**SUPPLEMENTAL MATERIAL**

**Stroke in male to female transgenders: A systematic review and meta-analysis**

Pages 1-2: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist

Pages 3-4: MOOSE Checklist for Meta-analyses of Observational Studies

Page 5: Supplementary table 1. Detailed search strategy used for review

Page 6: Supplementary table 2. Detailed quality assessment of comparative cohort studies using the Newcastle-Ottawa scale

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PRISMA 2009 Checklist

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | Title, Page 4 |
| **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.  | Page 1 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | Page 3 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | Page 4  |
| **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.  | Page 4 |
| 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.  | Page 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.  | Page 4  |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | Page 4-5, Supplement |
| 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).  | Page 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.  | Page 6 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | Page 6-7 |
| 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.  | Page 5-6 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | Page 6-7 |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | Page 6-7 |

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| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | Page 5 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | 6-7 |
| **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.  | Page 7 |
| 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.  | Page 7  |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | Page 8  |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | Tables 1-3, Figure 2 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Figure 2 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | Page 8 |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | - |
| **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).  | Page 9,10 |
| 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).  | Page 12 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | Page 12-13 |
| **FUNDING**  |  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | Page 18 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

**MOOSE Checklist for Meta-analyses of Observational Studies**

|  |  |  |
| --- | --- | --- |
| **Item No** | **Recommendation** | **Reported on Page No** |
| **Reporting of Background** |
| 1 | Problem definition | 3 |
| 2 | Hypothesis statement | 3 |
| 3 | Description of study outcome(s) | 3-4 |
| 4 | Type of exposure or intervention used | 3 |
| 5 | Type of study design used | 3 |
| 6 | Study population | 3 |
| **Reporting of Search Strategy** |
| 7 | Qualifications of searchers (eg, librarians and investigators) | 4 |
| 8 | Search strategy, including time period included in the synthesis and key words | 4 |
| 9 | Effort to include all available studies, including contact with authors | 5 |
| 10 | Databases and registries searched | 4 |
| 11 | Search software used, name and version, including special features used (eg, explosion) | 4, Supplement |
| 12 | Use of hand searching (eg, reference lists of obtained articles) | 5 |
| 13 | List of citations located and those excluded, including justification | 5 |
| 14 | Method for addressing articles published in languages other than English | 5 |
| 15 | Method of handling abstracts and unpublished studies | 5 |
| 16 | Description of any contact with authors | 5 |
| **Reporting of** **Methods** |
| 17 | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 5 |
| 18 | Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 6 |
| 19 | Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability) | 6 |
| 20 | Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | 6 |
| **Reporting Criteria** |
| 21 | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | 5 |
| 22 | Assessment of heterogeneity | 6 |
| 23 | Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 6-7 |
| 24 | Provision of appropriate tables and graphics | 7 |
| **Reporting of Results** |
| 25 | Graphic summarizing individual study estimates and overall estimate | Tables 1-3, Figure 2 |
| 26 | Table giving descriptive information for each study included | Tables 1-3 |
| 27 | Results of sensitivity testing (eg, subgroup analysis) | - |
| 28 | Indication of statistical uncertainty of findings | 10 |
| **Reporting of Discussion** |
| 29 | Quantitative assessment of bias (eg, publication bias) | 8 |
| 30 | Justification for exclusion (eg, exclusion of non-English language citations) | 5 |
| 31 | Assessment of quality of included studies | 8 |
| **Reporting of Conclusions** |
| 32 | Consideration of alternative explanations for observed results | 12 |
| 33 | Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | 13 |
| 34 | Guidelines for future research | 14 |
| 35 | Disclosure of funding source | 18 |

*From*: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

**Supplementary table 1.** Detailed search strategy used for review

|  |  |  |
| --- | --- | --- |
| **Electronic Database** | **Search Terms** | **Items Found** |
| Pubmed | ["Transgender persons" [Mesh] or transwomen or "male to female" or MTF or transsexual or trans or LGBTQ or bisexual or two-spirit or "gender dysphoria" or "gender identity disorder" or "sex reassignment"] AND {"Gonadal steroid hormones" [Mesh] or "Contraceptive agents" [Mesh] or CSHT or "cross-sex hormone therapy" or estrogens or "estrogens" [Mesh] or estradiol or anti-androgen or "oral contraceptives" or "sex steroids" or "hormone replacement therapy" or HRT or hormones} AND [stroke or "stroke" [Mesh] or "transient ischemic attack" or TIA or "ischemic attack, transient" [Mesh] or "cerebrovascular disease" or "cerebrovascular disorders" or "cerebrovascular disorders" [Mesh] or "cerebral infarct" or "cerebral infarction" [Mesh] or "intracranial hemorrhage" or "intracranial hemorrhages" [Mesh]] | 143 |
| Scopus | ["transgender persons" or transwomen or "male to female" or MTF or transsexual or trans or LGBTQ or bisexual or two-spirit or "gender dysphoria" or "gender identity disorder" or "sex reassignment"] AND ["gonadal steroid hormones" or "contraceptive agents" or CSHT or "cross-sex hormone therapy" or estrogens or estradiol or anti-androgen or "oral contraceptives" or "sex steroids" or "hormone replacement therapy" or HRT or hormones] AND [stroke or "transient ischemic attack" or TIA or "cerebrovascular disease" or "cerebrovascular disorders" or "cerebral infarct" or "cerebral infarction" or "intracranial hemorrhage”] | 67 |
| Cochrane | 1 |
| EBSCOHOST | 121 |
| EMBASE | 160 |
| Clinicaltrials.gov | [Stroke and (hormones or sex steroids)] AND [(transgender or trans or transsexual)] | 0 |
| HERDIN | 0 |

**Supplementary table 2.** Detailed quality assessment of comparative cohort studies

using the Newcastle-Ottawa scale

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Quality assessment criteria** | **Acceptable** | **Wierckx****2013** | **Getahun 2018** | **Nokoff****2018** |
| Representativeness of cohort | Representative of average MTF transgender ongoing hormone therapy | ★ | ★ | ★ |
| Selection of Non-exposed Cohort | Drawn from same community as exposed cohort  | ★ | ★ | ★ |
| Ascertainment of exposure | Records secured, survey done or population consulted at gender clinic | ★ | ★ | ★ |
| Demonstration that outcome of interest not present at start of study | Records secured or use of ICD codes  | ★ | ★ | - |
| Comparability: controls for vascular risk factors | Controls for vascular risk factors | ★ | ★ | - |
| Comparability: study controls for additional factors  | Controls for other factors: age, sex, comorbidities  | ★ | ★ | - |
| Assessment of outcome | Independent blind assessment | - | - | - |
|  | Record linkage, use of cranial imaging to detect cerebrovascular event  | ★ | ★ | - |
| Follow up long enough, all subjects accounted for  | Follow up enough for determination of stroke | ★ | ★ | - |
| Adequacy of follow up of cohorts | Complete follow-up or subjects lost to follow-up unlikely to introduce bias  | - | - | - |
| **Final Assessment** |  | **Good quality** | **Good quality** | **Poor quality**  |
| Rating of methodological quality using the Newcastle Ottawa Scale; Good quality: Selection domain: 3-4 stars; Comparability domain: 1-2 stars; Outcome/Exposure domain: 2-3 stars; Fair quality: Selection domain: 2; Comparability domain: 1-2 stars; Outcome/Exposure domain: 2-3 stars; Poor quality: Selection domain: 0-1 star; Comparability domain: 0 stars; Outcome/Exposure domain: 0-1 star. |

**Supplementary table 3.** Murad Tool for evaluating the methodological quality of case reports, case series

and noncomparative cohorts

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Domains** | **deMarinis 1978** | **Asscheman****1989** | **Biller****1995** | **vanKesteren 1997** | **Egan****2002** | **Mullins****2008** | **Asscheman 2011** | **Kwan****2019** | **LaHue****2019** | **Nota** **2019** | **James 2020** |
| **Selection** |  |  |  |  |  |  |  |  |  |  |  |
| Representativeness and clear selection method | Yes | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  |
| **Ascertainment** |  |  |  |  |  |  |  |  |  |  |  |
| Exposure | Yes | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  |
| Outcome | Yes | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  | Yes  |
| **Causality** |  |  |  |  |  |  |  |  |  |  |  |
| Alternative causes  | No | No | No  | No  | No  | No  | No  | No  | No  | No  | No  |
| Challenge/ rechallenge | No  | No  | Yes | No  | No  | No  | No  | No  | No  | No  | No  |
| Dose-response effect | No  | No  | No  | No  | No  | No  | No  | No  | No  | No  | No  |
| Follow-up long enough | No  | Yes | Yes  | Yes  | Yes  | Yes  | NA | Yes  | Yes  | Yes  | NA |
| **Reporting** |  |  |  |  |  |  |  |  |  |  |  |
| -Sufficient details | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| **Total** | **4** | **4** | **6** | **5** | **5** | **5** | **4** | **4** | **5** | **4** | **4** |
| **Quality** | **Moderate** | **Moderate** | **Good** | **Good** | **Good** | **Good** | **Moderate** | **Moderate** | **Good** | **Moderate** | **Moderate** |