Supplemental

Metabolic syndrome in antipsychotic-naïve patients with first episode psychosis: A systematic review and meta-analysis

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### Table S1. PRISMA statement and checklist

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Page(s)** |  |
|  | TITLE | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |  |
|  | ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1 |  |
|  | INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |  |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 |  |
|  | METHODS | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 3 |  |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3-4 |  |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 & table S3 |  |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4 & table S3 |  |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4-5 |  |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 4 |  |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4 |  |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5 |  |
| Summary measures | 13 | State the principal summary measures | 7 |  |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias (i.e. Newcastle-Ottawa Scale (NOS), that may affect the cumulative evidence. | 8 |  |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 6 |  |
|  | RESULTS | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Fig 1 |  |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 1 and 2 |  |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment. | 8 |  |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study a summary data for each intervention group. | Table 1 |  |
| Synthesis of results | 21 | Present results of study analysed. | 6 |  |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies | Table 2 |  |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression | 7  and table S11 |  |
|  | DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 9 |  |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |  |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 11 |  |
|  | FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support; role of funders for the systematic review. | 2 |  |

### Table S2. Moose checklist

|  |  |  |
| --- | --- | --- |
| **Criteria** | | **Brief description of how the criteria were handled in the meta-analysis** |
| **Reporting of background should include** | | |
| √ | Problem definition | It is unclear what the prevalence of “Metabolic Syndrome (MetS) in drug naïve First Episode of Psychosis (FEP) is, as previous meta-analyses were conducted in minimally exposed or drug naïve FEP patients with psychotic disorder at the later stages of disease; thus a meta-analysis examining MetS in this population is needed. |
| √ | Hypothesis statement | Altered metabolic parameters in FEPs are not exclusively due to antipsychotic treatments. |
| √ | Description of study outcomes | studies in which MetS diagnosis was confirmed or rejected based on current endocrinal criteria; i.e. it was defined according to any of these four sets of criteria: ATPIII-A, IDF, JIS 2009 and WHO |
| √ | Type of exposure or intervention used |  |
| √ | Type of study designs used | Cross sectional studies or baseline assessment of prospective and retrospective cohort studies |
| √ | Study population | Studies on FEP patients, (ii) Studies in which psychosis diagnosis was determined according to either DSM-IV, DSM IV-TR17, DSM-5 (American Psychiatric Association, 2013) or International Classification of Diseases, Ninth or Ten Revision (ICD-9 or ICD-10); (iii) Studies on individuals with FEP defined by the study authors as either drug-naïve (0 days) or minimal exposure regardless of the duration to antipsychotics will be considered for systematic review and studies on individuals with FEP and drug-naïve (0-day exposure to antipsychotic treatment) will be included in prevalence meta-analysis |
| **Reporting of search strategy should include** | | |
| √ | Qualifications of searchers | The credentials of the investigators are indicated in the author list. |
| √ | Search strategy, including time period included in the synthesis and keywords | The search strategy is included in table 3 of supplemental material |
| √ | Databases and registries searched | We searched the website of Science Core Collection, Embase and Medline via Embase and PubMed platforms from inception until November 2020. |
| √ | Use of hand searching | Included studies of relevant systematic reviews/ meta-analyses and the references from the included studies were manually screened and searched. |
| √ | List of citations located and those excluded, including justifications | Details of the literature search process are outlined in the results section and PRISMA flowchart. |
| √ | Method of addressing articles published in languages other than English | Only articles in the English language were selected. |
| √ | Method of handling abstracts and unpublished studies | Only original individual studies that were fully accessible were included in our study. |
| √ | Description of any contact with authors | Authors were contacted in the case of missing data or for further information, through email. If no response was given, there was one further attempt at contact. |
| **Reporting of methods should include** | | |
| √ | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Detailed inclusion and exclusion criteria are described in the methods section. |
| √ | Rationale for the selection and coding of data | Data extracted from each of the studies are relevant to the population characteristics, study design and study outcomes. |
| √ | Assessment of confounding | We did not investigate confounding factors |
| √ | Assessment of study quality and stratification or regression on possible predictors of study results | We evaluated the quality of the included studies using the JBI tool |
| √ | Assessment of heterogeneity | Heterogeneity was assessed with the I2 index. |
| √ | Description of statistical methods in sufficient detail to be replicated | A random-effects meta-analysis was used. Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated with the I2 index. |
| √ | Provision of appropriate tables and graphics | Figures are included to reflect the literature search process and forest plots of the meta-analyses conducted. Tables are also provided to depict additional data of all analyses conducted and to present relevant key information |
| **Reporting of results should include** | | |
| √ | Table summarizing individual study estimates and overall estimate | We reported this in the results and supplementary section. |
| √ | Table giving descriptive information for each study included | We have presented descriptive information for each study in the tables within the supplementary material. |
| √ | Results of sensitivity testing | Subgroup analyses were conducted as specified in the manuscript. |
| √ | Indication of statistical uncertainty of findings | We discuss in our limitations some potential bias that should be taken into account when interpreting our findings. |
| **Reporting of discussion should include** | | |
| √ | Quantitative assessment of bias | Our discussion discusses potential bias that have been taken into account |
| √ | Justification for exclusion | We excluded studies based on the rationale of other meta-analysis and our own judgement and this is documented in the methods section, supported with tables in SM and discussed in the main manuscript. |
| √ | Assessment of quality of included studies |  |
| **Reporting of conclusions should include** | | |
| √ | Consideration of alternative explanations for observed results | We have addressed this point in the discussion section. |
| √ | Generalization of the conclusions | We have addressed this point in the discussion section. |
| √ | Guidelines for future research | We have addressed this point in the discussion section. |
| √ | Disclosure of funding source | We have addressed this point at the end of the discussion section |

### Table S3. Search Strategy

|  |
| --- |
| **Pubmed Search Query**  (("first-episode"[All Fields] AND ("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields])) OR ("first-episode"[All Fields] AND ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields])) OR "FEP"[All Fields] OR "FES"[All Fields] OR ("psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]) OR ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia s"[All Fields])) AND ("antipsychotic-naive"[All Fields] OR "antipsychotic-free"[All Fields] OR "drug-naive"[All Fields] OR "drug-free"[All Fields] OR "neuroleptic-naive"[All Fields] OR "neuroleptic-free"[All Fields] OR "never-medicated"[All Fields] OR "untreated"[All Fields]) AND ("cholesterol"[MeSH Terms] OR "cholesterol"[All Fields] OR "cholesterol s"[All Fields] OR "cholesterole"[All Fields] OR "cholesterols"[All Fields] OR "HDL"[All Fields] OR ("oxidized low density lipoprotein"[Supplementary Concept] OR "oxidized low density lipoprotein"[All Fields] OR "ldl"[All Fields]) OR ("triglycerid"[All Fields] OR "triglycerides"[MeSH Terms] OR "triglycerides"[All Fields] OR "triglyceride"[All Fields] OR "triglycerids"[All Fields]) OR ("lipid s"[All Fields] OR "lipidate"[All Fields] OR "lipidated"[All Fields] OR "lipidates"[All Fields] OR "lipidation"[All Fields] OR "lipidations"[All Fields] OR "lipide"[All Fields] OR "lipides"[All Fields] OR "lipidic"[All Fields] OR "lipids"[MeSH Terms] OR "lipids"[All Fields] OR "lipid"[All Fields]) OR ("lipoprotein s"[All Fields] OR "lipoproteine"[All Fields] OR "lipoproteins"[MeSH Terms] OR "lipoproteins"[All Fields] OR "lipoprotein"[All Fields]) OR "MetS"[All Fields] OR ("metabolic"[All Fields] OR "metabolical"[All Fields] OR "metabolically"[All Fields] OR "metabolics"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolisms"[All Fields] OR "metabolism"[MeSH Subheading] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR "metabolic networks and pathways"[All Fields] OR "metabolities"[All Fields] OR "metabolization"[All Fields] OR "metabolize"[All Fields] OR "metabolized"[All Fields] OR "metabolizer"[All Fields] OR "metabolizers"[All Fields] OR "metabolizes"[All Fields] OR "metabolizing"[All Fields]) OR ("blood pressure"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "blood pressure determination"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields] AND "determination"[All Fields]) OR "blood pressure determination"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "arterial pressure"[MeSH Terms] OR ("arterial"[All Fields] AND "pressure"[All Fields]) OR "arterial pressure"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields])) OR (("metabolic"[All Fields] OR "metabolical"[All Fields] OR "metabolically"[All Fields] OR "metabolics"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolisms"[All Fields] OR "metabolism"[MeSH Subheading] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR "metabolic networks and pathways"[All Fields] OR "metabolities"[All Fields] OR "metabolization"[All Fields] OR "metabolize"[All Fields] OR "metabolized"[All Fields] OR "metabolizer"[All Fields] OR "metabolizers"[All Fields] OR "metabolizes"[All Fields] OR "metabolizing"[All Fields]) AND ("dysregulate"[All Fields] OR "dysregulated"[All Fields] OR "dysregulates"[All Fields] OR "dysregulating"[All Fields] OR "dysregulation"[All Fields] OR "dysregulations"[All Fields])))  **Translations**  **psychosis:** "psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]  **schizophrenia:** "schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia's"[All Fields]  **psychosis:** "psychotic disorders"[MeSH Terms] OR ("psychotic"[All Fields] AND "disorders"[All Fields]) OR "psychotic disorders"[All Fields] OR "psychosis"[All Fields]  **schizophrenia:** "schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields] OR "schizophrenias"[All Fields] OR "schizophrenia's"[All Fields]  **cholesterol:** "cholesterol"[MeSH Terms] OR "cholesterol"[All Fields] OR "cholesterol's"[All Fields] OR "cholesterole"[All Fields] OR "cholesterols"[All Fields]  **LDL:** "oxidized low density lipoprotein"[Supplementary Concept] OR "oxidized low density lipoprotein"[All Fields] OR "ldl"[All Fields]  **triglycerides:** "triglycerid"[All Fields] OR "triglycerides"[MeSH Terms] OR "triglycerides"[All Fields] OR "triglyceride"[All Fields] OR "triglycerids"[All Fields]  **lipids:** "lipid's"[All Fields] OR "lipidate"[All Fields] OR "lipidated"[All Fields] OR "lipidates"[All Fields] OR "lipidation"[All Fields] OR "lipidations"[All Fields] OR "lipide"[All Fields] OR "lipides"[All Fields] OR "lipidic"[All Fields] OR "lipids"[MeSH Terms] OR "lipids"[All Fields] OR "lipid"[All Fields]  **lipoproteins:** "lipoprotein's"[All Fields] OR "lipoproteine"[All Fields] OR "lipoproteins"[MeSH Terms] OR "lipoproteins"[All Fields] OR "lipoprotein"[All Fields]  **metabolic:** "metabolic"[All Fields] OR "metabolical"[All Fields] OR "metabolically"[All Fields] OR "metabolics"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolisms"[All Fields] OR "metabolism"[Subheading] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR "metabolic networks and pathways"[All Fields] OR "metabolities"[All Fields] OR "metabolization"[All Fields] OR "metabolize"[All Fields] OR "metabolized"[All Fields] OR "metabolizer"[All Fields] OR "metabolizers"[All Fields] OR "metabolizes"[All Fields] OR "metabolizing"[All Fields]  **blood pressure:** "blood pressure"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "blood pressure determination"[MeSH Terms] OR ("blood"[All Fields] AND "pressure"[All Fields] AND "determination"[All Fields]) OR "blood pressure determination"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields]) OR "blood pressure"[All Fields] OR "arterial pressure"[MeSH Terms] OR ("arterial"[All Fields] AND "pressure"[All Fields]) OR "arterial pressure"[All Fields] OR ("blood"[All Fields] AND "pressure"[All Fields])  **metabolic:** "metabolic"[All Fields] OR "metabolical"[All Fields] OR "metabolically"[All Fields] OR "metabolics"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolisms"[All Fields] OR "metabolism"[Subheading] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR "metabolic networks and pathways"[All Fields] OR "metabolities"[All Fields] OR "metabolization"[All Fields] OR "metabolize"[All Fields] OR "metabolized"[All Fields] OR "metabolizer"[All Fields] OR "metabolizers"[All Fields] OR "metabolizes"[All Fields] OR "metabolizing"[All Fields]  **dysregulation:** "dysregulate"[All Fields] OR "dysregulated"[All Fields] OR "dysregulates"[All Fields] OR "dysregulating"[All Fields] OR "dysregulation"[All Fields] OR "dysregulations"[All Fields]  **EMBASE Search Query**  ('first episode' AND ('psychosis'/exp OR 'psychosis' OR (('psychotic'/exp OR psychotic) AND ('disorders'/exp OR disorders)) OR 'psychotic disorders'/exp OR 'psychotic disorders' OR 'psychosis'/exp OR psychosis) OR ('first episode' AND ('schizophrenia'/exp OR 'schizophrenia' OR 'schizophrenia'/exp OR schizophrenia OR schizophrenias OR 'schizophrenia s')) OR fep OR fes OR (('psychotic'/exp OR psychotic) AND ('disorders'/exp OR disorders)) OR 'psychotic disorders'/exp OR 'psychotic disorders' OR 'psychosis'/exp OR psychosis OR 'schizophrenia'/exp OR schizophrenia OR schizophrenias OR 'schizophrenia s') AND ('antipsychotic naive' OR 'antipsychotic free' OR 'drug naive' OR 'drug free' OR 'neuroleptic naive' OR 'neuroleptic free' OR 'never medicated' OR untreated) AND ('cholesterol'/exp OR 'cholesterol' OR 'cholesterol'/exp OR cholesterol OR 'cholesterol s' OR cholesterole OR cholesterols OR 'hdl'/exp OR hdl OR 'oxidized low density lipoprotein[supplementary concept]' OR 'oxidized low density lipoprotein'/exp OR 'oxidized low density lipoprotein' OR 'ldl'/exp OR ldl OR triglycerid OR 'triacylglycerol'/exp OR 'triacylglycerol' OR 'triglycerides'/exp OR triglycerides OR 'triglyceride'/exp OR triglyceride OR triglycerids OR 'lipid s' OR lipidate OR lipidated OR lipidates OR 'lipidation'/exp OR lipidation OR lipidations OR lipide OR lipides OR lipidic OR 'lipid'/exp OR 'lipid' OR 'lipids'/exp OR lipids OR 'lipid'/exp OR lipid OR 'lipoprotein s' OR lipoproteine OR 'lipoproteins'/exp OR 'lipoproteins' OR 'lipoproteins'/exp OR lipoproteins OR 'lipoprotein'/exp OR lipoprotein OR mets OR metabolic OR metabolical OR metabolically OR metabolics OR 'metabolism'/exp OR 'metabolism' OR 'metabolism'/exp OR metabolism OR metabolisms OR (metabolic AND networks AND pathways) OR 'metabolic networks and pathways'/exp OR 'metabolic networks and pathways' OR metabolities OR 'metabolization'/exp OR metabolization OR metabolize OR metabolized OR metabolizer OR metabolizers OR metabolizes OR metabolizing OR (('blood'/exp OR blood) AND ('pressure'/exp OR pressure) AND determination) OR 'blood pressure determination'/exp OR 'blood pressure determination' OR 'blood pressure'/exp OR 'blood pressure' OR (arterial AND ('pressure'/exp OR pressure)) OR 'arterial pressure'/exp OR 'arterial pressure' OR (('blood'/exp OR blood) AND ('pressure'/exp OR pressure)) OR ((metabolic OR metabolical OR metabolically OR metabolics OR 'metabolism'/exp OR 'metabolism' OR 'metabolism'/exp OR metabolism OR metabolisms OR (metabolic AND networks AND pathways) OR 'metabolic networks and pathways'/exp OR 'metabolic networks and pathways' OR metabolities OR 'metabolization'/exp OR metabolization OR metabolize OR metabolized OR metabolizer OR metabolizers OR metabolizes OR metabolizing) AND (dysregulate OR dysregulated OR dysregulates OR dysregulating OR dysregulation OR dysregulations))) AND [embase]/lim  **Web of Science Core Collection**  Search in All Databases  TS=(first-episode psychosis or first-episode schizophrenia or FEP or FES or psychosis or schizophrenia) AND  #1 Results = 332828  TS=(antipsychotic-naïve or antipsychotic-free or drug-naïve or drug-free or neuroleptic-naïve or neuroleptic-free or never-medicated or untreated) AND  #2 Results = 307388  TS=(cholesterol or HDL or LDL or triglycerides or lipids or lipoproteins or metabolic syndrome or metabolic or blood pressure or metabolic dysregulation)  #3 Results = 5051070  #3 AND #2 AND #1  #4 Results = 1048 |

### Table S4. Diagnostic manuals’ codes associated with the relevant psychosis diagnoses included

|  |  |  |
| --- | --- | --- |
| **Diagnosis** | **Code used within ICD-10** | **Code used within DSM-IV** |
| **Schizophrenia** | F20 | 295.10/295.20/  295.30/295.60/  295.90 |
| **Brief psychotic disorder** | F23 | - |
| **Schizophreniform disorder** | F20.81 | Schizophreniform disorder |
| **Bipolar disorder with psychotic features** | F31.2 | 296.04/296.44/  296.54/296.64 |
| **Schizoaffective disorder** | F25.0 | 295.70 |
| **Psychosis, not otherwise specified** | F29 | 298.9 |

### Table S5. Inclusion criteria for outcomes measures used to metabolic syndrome

The instruments below were chosen for being the most common instruments used to assess metabolic syndrome in general population and were chosen by authors after careful examination of relevant reviews in the field and based on their previous experience in clinical practise. If during the full text screening, a new instrument not included in the initially considered, it was discussed in a group meeting whether it should be included or not. Only validated instruments were considered, which means that they went through a validation study process, where the usual parameters of quality were examined (inter-rater reliability, concurrent validity etc…)

|  |  |
| --- | --- |
| **ATP-IIIA** | Diagnosis is made when three or more are present:   * Waist circumference of more than 102 cm in men or more than 88 cm in women. * Fasting triglyceride level of 150 mg/dL or higher. * Blood pressure level of 130/85 mm Hg or higher. * Low HDL-C level (defined as < 1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women) |
| **IDF** | * **Central obesity and any 2 out of these 4 other factors:** * Triglyceride level of 1.7 mmol/L (150 mg/dL) or higher. * Low HDL-C level (defined as < 1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women) * Blood pressure of 130/85 mm Hg or higher. * Fasting hyperglycemia (defined as glucose level ≥5.6 mmol/L [100 mg/dL]) or previous diagnosis of diabetes or IGT. |
| **JIS-2009** | * > 3 out of these parameters: * Fasting glucose>100mg/dL * Blood pressure level of 130/85 mm Hg or higher. * Fasting triglyceride level of 150 mg/dL or higher. * Low HDL-C level (defined as < 1.04 mmol/L [40 mg/dL] in men or < 1.29 mmol/L [50 mg/dL] in women) |
| **WHO** | * Insulin resistance is defined as type 2 diabetes mellitus (DM) or impaired fasting glucose (IFG) (> 100 mg/dl) or impaired glucose tolerance (IGT), plus two of the following: * Abdominal obesity (waist-to-hip ratio > 0.9 in men or > 0.85 in women, or body mass index (BMI) > 30 kg/m2. * Triglycerides 150 mg/dl or greater, and/or high-density lipoprotein (HDL)-cholesterol < 40 mg/dl in men and < 50 mg/dl in women. * Blood pressure (BP) 140/90 mmHg or greater. * Microalbuminuria (urinary albumin secretion rate 20 μg/min or greater, or albumin-to-creatinine ratio 30 mg/g or greater). |

### Table S6 All (18) full text selected studies, quality assessment and their respective reasoning for the exclusion of meta-analysis (K=18)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Autor** | **Year** | **Patients** | **Strictly Naïve (0 days)** | **MetS** | **Risk of bias** | **Reason of exclusion** |
| Chilliza | 2015 | FEP | Yes | Yes | Low | Not strictly naive |
| Grover | 2012 | Schizophrenia | Yes | Yes | Low | Included |
| Kraemer | 2011 | FEP | Yes | Yes | Low | Included |
| Medved | 2009 | FEP | Yes | Yes | Low | Included |
| Owiredu | 2012 | Schizophrenia | Yes | Yes | Moderate | Included |
| Pallava | 2012 | FEP | No | Yes | Low | Not strictly naive |
| Srivastava | 2018 | FEP | Yes | Yes | Moderate | Included |
| Martin Otano | 2013 | FEP | Yes | Yes | Low | Included |
| Kraemer | 2011 | FEP | Yes | Yes | Low | Included |
| Saloojee | 2018 | FEP | Yes | Yes | Moderate | Included |
| Fleichhacker | 2013 | FEP | No | Yes | Low | Not strictly naive |
| De hert | 2008 | FEP | Yes | Yes | Low | Included |
| Enez Darcin | 2015 | FEP | Yes | Yes | Moderate | Included |
| Sahpolat | 2020 | FEP | Yes | Yes | Moderate | Included |
| Srihari | 2013 | FEP | No | Yes | Low | Not strictly naive |
| Garcia Rizo | 2017 | FEP | Yes | Yes | Low | Included |
| Correll | 2014 | FEP | No | Yes | Low | Not strictly naive |
| Effat | 2012 | FEP | Yes | Yes | Low | Included |
| Saddicha | 2008 | FEP | Yes | Yes | Low | Included |

### Table S7. Full text excluded articles and their respective reasoning for exclusion (K=94)

|  |  |  |
| --- | --- | --- |
| **Author** | **Title** | **Reason of exclusion** |
| Aguilar, Eva, Coronas, Ramon, Caixas, Assumpta | Metabolic syndrome in patients with schizophrenia and antipsychotic treatment | No naïve |
| Al-Amin, Md. Mamun, Uddin, Mir Muhammad Nasir, Reza, Hasan Mahmud | Effects of Antipsychotics on the Inflammatory Response System of Patients with Schizophrenia in Peripheral Blood Mononuclear Cell Cultures | No MetS |
| Alvarez-Jimenez, M, Conzalez-Blanch, C, Perez-Iglesias, R, Crespo-Facorro, B, Vazquez-Barquero, JL | Attenuation of antipsychotic-induced weight gain with early behavioural intervention in drug-naive first episode psychosis patients: a randomized controlled trial | Type of Study |
| Argo, Tami, Carnahan, Ryan, Barnett, Mitchell, Holman, Timothy L., Perry, Paul J. | Diabetes prevalence estimates in schizophrenia and risk factor assessment | No naïve |
| Arranz, B, Duenas, R, Ramirez, N, Fernandez, P, Sarro, S, San, L | Initial stages of insulin resistance in young antipsychotic-free and not in antipsychotic-naive schizophrenic patients | No MetS |
| Atbasoglu, E. Cem, Gumus-Akay, Guvem, Guloksuz, Sinan, Saka, Meram Can, Ucok, Alp, Alptekin, Koksal, Gullu, Sevim, van Os, Jim | Higher schizotypy predicts better metabolic profile in unaffected siblings of patients with schizophrenia | No naïve |
| Baeza, Immaculada, Castro-Fornieles, Josefina, Deulofeu, Ramon, de la Serna, Elena, Goti, Javier, Salvà, Joan, Bernardo, Miquel | Plasma homovanillic acid differences in clinical subgroups of first episode schizophrenic patients | No MetS |
| Baptista, Trino, Serrano, Ana, Uzcategui, Euderruh, ElFakih, Yamily, Rangel, Nairy, Carrizo, Edgardo, Fernandez, Virginia, Connell, Lisette, Araujo de Baptista, Enma, Quiroz, Segundo, Uzcategui, Marycelvia, Rondon, Juana, Matos, Yimber, Uzcategui, Lilia, Gomez, Roald, Valery, Lenin, Novoa-Montero, Dario | The metabolic syndrome and its constituting variables in atypical antipsychotic-treated subjects: Comparison with other drug treatments, drug-free psychiatric patients, first-degree relatives and the general population in Venezuela | No naïve |
| Barnett, A. H., Mackin, P., Chaudhury, I., Farooqi, A., Gadsby, R., Heald, A., Hill, J., Millar, H., Peveler, R., Rees, A., Singh, V., Taylor, D., Vora, J., Jones, P. B. | Minimising metabolic and cardiovascular risk in schizophrenia: diabetes, obesity and dyslipidaemia | No naïve |
| Bocchio-Chiavetto, Luisella, Zanardini, Roberta, Tosato, Sarah, Ventriglia, Mariacarla, Ferrari, Clarissa, Bonetto, Chiara, Lasalvia, Antonio, Giubilini, Franco, Fioritti, Angelo, Pileggi, Francesca, Pratelli, Michela, Pavanati, Michele, Favaro, Angela, De Girolamo, Giovanni, Frisoni, Giovanni Battista, Ruggeri, Mirella, Gennarelli, Massimo | Immune and metabolic alterations in first episode psychosis (FEP) patients | No MetS |
| Brunero, Scott, Lamont, Scott | Systematic screening for metabolic syndrome in consumers with severe mental illness | No MetS |
| Bushe, Chris | Glucose Abnormalities in Schizophrenia, Bipolar and Major Depressive Disorders | No naïve |
| Çakici, Nuray, Mill, Nina H van, Roza, Sabine J, Haan, Lieuwe De, Luik, Annemarie I, Beveren, Nico J van | T68. SUBCLINICAL PSYCHOTIC PHENOMENA ARE ASSOCIATED WITH MARKERS OF AN ALTERED METABOLISM IN A LARGE COMMUNITY SAMPLE. | No psychosis |
| Castillo Sanchez, Miguel, Fabregas Escurriola, Mireia, Berge Baquero, Daniel, Goday Arno, Albert, Valles Callol, Joan Antoni | Psychosis, cardiovascular risk and associated mortality: Are we on the right track? | No naïve |
| Castillo, Rolando I., Rojo, Leonel E., Henriquez-Henriquez, Marcela, Silva, Hernán, Maturana, Alejandro, Villar, María J., Fuentes, Manuel, Gaspar, Pablo A. | From Molecules to the Clinic: Linking Schizophrenia and Metabolic Syndrome through Sphingolipids Metabolism | Type of study |
| Chen, D. C., Du, X. D., Yin, G. Z., Yang, K. B., Nie, Y., Wang, N., Li, Y. L., Xiu, M. H., He, S. C., Yang, F. D., Cho, R. Y., Kosten, T. R., Soares, J. C., Zhao, J. P., Zhang, X. Y. | Impaired glucose tolerance in first-episode drug-naive patients with schizophrenia: relationships with clinical phenotypes and cognitive deficits | No MetS |
| Chen, Jinhong, Tan, Liwen, Long, Zhou, Wang, Lifeng, Hu, Li, Yang, Dong | Drug-naive patients with schizophrenia have metabolic disorders that are not associated with polymorphisms in the LEP (-2548G/A) and 5-HTR2C (-759C/T) genes | No MetS |
| Chen, Song, Broqueres-You, Dong, Yang, Guigang, Wang, Zhiren, Li, Yanli, Wang, Ning, Zhang, Xiangyang, Yang, Fude, Tan, Yunlong | Relationship between insulin resistance, dyslipidaemia and positive symptom in Chinese antipsychotic-naive first-episode patients with schizophrenia | No MetS |
| Chen, Song, Broqueres-You, Dong, Yang, Guigang, Wang, Zhiren, Li, Yanli, Yang, Fude, Tan, Yunlong | Male sex may be associated with higher metabolic risk in first-episode schizophrenia patients: A preliminary study | No MetS |
| Choong, Eva, Quteineh, Lina, Cardinaux, Jean-Rene, Gholam-Rezaee, Mehdi, Vandenberghe, Frederik, Dobrinas, Maria, Bondolfi, Guido, Etter, Manuela, Holzer, Laurent, Magistretti, Pierre, von Gunten, Armin, Preisig, Martin, Vollenweider, Peter, Beckmann, Jacques S., Pralong, Francois P., Waeber, Gerard, Kutalik, Zoltan, Conus, Philippe, Bochud, Murielle, Eap, Chin B. | Influence of CRTC1 Polymorphisms on Body Mass Index and Fat Mass in Psychiatric Patients and the General Adult Population | No naïve |
| Chouinard, Virginie-Anne, Henderson, David C., Dalla Man, Chiara, Valeri, Linda, Gray, Brianna E., Ryan, Kyle P., Cypess, Aaron M., Cobelli, Claudio, Cohen, Bruce M., Ongur, Dost | Impaired insulin signaling in unaffected siblings and patients with first-episode psychosis | No MetS |
| Citrome, L, Blonde, L, Damatarca, C | Metabolic issues in patients with severe mental illness | No naïve |
| Cohn, TA, Wolever, T, Bois, D, Zipursky, RB, Remington, G | First episode and neuroleptic free patients with schizophrenia have reduced insulin sensitivity: A minimal model analysis | No MetS |
| Cordes, J., Bechdolf, A., Moebus, S. | Prevalence of the metabolic syndrome in patients at risk of psychosis | No psychosis |
| Cordes, Joachim, Bechdolf, Andreas, Engelke, Christina, Kahl, Kai G., Balijepalli, Chakrapani, Lösch, Christian, Klosterkötter, Joachim, Wagner, Michael, Maier, Wolfgang, Heinz, Andreas, de Millas, Walter, Gaebel, Wolfgang, Winterer, Georg, Janssen, Birgit, Schmidt-Kraepelin, Christian, Schneider, Frank, Lambert, Martin, Juckel, Georg, Wobrock, Thomas, Riedel, Michael, Moebus, Susanne | Prevalence of metabolic syndrome in female and male patients at risk of psychosis | No psychosis |
| Curtis, Jackie, Henry, Catherine, Watkins, Andrew, Newall, Hannah, Samaras, Katherine, Ward, Philip B. | Metabolic abnormalities in an early psychosis service: a retrospective, naturalistic cross-sectional study | No Naïve |
| Darcin, Asli Enez, Cavus, Sercin Yalcin, Dilbaz, Nesrin, Kaya, Hasan, Dogan, Eylem | Metabolic syndrome in drug-naive and drug-free patients with schizophrenia and in their siblings | Type of Study |
| Dasgupta, Anindya, Singh, Om Prakash, Rout, Jayanta Kumar, Saha, Tanmay, Mandal, Sonai | Insulin resistance and metabolic profile in antipsychotic naive schizophrenia patients | No MetS |
| Duda-Sobczak, Anna, Wierusz-Wysocka, Bogna | Diabetes mellitus and psychiatric diseases | No naïve |
| Ebert, Tanya, Midbari, Yael, Shmilovitz, Ronen, Kosov, Ira, Kotler, Moshe, Weizman, Abraham, Ram, Anca | Metabolic effects of antipsychotics in prepubertal children: a retrospective chart review | No naïve |
| Emul, Murat, Kalelioglu, Tevfik | Etiology of cardiovascular disease in patients with schizophrenia: current perspectives | Type of study |
| Enger, Cheryl, Jones, Meghan E, Kryzhanovskaya, Ludmila, Doherty, Michael, McAfee, Andrew T | Risk of developing diabetes and dyslipidemia among adolescents with bipolar disorder or schizophrenia. | No naïve |
| Foley, Debra L., Mackinnon, Andrew, Watts, Gerald F., Shaw, Jonathan E., Magliano, Dianna J., Castle, David J., McGrath, John J., Waterreus, Anna, Morgan, Vera A., Galletly, Cherrie A. | Cardiometabolic Risk Indicators That Distinguish Adults with Psychosis from the General Population, by Age and Gender | No naïve |
| Fraguas, David, Merchán-Naranjo, Jessica, Laita, Paula, Parellada, Mara, Moreno, Dolores, Ruiz-Sancho, Ana, Cifuentes, Alicia, Giráldez, Marisa, Arango, Celso | Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics | No MetS |
| Ganesh, Suhas, Ashok, Abhishekh Hulegar, Kumar, Chennaveerachari Naveen, Thirthalli, Jagadish | Prevalence and determinants of metabolic syndrome in patients with schizophrenia: A systematic review and meta-analysis of Indian studies | Type of Study |
| Graham, Karen A., Cho, Hyunsoon, Brownley, Kimberly A., Harp, Joyce B. | Early treatment-related changes in diabetes and cardiovascular disease risk markers in first episode psychosis subjects | No naïve |
| Grimm, Oliver, Kaiser, Stefan, Plichta, Michael M., Tobler, Philippe N. | Altered reward anticipation: Potential explanation for weight gain in schizophrenia? | No naïve |
| Hepgul, N., Pariante, C. M., Dipasquale, S., DiForti, M., Taylor, H., Marques, T. R., Morgan, C., Dazzan, P., Murray, R. M., Mondelli, V. | Childhood maltreatment is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients | No MetS |
| Horsdal, Henriette Thisted, Benros, Michael Eriksen, Kohler-Forsberg, Ole, Krogh, Jesper, Gasse, Christiane | Metabolic profile at first-time schizophrenia diagnosis: a population-based cross-sectional study | No MetS |
| Khuhro, Quratulain, Channa, Naseem Aslam, Amur, Safdar Ali, Mugheri, Muhammad Haneef, Paras, Muzna, Soomro, Najaf Ali | Atypical Antipsychotics and Dyslipidemia- Experience at Psychiatry Hospital Hyderabad, Pakistan | No MetS |
| Kirkpatrick, Brian W., Garcia-Rizo, Clemente, Fernandez-Egea, E., Miller, Brian, Bernardo, M. | METABOLIC ABNORMALITIES IN NEWLY DIAGNOSED, ANTIPSYCHOTIC-NAIVE PATIENTS WITH SCHIZOPHRENIA AND RELATED DISORDERS | No MetS |
| Luckhoff, H. K., Kilian, S., Olivier, M. R., Phahladira, L., Scheffler, F., du Plessis, S., Chiliza, B., Asmal, L., Emsley, R. | Relationship between changes in metabolic syndrome constituent components over 12months of treatment and cognitive performance in first-episode schizophrenia | Type of Study |
| Maayan, Lawrence, Correll, Christoph U. | Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents | No naïve |
| Malhotra, Nidhi, Grover, Sandeep, Chakrabarti, Subho, Kulhara, Parmanand | Metabolic syndrome in schizophrenia. | Type of Study |
| Misiak, Błażej, Stańczykiewicz, Bartłomiej, Łaczmański, Łukasz, Frydecka, Dorota | Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: A systematic review and meta-analysis | No MetS |
| Mizrahi, Romina, Agid, Ofer, Borlido, Carol, Suridjan, Ivonne, Rusjan, Pablo, Houle, Sylvain, Remington, Gary, Wilson, Alan A., Kapur, Shitij | Effects of antipsychotics on D3 receptors: a clinical PET study in first episode antipsychotic naive patients with schizophrenia using [11C]-(+)-PHNO | No MetS |
| Mondelli, Valeria, Pariante, Carmine M. | Metabolic syndrome and obesity in psychosis: the possible mechanisms | Type of Study |
| Osby, Urban, Olsson, Eric, Edman, Gunnar, Hilding, Agneta, Eriksson, Sven V., Ostenson, Claes Goran | Psychotic disorder is an independent risk factor for increased fasting glucose and waist circumference | No naïve |
| Padmavati, Ramachandran, McCreadie, Robin G., Tirupati, Srinivasan | Low prevalence of obesity and metabolic syndrome in never-treated chronic schizophrenia | never teated but chronic patients. No FEP |
| Park, Jong Suk, Kim, Chan-Hyung, Ahn, Chul Woo, Kim, Kyung-Rae, | A determinant of insulin resistance in patients with schizophrenia | No MetS |
| Pascual-Marqui, R. D., Lehmann, D., Koenig, T., Kochi, K., Merlo, M. C., Hell, D., Koukkou, M. | Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia | No MetS |
| Perez-Iglesias, Rocio, Martinez-Garcia, Obdulia, Pardo-Garcia, Gema, Antonio Amado, Jose, Teresa Garcia-Unzueta, M., Tabares-Seisdedos, Rafael, Crespo-Facorro, Benedicto | Course of weight gain and metabolic abnormalities in first treated episode of psychosis: the first year is a critical period for development of cardiovascular risk factors | Type of Study |
| Perez-Iglesias, Rocio, Mata, Ignacio, Pelayo-Teran, Jose M., Amado, Jose A., Garcia-Unzueta, Maria T., Berja, Ana, Martinez-Garcia, Obdulia, Vazquez-Barquero, Jose L., Crespo-Facorro, Benedicto | Glucose and lipid disturbances after 1 year of antipsychotic treatment in a drug-naive population | Type of Study |
| Petrikis, Petros, Tigas, Stelios, Tzallas, Alexandros T., Papadopoulos, Ioannis, Skapinakis, Petros, Mavreas, Venetsanos | Parameters of glucose and lipid metabolism at the fasted state in drug-naive first-episode patients with psychosis: Evidence for insulin resistance | No MetS |
| Pillinger, Toby, Beck, Katherine, Stubbs, Brendon, Howes, Oliver D. | Cholesterol and triiglyceride levels first-episode psychosis systematic review and meta analysis | No MetS |
| Pillinger, Toby, D'Ambrosio, Enrico, McCutcheon, Robert, Howes, Oliver D. | Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models | Type of Study |
| Pillinger, Toby, D’Ambrosio, Enrico, McCutcheon, Rob, Howes, Oliver | F18. IS SCHIZOPHRENIA A MULTI-SYSTEM DISORDER? CONSIDERING NEUROLOGICAL, IMMUNE, CARDIOMETABOLIC, AND ENDOCRINE ALTERATIONS IN FIRST EPISODE PSYCHOSIS | No naïve |
| Reddy, S., Goudie, C., Agius, M. | 2755 – The metabolic syndrome in untreated schizophrenia patients: prevalence and suggested mechanisms. | No published. No response from authors |
| Russell, Alice, Ciufolini, Simone, Gardner-Sood, Poonam, Bonaccorso, Stefania, Gaughran, Fiona, Dazzan, Paola, Pariante, Carmine M., Mondelli, Valeria | Inflammation and metabolic changes in first episode psychosis: Preliminary results from a longitudinal study | No MetS |
| Santo, Paola, Lasalvia, Antonio | Risk factors associated with metabolic abnormalities in first-episode psychotic patients. A systematic review | Type of Study |
| Sengupta, Sarojini, Parrilla-Escobar, Maria A., Klink, Ruby, Fathalli, Ferid, Ng, Ying Kin, Stip, Emmanuel, Baptista, Trino, Malla, Ashok, Joober, Ridha | Are metabolic indices different between drug-naive first-episode psychosis patients and healthy controls? | No MetS |
| Sugawara, Norio, Yasui-Furukori, Norio, Sato, Yasushi, Umeda, Takashi, Kishida, Ikuko, Yamashita, Hakuei, Saito, Manabu, Furukori, Hanako, Nakagami, Taku, Hatakeyama, Mitsunori, Nakaji, Shigeyuki, Kaneko, Sunao | Prevalence of metabolic syndrome among patients with schizophrenia in Japan | No naïve |
| Sun, Langston, Getz, Mara, Daboul, Sulaima, Jay, Melanie, Sherman, Scott, Rogers, Erin, Aujero, Nicole, Rosedale, Mary, Goetz, Raymond R., Weissman, Judith, Malaspina, Dolores, Ahmad, Samoon | Independence of diabetes and obesity in adults with serious mental illness: Findings from a large urban public hospital | No MetS |
| Suriya Moorthi, M | A Comparative study Between First Generation and Second Generation Antipsychotics over the Development of Metabolic Syndrome in persons with First Episode Drug Naïve Schizophrenia. | Type of Study |
| Thakore, JH | Metabolic syndrome and schizophrenia | No naïve |
| Thakore, Jogin H. | Metabolic disturbance in first-episode schizophrenia | No naïve |
| Uzbekov, Marat G., Misionzhnik, Eduard, Gurovich, Isaak, Shmukler, Alexander, Moskvitina, Tatjana | Aspects of metabolic changes in first-episode drug-naive schizophrenic patients | No MetS |
| van Nimwegen, Lonneke J. M., Storosum, Jitschak G., Blumer, Regje M. E., Allick, Gideon, Venema, Henk W., de Haan, Lieuwe, Becker, Hiske, van Amelsvoort, Therese, Ackermans, Mariette T., Fliers, Eric, Serlie, Mireille J. M., Sauerwein, Hans P. | Hepatic insulin resistance in antipsychotic naive schizophrenic patients: stable isotope studies of glucose metabolism | No MetS |
| Vázquez Bourgon, J., Pérez-Iglesias, R., Ortiz-García de la Foz, V., Crespo-Facorro, B. | Long-term metabolic effect of second-generation antipsychotics in first episode of psychosis: Abstract of the 25th European Congress of Psychiatry | No MetS |
| Vázquez-Bourgon, Javier, Pérez-Iglesias, Rocío, Ortiz-García de la Foz, Víctor, Suárez Pinilla, Paula, Díaz Martínez, Álvaro, Crespo-Facorro, Benedicto | Long-term metabolic effects of aripiprazole, ziprasidone and quetiapine: a pragmatic clinical trial in drug-naïve patients with a first-episode of non-affective psychosis | No MetS |
| Vázquez-Bourgon, Javier, Sanchez Blanco, Lucía, Landera Rodriguez, Ruth, Setién Suero, Esther, Romero Jiménez, Rodrigo, Tordesillas-Gutiérrez, Diana, Ayesa Arriola, Rosa, Crespo-Facorro, Benedicto | F101. CANNABIS USE AND HEPATIC STEATOSIS IN PSYCHOSIS: RESULTS FROM A 3-YEAR LONGITUDINAL STUDY | No MetS |
| Vazquez-Bourgon, Javier, Setien-Suero, Esther, Pilar-Cuellar, Fuencisla, Romero-Jimenez, Rodrigo, Ortiz-Garcia de la Foz, Victor, Castro, Elena, Crespo-Facorro, Benedicto | Effect of cannabis on weight and metabolism in first-episode non-affective psychosis: Results from a three-year longitudinal study | No MetS |
| Verma, Swapna K., Subramaniam, Mythily, Liew, Alvin, Poon, Lye Yin | Metabolic Risk Factors in Drug-Naive Patients With First-Episode Psychosis | No MetS |
| Vinay, H.R., Sundar, G.S. Keerthi, Behere, Rishikesh V., Arasappa, Rashmi, Rao, Naren P., Venkatasubramanian, Ganesan, Sivakumar, P.T., Gangadhar, B.N. | Effect of risperidone on metabolic parameters in antipsychotic-naïve schizophrenia: A prospective one year follow-up study | Type of Study |
| Wood, Stephen J., Berger, Gregor E., Lambert, Martin, Conus, Phillipe, Velakoulis, Dennis, Stuart, Geoffrey W., Desmond, Patricia, McGorry, Patrick D., Pantelis, Christos | Prediction of functional outcome 18 months after a first psychotic episode: a proton magnetic resonance spectroscopy study | No MetS |
| Wu, Xiaoli, Huang, Zeping, Han, Hongying, Zhong, Zhiyong, Gan, Zhaoyu, Guo, Xiaofeng, Diao, Feici, Han, Zili, Zhao, Jingping | The comparison of glucose and lipid metabolism parameters in drug-naive, antipsychotic-treated, and antipsychotic discontinuation patients with schizophrenia | No MetS |
| Wu, Xiaoli, Huang, Zeping, Wu, Renrong, Zhong, Zhiyong, Wei, Qinling, Wang, Houliang, Diao, Feici, Wang, Jihui, Zheng, Liangrong, Zhao, Jingping, Zhang, Jinbei | The comparison of glycometabolism parameters and lipid profiles between drug-naive, first-episode schizophrenia patients and healthy controls | No MetS |
| Yezhe Lin, Yanmin Peng, Shen He, Jingjie Xu, Yuan Shi, Yousong Su, Cuizhen Zhu, Xinyi Zhang, Rubai Zhou, Donghong Cui | Serum IL-1ra, a novel biomarker predicting olanzapine-induced dyslipidemia and hyperleptinemia in Schizophrenia | No MetS |
| Zhai, Desheng, Cui, Taizhen, Xu, Yahui, Feng, Yihang, Wang, Xin, Yang, Yuxin, Li, Songji, Zhou, Dushuang, Dong, Gaopan, Zhao, Ying, Yang, Yunlei, Zhang, Ruiling | Cardiometabolic risk in first-episode schizophrenia (FES) patients with the earliest stages of both illness and antipsychotic treatment | No MetS |
| Zhai, Desheng, Lang, Yan, Feng, Yihang, Liu, Yijun, Dong, Gaopan, Wang, Xin, Cao, Ying, Cui, Taizhen, Ni, Chenyang, Ji, Yonggan, Zhang, Xiaodan, Zhao, Ying, Zhang, Ruiling | Early onset of cardiometabolic risk factor profiles in drug naive adolescents and young adults with first-episode schizophrenia | No MetS |
| Zhang, Yamin, Wang, Qiang, Reynolds, Gavin P, Yue, Weihua, Deng, Wei, Yan, Hao, Tan, Liwen, Wang, Chuanyue, Yang, Guigang, Lu, Tianlan, Wang, Lifang, Zhang, Fuquan, Yang, Jianli, Li, Keqing, Lv, Luxian, Tan, Qingrong, Li, Yinfei, Yu, Hua, Zhang, Hongyan, Ma, Xin, Yang, Fude, Li, Lingjiang, Chen, Qi, Wei, Wei, Zhao, Liansheng, Wang, Huiyao, Li, Xiaojing, Guo, Wanjun, Hu, Xun, Tian, Yang, Ren, Hongyan, Ma, Xiaohong, Coid, Jeremy, Zhang, Dai, Li, Tao | Metabolic Effects of 7 Antipsychotics on Patients With Schizophrenia: A Short-Term, Randomized, Open-Label, Multicenter, Pharmacologic Trial. | Type of Study |
| Sjo, C., Bilenberg, N. | Second-generation antipsychotics and the metabolic syndrome in drug-naive adolescents | Age < 18 |
| Bashyal, Bishnu, Goswami, Hiranya Kumar | Metabolic Syndrome and their association with drug naive Schizophrenia and Mood Disorders-A comparative study | Incomplete data |
| Bioque, Miquel, Paz Garcia-Portilla, Ma, Garcia-Rizo, Clemente, Cabrera, Bibiana, Lobo, Antonio, Gonzalez-Pinto, Ana, Diaz-Caneja, Covadonga M., Corripio, Iluminada, Vieta, Eduard, Castro-Fornieles, Josefina, Bobes, Julio, Gutierrez-Fraile, Miguel, Rodriguez-Jimenez, Roberto, Mezquida, Gisela, Llerena, Adrian, Saiz-Ruiz, Jeronimo, Bernardo, Miguel | Evolution of metabolic risk factors over a two-year period in a cohort of first episodes of psychosis | Incomplete data of total naïve sample |
| Chadda, Rakesh K., Ramshankar, Prashanth, Deb, Koushik S., Sood, Mamta | Metabolic syndrome in schizophrenia: Differences between antipsychotic-naive and treated patients | Duplicate sample |
| Keinanen, Jaakko, Mantere, Outi, Kieseppa, Tuula, Mantyla, Teemu, Torniainen, Minna, Lindgren, Maija, Sundvall, Jouko, Suvisaari, Jaana | Early insulin resistance predicts weight gain and waist circumference increase in first-episode psychosis - A one year follow-up study | No MetS data |
| Pallava, Abhishek, Chadda, Rakesh K., Sood, Mamta, Lakshmy, R | Metabolic syndrome in schizophrenia: A comparative study of antipsychotic-free/naive and antipsychotic-treated patients from India | Not strictly naive |
| Nyboe, L., Vestergaard, C. H., Moeller, M. K., Lund, H., Videbech, P. | Metabolic syndrome and aerobic fitness in patients with first-episode schizophrenia, including a 1-year follow-up | Not naïve data |
| Sjo, Christina Power, Stenstrøm, Anne Dorte, Bojesen, Anders Bo, Frølich, Jacob Stampe, Bilenberg, Niels | Development of Metabolic Syndrome in Drug-Naive Adolescents After 12 Months of Second-Generation Antipsychotic Treatment | Age < 18 |
| Smith, Jo, Griffiths, Lisa, Horne, Dominic | Prevalence of Cardiometabolic Risk Factors in First Episode Psychosis Patients | Not peer review published |
| Arango, Celso, Giraldez, Miriam, Merchan-Naranjo, Jessica, Baeza, Inmaculada, Castro-Fornieles, Josefina, Alda, Jose-Angel, Martinez-Cantarero, Carmen, Moreno, Carmen, de Andres, Pilar, Cuerda, Cristina, de la Serna, Elena, Correll, Christoph U., Fraguas, David, Parellada, Mara | Second-Generation Antipsychotic Use in Children and Adolescents: A Six-Month Prospective Cohort Study in Drug-Naive Patients | Age < 18 |
| Anjum, Shazia, Bathla, Manish, Panchal, Saminder, Singh, Gurvinder Pal, Singh, Manpreet | Metabolic syndrome in drug naïve schizophrenic patients | MetS Prevalence is not reported |
| Grover, Sandeep, Nebhinani, Naresh, Padmavati, Ramachandran, Chadda, Rakesh K., Tirupati, Srinivasan, Pallava, Abhishek | Metabolic syndrome in antipsychotic naive patients with schizophrenia: pooled analysis of data from three Indian studies | Duplicate sample |
| Parrilla, M. A., Sengupta, S. M., Kin, N. M., Klink, R., Stip, E., Baptista, T., Malla, A., Joober, R. | Comparison of baseline metabolic variables between drug-naive first-episode psychosis patients and healthy controls | Duplicate sample |

### Table S8. Contact with authors

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Autor** | **Year** | **Patients** | **Strictly Naïve (0 days)** | **MetS** | **Risk of bias** | **Reason of exclusion** | **Author contacted** | **Response** |
| Bashyal | 2015 | FEP | Yes | Yes | Moderate | Incomplete data | Yes | yes |
| Bioque | 2018 | FEP | Yes | Yes | low | Incomplete data of total naïve sample | Yes | yes |
| Keinanen | 2015 | FEP | Yes | Yes | low | No MetS data | Yes | no |
| Nyboe | 2015 | FEP | Yes | Yes | Moderate | Not naïve data | Yes | no |
| Smith | 2016 | FEP | Yes | Yes | Moderate | Not peer review published | Yes | no |
| Anjum | 2018 | Schizophrenia | Yes | Yes | low | MetS Prevalence is not reported | Yes | no |
| Effat | 2012 | FEP | Yes | Yes | Low | Included | Yes | yes |

### Table S9. Operationalization of the diagnostic criteria for MetS

|  |  |  |
| --- | --- | --- |
| **Criteria** | **Utilised by** | **Total number of studies** |
| **ATP-IIIA** | De Hert 2008  Kraemer 2011  Otaño-Matín 2012  García-Rizo 2017 | 4 |
| **Both ATP-IIIA & IDF** | Grover 2011  Enez Darzin 2015  Saddicha 2008  Sahpolat 2020  Owiredu 2012 | 5 |
| **IDF** | Effat 2011  Medved 2009  Srivastava 2011 | 3 |
| **JIS-2009** | Saloojee 2017 | 1 |
| **OMS** | Owiredu 2012 | 1 |

### Table S10. Sensitivity analyses and heterogeneity

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group** | **No. of Studies** | **Sample size** | **Prevalence** | | | **Z score** | **P** | **Test of heterogeneity** | | | | **Heterogeneity\* between subgroups** | | |
|
| SubGroup | **%** | **95% CI** | |  |  | **Q** | **df** | **I2** | **P** | **Q** | **df** | **P** |
| **MetS criteria** | | | | | | | | | | | | 7.570 | 2 | **0.023** |
| ATP-IIIA | 9 | 736 | 11.4 | 6.4 | 19.5 | -14.31 | <0.001 | 61.4 | 8 | 83.0 | 0.000 |
| IDF | 3 | 206 | 21.8 | 12.8 | 34.8 | -7.73 | <0.001 | 6.9 | 2 | 57.0 | 0.070 |
| Others | 1 | 67 | 4.5 | 1.5 | 13.0 | -5.18 | <0.001 | 0.0 | 0 | 0.0 | 1.000 |
| **Geographical location** | | | | | | | | | | | | 3.466 | 2 | 0.177 |
| Europe | 5 | 507 | 9.7 | 4.7 | 18.0 | -5.65 | <0.001 | 21.7 | 4 | 81.6 | 0.000 |
| Asia | 5 | 315 | 19.6 | 12.5 | 29.3 | -5.21 | <0.001 | 12.7 | 4 | 68.6 | 0.113 |
| Africa | 3 | 187 | 8.3 | 1.0 | 44.0 | -2.15 | 0.032 | 22.3 | 2 | 91.0 | 0.000 |
| **Risk of bias** | | | | | | | | | | | | 0.143 | 1 | 0.705 |
| Low | 9 | 730 | 13.9 | 8.7 | 21.0 | -6.798 | <0.001 | 39.5 | 8 | 79.7 | 0.000 |
| Moderate | 4 | 279 | 11.0 | 8.5 | 32.0 | -3.771 | <0.001 | 31.1 | 5 | 83.9 | 0.000 |

\*Only ATP-IIIA and IDF included in the subgroup analysis

### Table S11. Meta-regressions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Group | Q | df | p | R2 |
| MetS criteria | 3.60 | 2 | 0.165 | 0.07 |
| Geographical location | 2.66 | 2 | 0.648 | 0.00 |
| Risk of bias | 0.07 | 1 | 0.794 | 0.00 |
| Ethnicity | 17 | 3 | 0.000 | 0.50 |

#### 

### Table S12. Grey Literature

|  |  |
| --- | --- |
| Reports unrelated to MetS prevalence in FEP | 118 |
| Electronic resources | 31 |
| Magazines | 30 |
| Dissertations/Theses | 14 |
| Books | 13 |
| News | 5 |
| Conference proceedings | 3 |
| Electronic books | 1 |
| Videos | 1 |
| Opinion letter | 1 |
| Unpublished abstracts (Reddy et al., 2013) | 2 |

## Forest plots

We performed sensitivity analyses removing studies based on exposure to antipsychotics (0 days, 0 days & 0-14 days, and up to 47 days) and also one study removed analysis. Of particular note is that there is no significant difference in prevalence among the three groups. The prevalence of MetS in strictly naïve patients is 13.2% (Figure 2). The prevalence of MetS was 12.2% only with 0 days & 0-14 days of exposure, n=1085, k=14 (Figure S3) and 12.2% with up to 47 days of exposure, n=711, k=4 (Figure S4), while the overall prevalence of MetS patients reported as naïve in all the included studies was 12.3% (95% CI: 0.8-17) (n=1796, k=18).

### Figure S1. Funnel plot

****

### Figure S2. Forest plot showing one study removed analysis

****

### Figure S3. Forest plot showing MetS prevalence in patients Strictly naïve (0 days) and minimally treated (0-14 days)



### Figure S4. Forest plot showing MetS prevalence in patients treated up 47 days



### Figure S5. Forest plot showing MetS prevalence in patients minimally treated (0-14 days) and up to 47 days

****

### Figure S6. Forest plot showing subgroups by geographical location



### Figure S7a. Sensitivity analysis by ethnicity removing afrodescendants



### Figure S7b. MetS prevalence in Afrodescendants



### Figure S7c. MetS prevalence in studies from India



### Figure S7d. MetS prevalence in Caucasian



### Figure S7e. MetS prevalence in Middle East



### Figure S8. Forest plot showing subgroups by risk of bias



### Figure S9. Subgroups analysis according to MetS criteria

****

### Figure S10. Overall MetS prevalence in naïve (0 days) patients using IDF

### Figure S11. Studies that reported both ATP-III and IDF criteria: Forest plot showing meta-analysis with ATP-III criteria



### Figure S12. Studies that reported both ATP-III and IDF criteria: Forest plot showing meta-analysis with IDF criteria. (same studies than S11)



### Figure S13. Forest plot showing studies that reported MetS prevalence in men



### Figure S14. Forest plot showing studies that reported MetS prevalence in women

****

## Quality Assessment procedures

### Table S13. Quality Assessment Procedures

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Year | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 |
| Chiliza | 2015 | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Effat | 2012 | No | No | No | Yes | Yes | Yes | Yes | Yes | No | No |
| Grover | 2011 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Kraemer | 2011 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Medved | 2008 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Owiredu | 2012 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Pallava | 2011 | No | No | No | Yes | No | Yes | Yes | Yes | Yes | Yes |
| Srivastava | 2018 | Yes | Yes | No | No | No | Yes | Yes | No | No | No |
| Otaño Martín | 2012 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | No |
| Saddichha | 2008 | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Saloojee | 2017 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | No |
| García-Rizo | 2017 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Fleischhacker | 2012 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| De Hert | 2008 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Srihari | 2013 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Correll | 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Enez Darcin | 2015 | Yes | Yes | No | Yes | Yes | No | No | Yes | No | No |
| Sahpolat | 2020 | Yes | Yes | No | Yes | Yes | No | No | Yes | No | No |

The quality assessment was carried out by two independent reviewers (NGT and AR) using JBI appraisal for cohorts and also the version for prevalence studies. Those papers over which there was disagreement were discussed at a project group meeting.

### JBI (cross sectional)

* Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. Int J Evid Based Healthc. 2015;13(3):147–153.

### JBI (cohorts)

* Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk . In: Aromataris E, Munn Z (Editors). JBI. Manual for Evidence Synthesis. JBI, 2020. Available from <https://synthesismanual.jbi.global>

Note: This scale has been adapted from the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data. The individual components listed below are summed to generate a total Methodological Quality score for each study. Total scores range from 0 to 10. For the total score grouping, studies were judged to be of low risk of bias (≥7 points), moderate risk of bias (4-6 points) and high risk of bias (<4 points).

1) **Was the sample representative of the target population?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable

2) **Were study participants recruited in an appropriate way?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable

3) **Was the sample size adequate?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable

4) **Were the study subjects and the setting described in detail?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable

5) **Was the data analysis conducted with sufficient coverage of the identified sample?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable

6) **Were the objective, standard criteria used for the measurement of the condition?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable

7) **Was the condition measured reliably?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable

8) **Was there an appropriate reporting of statistical analysis?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable

9) **Are all important confounding factors, subgroups, or potential differences identified and accounted for?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable

10) **Were subpopulations identified using objective criteria?**

a) Yes**\***

b) No

c) Unclear/no description

d) Not applicable