsychotic*':ti,ab,kw OR 'second generation antipsychotic*':ti,ab,kw OR 'second-generation antipsychotic*':ti,ab,kw OR antipsychotic* OR neuroleptic* |
| **3** | [Body Weight Changes] explode all trees OR 'weight gain':ti,ab,kw OR 'metabolic side effect*':ti,ab,kw OR 'metabolic side-effect*':ti,ab,kw OR 'antipsychotic induced weight gain':ti,ab,kw OR 'antipsychotic-Induced weight gain':ti,ab,kw |
| **4** | schizo*:ti,ab,kw OR psycho*:ti,ab,kw OR delusion*:ti,ab,kw OR 'first episode psycho*':ti,ab,kw OR 'first-episode psycho*':ti,ab,kw OR [Psychotic Disorders] explode all trees |

Continued.

| **Search strategies** | |
|---|---|
| **5** | #1 AND #2 AND #3 AND #4 |
| **6** | (amisulpride OR aripiprazole OR asenapine OR cariprazine OR clozapine OR chlorpromazine OR fluphenazine OR flupenthixol OR haloperidol OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR sulpiride OR ziprasidone OR zuclopenthixol):ti,ab,kw |
| **7** | (#2 OR #6) AND [Metabolic Syndrome] |
| **8** | Prospective:ti,ab,kw AND #3 AND (#2 OR #6) |
| **9** | #1 AND #3 AND (#2 OR #6) |
| **10** | "Overweight"[Mesh] |
| **11** | (#2 OR #6) AND #10 |
| **12** | correlate* [tw] |
| **13** | (#2 OR # 6) AND #3 AND #12 |
| **PscyINFO search strategy** | |
| **1** | AB(risk OR predict* OR prognos* OR “risk factor*”) |
| **2** | AB(MM"Neuroleptic Drugs" OR ("first generation antipsychotic*" OR "first-generation antipsychotic*" OR "second-generation antipsychotic*" OR "second generation antipsychotic*") |
| **3** | AB(DE "Body Weight" OR DE "Overweight" OR DE "Weight Control" OR DE "Weight Gain" OR DE "Weight Loss") |
| **4** | AB(DE "Psychosis" OR DE "Acute Psychosis" OR DE "Affective Psychosis" OR DE "Hallucinosis" OR DE "Paranoia (Psychosis)" OR DE "Postpartum Psychosis" OR DE "Reactive Psychosis" OR DE "Schizophrenia" Or “first-episode psychosis” OR “first episode psychosis”) |
| **5** | #1 AND #2 AND #3 AND #4 |
| **6** | AB(amisulpride OR Asenapine OR aripiprazole OR cariprazine OR chlorpromazine OR clozapine OR flupenthixol OR fluphenazine OR haloperidol OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR sulpiride OR ziprasidone OR zuclopenthixol) |
| **7** | (#2 OR #6) AND (MM "Metabolic Syndrome") |
| **8** | Prospective* AND #3 AND (#2 OR #6) |
| **9** | #1 AND #3 AND (#2 OR #6) |
| **10** | (DE "Overweight" OR DE "Obesity") |
| **11** | (#2 OR 6) AND #10 |
| **12** | AB(correlat*) |
| **13** | (#2 OR 6) AND #3 AND #12 |
| **CENTRAL search strategy** | |
| **1** | Predict*:ti,ab,kw OR Risk*:ti,ab,kw OR prognos*:ti,ab,kw |
| **2** | [Antipsychotic Agents] explode all trees OR 'first generation antipsychotic*':ti,ab,kw OR 'first-generation antipsychotic*':ti,ab,kw OR 'second generation antipsychotic*':ti,ab,kw OR 'second-generation antipsychotic*':ti,ab,kw OR antipsychotic* OR neuroleptic* |
| **3** | [Body Weight Changes] explode all trees OR 'weight gain':ti,ab,kw OR 'metabolic side effect*':ti,ab,kw OR 'metabolic side-effect*':ti,ab,kw OR 'antipsychotic induced weight gain':ti,ab,kw OR 'antipsychotic-Induced weight gain':ti,ab,kw |
| **4** | schizo*:ti,ab,kw OR psycho*:ti,ab,kw OR delusion*:ti,ab,kw OR 'first episode psycho*':ti,ab,kw OR 'first-episode psycho*':ti,ab,kw OR [Psychotic Disorders] explode all trees |
| **5** | #1 AND #2 AND #3 AND #4 |
| **6** | (amisulpride OR aripiprazole OR asenapine OR cariprazine OR clozapine OR chlorpromazine OR fluphenazine OR flupenthixol OR haloperidol OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR sulpiride OR ziprasidone OR zuclopenthixol):ti,ab,kw |
| **7** | (#2 OR #6) AND [Metabolic Syndrome] |
| **8** | Prospective:ti,ab,kw AND #3 AND (#2 OR #6) |
| **9** | #1 AND #3 AND (#2 OR #6) |
| **10** | "Overweight"[Mesh] |
| **11** | (#2 OR #6) AND #10 |
| **12** | correlate* [tw] |
| **13** | (#2 OR #6) AND #3 AND #12 |
| Limits set to: English language | |

### *3. Copy of modified CHARMS-PF data collection tool*

Study author, title, year of publication

Note the following before beginning:

1. Fill in Yes/No for each question below.
2. Endorse not reported on when same is not available in the study report or associated documents.
3. Highlight for further follow up with author where report suggested an aspect of the quality assessment check was conducted or undertaken but not reported on.
4. Where confirmation is required e.g., study design, please complete in notes section.

**Copy of modified CHARMS-PF data collection tool.**

| Domain and key items | | Yes | No | Unclear | Notes/comments |
|---|---|---|---|---|---|
| **1.** | **Study report** | | | | |
| a) | Did the study protocol make reference to a study protocol | | | | |
| b) | Did the study protocol make reference to a prespecified statistical analysis protocol | | | | |
| **2.** | **Source of data/Study design** (e.g., prospective cohort study, randomised trial) | | | | |
| **3.** | **Participants** | | | | |
| a. | Participant eligibility and recruitment method – e.g., consecutive participants, geographic location, number of centres, setting (e.g. clinical trial population, healthcare system, clinical practice, inclusion and exclusion criteria | | | | |
| b. | Participant description [antipsychotic treated group(s)] – including total numbers, sex (% F), ethnicity (% predominant race), age (mean + SD), baseline BMI (mean + SD) | | | | |
| c. | Details of diagnosis (if >1, record % of each) | | | | |
| d. | Details of antipsychotic prescription(s) – % prescribed each antipsychotic, antipsychotic dose (mean + SD) | | | | |
| e. | Details of previous antipsychotic exposure (if any) – antipsychotic + duration of exposure | | | | |
| f. | Details of other concomitant medication – agent(s), doses (mean+ SD), % participants receiving same across different groupings | | | | |
| g. | Study dates | | | | |
| **4.** | **Outcomes to be predicted** | | | | |
| a. | Definition and method of measurement of outcomes – confirm primary and list secondary outcomes assessed | | | | |
| b. | Was the same outcome definition used in all participants? | | | | |
| c. | Summary of duration of follow-up (median/mean follow-up time) | | | | |
| **5.** | **Prognostic factors** | | | | |
| a. | Number and type of prognostic factors assessed e.g. clinical or demographic* (list all factors here even those not found to be significant but were controlled for) | | | | |
| b. | Definition and method of measurement of prognostic factor (where relevant) e.g., treatment response defined as a prognostic risk factor, body mass index in those of varying ethnicities | | | | |
| c. | Timing of prognostic factor assessment, where relevant e.g "baseline" BMI (e.g. at presentation, diagnosis, treatment initiation) | | | | |
| d. | Were prognostic factors assessed blinded for outcome and for each other, if relevant e.g scoring of social functioning as a prognostic factor on weight changes. | | | | |
| e. | Handling of prognostic factors in the analysis (e.g. continuous, linear, non-linear transformations or categorised) | | | | |

Continued.

| Domain and key items | | Yes | No | Unclear | Notes/comments |
|---|---|---|---|---|---|
| **6.** | **Sampling size** | | | | |
| a. | Was a sampling size calculation conducted and if so, how? | | | | |
| b. | Are the number of participants and number of outcomes or events reported? | | | | |
| c. | Are the number of outcomes or events in relation the number of candidate prognostic factors (events per variable) reported? | | | | |
| **7.** | **Missing data** | | | | |
| a) | Number of participants with any missing value (in the prognostic factors and outcomes) | | | | |
| b) | Number of participants with missing data for each prognostic factor of interest (e.g. % lost to follow-up) | | | | |
| c) | Details of attrition (reasons for loss to follow-up) | | | | |
| d) | Methods for handling of missing data (e.g., complete case analysis, imputation, or other methods) | | | | |
| **8.** | **Analysis** | | | | |
| a) | Unadjusted or adjusted prognostic factors reported (or both)? | | | | |
| b) | In the case of unadjusted prognostic factors reported, method of assessment undertaken (e.g. univariate regression, test of independence) | | | | |
| c) | In the case of adjusted prognostic factors reported, outline the multivariable modelling methods (e.g. linear or logistic regression) | | | | |
| d) | In the case of adjusted prognostic factors reported, method for selection of prognostic factors for inclusion in multivariable modelling (e.g. all candidate prognostic factors considered, preselection of established prognostic factors, retain only those significant from univariable analysis) | | | | |
| e) | How modelling assumptions were checked | | | | |
| f) | Method for selection or exclusion of prognostic factors (including those of interest and those used as adjustment factors) during multivariable modelling (e.g. backward or forward selection, or full model approach including all factors regardless) and criteria used for any selection or exclusion (e.g. P value) | | | | |
| g) | Method of handling each continuous prognostic factor (e.g. dichotomisation, categorisation, linear, non-linear) including values used of any cut points and their justification | | | | |
| **9.** | **Results** | | | | |
| a) | Unadjusted and adjusted prognostic effect estimates (e.g. risk ratios, odds ratios, mean differences) and the corresponding 95% confidence interval (or standard error or variance) + P value for each prognostic factor studied. | | | | |
| b) | For multivariable analysis, % variation in the dependent variable explained by the combination of prognostic factors | | | | |
| c) | If applicable – any details of non-linear relationships and whether modelling assumptions hold | | | | |
| d) | For each extracted adjusted prognostic effect estimate of interest the set of adjustment factors used | | | | |
| **10.** | **Interpretation and discussion** | | | | |
| a) | Interpretation of presented results | | | | |
| b) | Comparison with other studies, discussion of generalisability, strengths and limitations | | | | |

*Examples of clinical prognostic/risk factors = Baseline weight/body mass index, baseline psychiatric symptom severity, concomitant treatment, duration of antipsychotic treatment, schizophrenia subtype, antipsychotic dose, inpatient or outpatient status, trend of weight gain e.g. rapid vs. slow initial weight gain. *Examples of demographic prognostic/risk factors = include age, sex, social economic status, ethnicity, employment status.