**Long-term effects of oral antidiabetic drugs during pregnancy on offspring: a systematic review and meta-analysis of follow-up studies of RCTs**

**Electronic supplementary material**

Content

Appendix 1. Protocol
Appendix 2. Search strategies
Appendix 3. Data extraction form and quality assessment form
Appendix 4. Supplementary Tables and Figures

Appendix 5. Grading of Recommendations Assessment, Development and Evaluation (GRADE)
Appendix 6. PRISMA checklist

**Appendix 1. Protocol**

Long-term effects of oral antidiabetic drugs during pregnancy on offspring: a systematic review and meta-analysis of follow-up studies of RCTs

W. van Weelden, V. Wekker, R.C. Painter

**Citation**

W. van Weelden, V. Wekker, R.C. Painter. Long-term effects of oral antidiabetic drugs during pregnancy on offspring: a systematic review and meta-analysis of follow-up studies of RCTs. PROSPERO 2016

CRD42016032674 Available from:

<http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016032674>

**Review question**

What are the long-term effects on the offspring when their mothers were randomized to oral antidiabetic drugs in comparison to other antidiabetic drugs, insulin, placebo or non-treatment during pregnancy?

**Searches**

A clinical librarian (J.L.) performed a systematic search in OVID MEDLINE (including Epub Ahead of Print, In- Process & Other Non-Indexed Citations), OVID EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to July 17th 2017 to find randomized controlled trials (RCTs) on effects of prenatal exposure to oral hypoglycemic agents on the offspring. To this end we searched for controlled terms (i.e. MESH) and free text terms for (1) hypoglycemic agents including metformin and (2) prenatal exposure (or pregnancy and offspring/child). We used an RCT-filter adapted from the Cochrane to identify RCTs (16).

Animal studies were excluded. No language or date restrictions were applied. We cross-checked the reference lists and the citing articles of the identified relevant papers and adapted the search in case of additional relevant studies. The bibliographic records retrieved were imported and de-duplicated in ENDNOTE.

**Types of study to be included**

Randomized controlled trials (published studies and conference abstracts) that examine the long-term effects of maternal oral antidiabetic drug treatment in comparison to other antidiabetic drugs, insulin, placebo or non- treatment during pregnancy on offspring health in later life.

**Condition or domain being studied**

The prevalence of obesity and the number of patients with insulin resistance and gestational diabetes

mellitus is increasing. As a result more pregnant women are eligible for treatment with oral antidiabetic drugs or insulin. In addition, these drugs are used by women with metabolic syndrome and polycystic ovary syndrome (PCOS). Doctors may be more reluctant to prescribe oral antidiabetic drugs during pregnancy because of potential damage effects on the child, partly because some of these drugs (e.g. Metformin) can cross the placenta. Recently several systematic reviews have studies the short-time health outcomes on offspring of in utero Metformin exposure compared to insulin exposure and no short-term adverse perinatal outcomes were reported. However, the available systematic reviews do discuss any possible long-term effects of oral anti-diabetic drugs on offspring health in later life. Therefore, the aim of this systematic review is to examine the long-term effects of maternal use of oral antidiabetic drug during pregnancy on their offspring compared to other antidiabetic drugs, insulin, placebo or non-treatment during pregnancy.

**Participants/population**

Pregnant women.

**Intervention(s), exposure(s)**

Oral antidiabetic drug usage during pregnancy. The following oral antidiabetic drugs will be included: Metformin, Sulfonylureas (Glybenclamide, Gliclazide, Glimepiride, Glipizide and Tolbutamide) and Acarbose.

**Comparator(s)/control**

Articles should report on number of participants with oral antidiabetic drug treatment during pregnancy and participants with other antidiabetic drugs or insulin treatment, placebo or non-treatment during pregnancy as a comparison group.

**Context**

Inclusion criteria:

- Children of whom their mothers were randomized to oral antidiabetic drugs in comparison to other antidiabetic drugs, insulin, placebo or non-treatment during pregnancy

- Study type: human RCT’s

- Original articles using data not overlapping with other articles that are included in this systematic review

Exclusion criteria:

- No comparison group

- Animal studies

- (Systematic) review, prospective observational studies, retrospective observational studies, cross-sectional studies and case control studies

**Primary outcome(s)**

Development (e.g.: somatic growth (head / waist circumference, weight and length growth), childhood growth milestones, secondary sexual development, social development and integration and neurodevelopment). - Mental health (e.g.: IQ, Level of education and anxiety-, depression- or attention deficit disorder). - Cardiometabolic health (e.g.: BMI, body composition, fat distribution and body fat percentage, lipid profile: LDL, HDL, total cholesterol and triglycerides, glucose tolerance, (fasting) glucose, HbA1c, oral glucose tolerance test (OGTT), homeostasis model assessment (HOMA), insulin-to-glucose ratio, insulin resistance, diabetes mellitus type 2, blood pressure, hypertension, hs-CRP, heart function.

**Secondary outcome(s)**

None

**Data extraction (selection and coding)**

Two authors (W. van Weelden and V. Wekker) will independently perform the complete data selection and assessment of the quality of all potential literature as a result of the search strategy. Articles selection will be done using Covidence®. To guarantee consistency among the reviewers, we will use a predefined list of inclusion and exclusion criteria. First screening will be based on title and abstract. In case of any doubt or inconsistency among both authors we will screen the full text article. During further selection we will use a predefined and tested data selection form based on inclusion and exclusion criteria.

Any discrepancies in data selection will be solved by discussion. The following variables will be extract of all included studies: title article, first author, year of publication, country of publication, study design, language of the article, population descriptions, information about the participants and offspring, intervention, outcome measures, results (including RR, OR of HR and confidence intervals), inclusion and exclusion criteria, any comments, publication status, setting, start date and end date of the study, ethical approval, duration of

follow-up, key conclusions and type and source of funding. In case of missing data, authors of the articles will be contacted by e-mail.

**Risk of bias (quality) assessment**

Two authors (V. Wekker and W. van Weelden) will perform the evaluation of the methodological quality of potential studies, using The Cochrane Collaboration’s tool for assessing risk of bias. This tool rates

individual studies according to the potential risk of bias associated with six domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. In case of differences in quality assessment results, this will be discussed and solved. If necessary a third author (R.C. Painter) will be consulted. We plan to summarize the risk of bias assessment across studies in an ‘risk of bias’ table. High risk of bias is

no reason for exclusion, but will be used in later quality assessment. We will contact authors to obtain further information if reporting bias is expected. We will also check if the authors published a study protocol and compare planned outcomes with the published outcomes. If the number of studies is sufficient, publication bias will be assessed using funnel plots. If possible, we will perform a sensitivity analysis for subgroups with

a low risk of bias.

**Strategy for data synthesis**

Statistical analyses will be performed using Review Manager (RevMan). An outcome table will enumerate all the results of the included studies. If possible, meta-analysis will be performed for all outcomes separately, using the Mantel-Haenszal method. We decided to use the random effect model in our meta-analysis

because we expect that there will be at least some heterogeneity across the included studies. The results will be displayed in forest plots. Heterogeneity will be appraised by using Chi square and I-squared statistics. Furthermore the effect of the largest and smallest studies will be evaluated by cumulative meta-analysis. We will use risk ratio (RR) and 95% confidence interval (CI) to present to results. We will use the Peto Odds

Ratio Meta-analysis for combining RR and HR ratios to produce a pooled RR and 95% CI.

**Analysis of subgroups or subsets**

We plan to analyze the following subgroup analysis:

- Differentiation based on follow-up duration of studies

– Differentiation between gender of offspring

– Differentiation between type of antidiabetic drug

– Differentiation between indications for antidiabetic drugs use (DM; Diabetes gravidarum; Metabole syndrome; PCOS).

– Differentiation between timing, duration and dose of exposure.

**Contact details for further information**

Drs. Wekker

v.wekker@amc.nl

**Organisational affiliation of the review**

Department of Gynaecology and Obstetrics, Academic Medical Centre, Amsterdam, the Netherlands. [www.amc.nl](http://www.amc.nl)

**Review team members and their organisational affiliations**

Ms W. van Weelden. Medical student, Academic Medical Centre, University of Amsterdam, The Netherlands Mr V. Wekker. Medical Doctor, PhD candidate at the Department of Gynaecology and Obstetrics and the Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, Amsterdam, the Netherlands
Dr R.C. Painter. Gynecologist, PhD, Department of Gynaecology and Obstetrics, Academic Medical Centre, Amsterdam, the Netherlands

**Collaborators**

Dr B. van Rijn. Gynecologist, associate proffer, PhD, Department of Obstetrics, Wilhelmina Children's Hospital Birth Centre, University Medical Centre Utrecht, University of Utrecht, The Netherlands Professor J. de Vries. Endocrinologist, Professor, PhD, Department of Endocrinology, Academic Medical Centre, University of Amsterdam, The Netherlands

Professor T.J. Roseboom. Biologist, Professor of early development and health, PhD, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Department of Obstetrics and Gynaecology, Amsterdam Public Health research institute, Academic Medical Centre, University of Amsterdam, The Netherlands
Dr J. Limpens. Clinical Librarian, PhD, Medical Library, Academic Medical Centre, University of Amsterdam, The Netherlands
Dr A. van Wassenaer-Leemhuis. Pediatrician, Department of Neonatology, Emma Children's Hospital, Academic Medical Centre, University of Amsterdam, The Netherlands
Mr L. de Wit. Medical Doctor, PhD candidate at the Department of Gynaecology and Obstetrics, Wilhelmina Children's Hospital Birth Centre, University Medical Centre Utrecht, Utrecht, the Netherlands
Dr H Ijäs. Gynecologist, PhD, Department of Obsterics and Gynecology, Oulu University Hospital, Oulu, Finland

**Anticipated or actual start date**

13 December 2015

**Anticipated completion date**

30 September 2017

**Funding sources/sponsors**

 V. Wekker is funded by the Dutch Heart Foundation grant: 2013T085.

 **Conflicts of interest**

None known

**Language**

English

**Country**

Netherlands

**Stage of review**

Ongoing

**Subject index terms status**

Subject indexing assigned by CRD

**Subject index terms**

Family; Female; Humans; Hypoglycemic Agents; Pregnancy; Time

**Date of registration in PROSPERO**

25 March 2016

**Date of publication of this version**

14 August 2017

**Revision note for this version**

Review almost completed. Changes: title; adding members to review team; changing anticipated completing date and review stage; changes details about the search because we have performed an update on the 17th of July 2017.

**Versions**

13 September 2017

14 August 2017

25 March 2016

**Stage of review at time of this submission**

Stage Started Completed Preliminary searches Yes Yes Piloting of the study selection process Yes Yes Formal screening of search results against eligibility criteria Yes Yes Data extraction Yes Yes Risk of bias (quality) assessment Yes Yes Data analysis Yes Yes

PROSPERO This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.

**Appendix 2. Search strategies**Database(s): **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)**1946 to Present
Search Strategy: **2018-04-27**

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | hypoglycemic agents/ | 56584 |
| 2 | metformin/ or exp sulfonylurea compounds/ or acarbose/ | 28614 |
| 3 | (metformin\* or sulfonylure\* or acetohexamid\* or carbutamid\* or gl#butamid\* or clorpropamid\* or gl#clazid\* or gl#pizid\* or gl#diazinamid\* or gl#pidizine or gl#diazinamide or gl#burid\* or gl#benclamid\* or tolbutamid\* or glimepirid\* or tolazamid\* or acarbos\*).tw,kf. | 36457 |
| 4 | ((antihyperglyc?em\* or anti-hyperglyc?em\* or antidiabetic\* or anti-diabetic\* or hypoglyc?em\*) adj3 (agent\* or drug\* or medicat\* or oral\*)).tw,kf. | 17646 |
| 5 | (antihyperglyc?emics or anti-hyperglyc?emics or antidiabetics or anti-diabetics or hypoglyc?emics).tw,kf. | 3696 |
| **6** | **or/1-5 [oral hypoglycemics]** | **89509** |
| 7 | prenatal exposure delayed effects/ | 25598 |
| 8 | ((prenat\* or pre-nat\* or antenat\* or ante-nat\* or intra-uterine or intrauterine or "in utero") adj6 (expos\* or metformin\* or sulfonylure\* or acetohexamid\* or carbutamid\* or gl#butamid\* or clorpropamid\* or gl#clazid\* or gl#pizid\* or gl#diazinamid\* or gl#pidizine or gl#diazinamide or gl#burid\* or gl#benclamid\* or tolbutamid\* or glimepirid\* or tolazamid\* or acarbos\* or ((antihyperglyc?em\* or anti-hyperglyc?em\* or antidiabetic\* or anti-diabetic\* or hypoglyc?em\*) adj3 (agent\* or drug\* or medicat\* or oral\*)))).tw,kf. | 21476 |
| 9 | ((f?etus\* or f?etal) adj3 (expos\* or metformin\* or sulfonylure\* or acetohexamid\* or carbutamid\* or gl#butamid\* or clorpropamid\* or gl#clazid\* or gl#pizid\* or gl#diazinamid\* or gl#pidizine or gl#diazinamide or gl#burid\* or gl#benclamid\* or tolbutamid\* or glimepirid\* or tolazamid\* or acarbos\* or ((antihyperglyc?em\* or anti-hyperglyc?em\* or antidiabetic\* or anti-diabetic\* or hypoglyc?em\*) adj3 (agent\* or drug\* or medicat\* or oral\*)))).tw,kf. | 6924 |
| 10 | ((born or child\* or infant\*) adj6 mother\*).tw,kf. | 73449 |
| 11 | (born adj3 women).tw,kf. | 5194 |
| **12** | **or/7-11 [prenatal exposure I]** | **114640** |
| 13 | maternal exposure/ or pregnant women/ or pregnancy/ or exp pregnancy trimesters/ or pregnancy outcome/ or pregnancy complications/ or "Pregnancy in Diabetics"/ or "Diabetes, Gestational"/ | 817846 |
| 14 | exp "embryonic and fetal development"/ or fertilization/ | 259936 |
| 15 | (pregnan\* or gestat\* or gravidit\* or trimester\* or GDM or prenat\* or pre-nat\* or antenat\* or ante-nat\* or intra-uterine or intrauterine or "in utero" or f?etus\* or f?etal or maternal).tw,kf. | 868745 |
| 16 | (preconcept\* or conception or periconcept\* or postconcept\* or prepregnan\* or pregestat\* or perigestat\* or pregravid\* or perigravid\* or fertili#at\*).tw,kf. | 94816 |
| **17** | **or/13-16 [(pre)-pregnancy]** | **1355511** |
| 18 | exp child/ or infant/ | 1987626 |
| 19 | (child\* or infant\* or offspring\* or progeny or progenies or toddler\* or kid or kids or (boys and girls) or schoolage\* or school-age\* or preteen\* or teen\* or puber\* or youth\* or juveniles or minors or menarch\* or adrenarch\*).tw,kf. | 1732080 |
| 20 | (birth adj3 (cohort\* or onwards or follow-up or "through" or (age\*1 adj3 year\*) or until or since)).tw. | 25830 |
| 21 | ((two or three or four or five or six or nine or twelve or fifteen or eightteen or "2" or "3" or "4" or "5" or "6" or "9" or "12" or "15" or "18" or "24") adj3 month\* adj2 (old\* or age or ages or aged)).tw. | 107265 |
| 22 | ((age or ages or aged) adj3 (two or three or four or five or six or nine or twelve or fifteen or eightteen or "2" or "3" or "4" or "5" or "6" or "9" or "12" or "15" or "18" or "24") adj3 month\*).tw. | 71880 |
| 23 | (("one" or two or three or four or five or six or seven or eight or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8") adj3 (yr or yrs or year\*) adj2 (old\* or age or ages or aged)).tw. | 288383 |
| 24 | ((age or ages or aged) adj3 ("one" or two or three or four or five or six or seven or eight or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8") adj3 (yr or yrs or year\*)).tw. | 219665 |
| 25 | (next generation not Next Generation FlexPen).tw,kf. | 41972 |
| 26 | ((long-term or longterm or follow-up) adj6 (neonat\* or neo-nat\* or postnat\* or post-nat\* or perinat\* or newborn\* or birth\* or childbirth)).tw,kf. | 9304 |
| 27 | ((long-term or longterm) adj2 (adverse effect\* or side effect\* or harm or safety or risk\*)).tw,kf. | 21499 |
| 28 | child development/ or language development/ or child language/ or exp learning/ or cognition/ | 446769 |
| 29 | neurobehavioral manifestations/ or memory disorders/ or exp neurodevelopmental disorders/ or exp neurocognitive disorders/ | 389551 |
| 30 | (learning or memory or (language not (language adj2 restriction\*)) or linguistic or Bayley).tw,kf. | 521067 |
| 31 | programming.tw,kf. | 29582 |
| 32 | (develop\* adj3 (long-term or longterm or postnatal\* or post-natal\* or brain or hippocamp\* or mesolimb\* or neurologic\* or growth or problem\* or motor or social)).tw,kf. | 147690 |
| 33 | (neurodevelopment\* or neurobehavio?r\* or behavio?r\* or ADHD or "ADD" or attention deficit\* or hyperactivit\* or neurocognit\* or cogniti\* or motor skill\*).tw,kf. | 1434573 |
| **34** | **or/18-33 [child - offspring -development]** | **4733053** |
| **35** | **17 and 34 [prenatal & child II ]** | **408346** |
| **36** | **12 or 35 [prenatal exposure I II ]** | **448518** |
| **37** | **6 and 36 [prenatal exposure to hypoglycemic agents]** | **934** |
| 38 | randomized controlled trial/ or controlled clinical trial/ or random allocation/ or double-blind method/ or single-blind method/ or (randomi?ed or placebo or randomly or (random adj3 allocat\*) or ((random\* or controlled) adj2 (study or trial)) or ((singl\* or doubl\* or treb\* or tripl\*) adj (blind\*3 or mask\*3))).tw,kf. or trial.ti. [RCT-filter] | 1145022 |
| **39** | **37 and 38 [RCTs on prenatal exposure to oral hypoglycemics]** | **175** |
| 40 | (exp animals/ not humans/) or (animal or tilapia or primate\* or monkey\* or cow or cowes or calf or calves or bovine or sheep or lamb or lambs or ovine or pig or pigs or porcine or cat or cats or feline or dog or dogs or bitch\* or canine or rodent\* or rabbit\* or rat or rats or mouse or mice or murine or chicken\* or dam or dams or pup or pups).ti. [animal filter] | 4815102 |
| **41** | **39 not 40 [human RCTs on prenatal exposure to oral hypoglycemics]** | **162** |
| **42** | **remove duplicates from 41** | **156** |

Database(s): **Embase Classic+Embase**1947 to 2018 April 26
Search Strategy: **2018-04-27**

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | oral antidiabetic agent/ | 17412 |
| 2 | metformin/ or exp sulfonylurea derivative/ or acarbose/ | 100849 |
| 3 | (metformin\* or sulfonylure\* or acetohexamid\* or carbutamid\* or gl#butamid\* or clorpropamid\* or gl#clazid\* or gl#pizid\* or gl#diazinamid\* or gl#pidizine or gl#diazinamide or gl#burid\* or gl#benclamid\* or tolbutamid\* or glimepirid\* or tolazamid\* or acarbos\*).tw,kw. | 57319 |
| 4 | ((antihyperglyc?em\* or anti-hyperglyc?em\* or antidiabetic\* or anti-diabetic\* or hypoglyc?em\*) adj3 (agent\* or drug\* or medicat\* or oral\*)).tw,kw. | 29761 |
| 5 | (antihyperglyc?emics or anti-hyperglyc?emics or antidiabetics or anti-diabetics or hypoglyc?emics).tw,kw. | 3718 |
| **6** | **or/1-5 [oral hypoglycemics]** | **131294** |
| 7 | prenatal drug exposure/ | 9212 |
| 8 | ((prenat\* or pre-nat\* or antenat\* or ante-nat\* or intra-uterine or intrauterine or "in utero") adj6 (expos\* or metformin\* or sulfonylure\* or acetohexamid\* or carbutamid\* or gl#butamid\* or clorpropamid\* or gl#clazid\* or gl#pizid\* or gl#diazinamid\* or gl#pidizine or gl#diazinamide or gl#burid\* or gl#benclamid\* or tolbutamid\* or glimepirid\* or tolazamid\* or acarbos\* or ((antihyperglyc?em\* or anti-hyperglyc?em\* or antidiabetic\* or anti-diabetic\* or hypoglyc?em\*) adj3 (agent\* or drug\* or medicat\* or oral\*)))).tw,kw. | 28382 |
| 9 | ((f?etus\* or f?etal) adj3 (expos\* or metformin\* or sulfonylure\* or acetohexamid\* or carbutamid\* or gl#butamid\* or clorpropamid\* or gl#clazid\* or gl#pizid\* or gl#diazinamid\* or gl#pidizine or gl#diazinamide or gl#burid\* or gl#benclamid\* or tolbutamid\* or glimepirid\* or tolazamid\* or acarbos\* or ((antihyperglyc?em\* or anti-hyperglyc?em\* or antidiabetic\* or anti-diabetic\* or hypoglyc?em\*) adj3 (agent\* or drug\* or medicat\* or oral\*)))).tw,kw. | 9436 |
| 10 | ((born or child\* or infant\*) adj6 mother\*).tw,kw. | 97124 |
| 11 | (born adj3 women).tw,kw. | 6352 |
| **12** | **or/7-11 [prenatal exposure I]** | **137765** |
| 13 | pregnant woman/ or pregnancy/ or first trimester pregnancy/ or second trimester pregnancy/ or third trimester pregnancy/ or gestation period/ or gestational age/ or pregnancy outcome/ or pregnancy complication/ or pregnancy diabetes mellitus/ | 858868 |
| 14 | conception/ or exp prenatal development/ | 235209 |
| 15 | (pregnan\* or gestat\* or gravidit\* or trimester\* or GDM or prenat\* or pre-nat\* or antenat\* or ante-nat\* or intra-uterine or intrauterine or "in utero" or f?etus\* or f?etal or maternal).tw,kw. | 1142617 |
| 16 | (preconcept\* or conception or periconcept\* or postconcept\* or prepregnan\* or pregestat\* or perigestat\* or pregravid\* or perigravid\* or fertili#at\*).tw,kw. | 120884 |
| **17** | **or/13-16 [(pre)-pregnancy]** | **1586044** |
| 18 | child/ or infant/ or preschool child/ or school child/ or toddler/ | 2275880 |
| 19 | progeny/ | 51342 |
| 20 | (child\* or infant\* or offspring\* or progeny or progenies or toddler\* or kid or kids or (boys and girls) or schoolage\* or school-age\* or preteen\* or teen\* or puber\* or youth\* or juveniles or minors or menarch\* or adrenarch\*).tw,kw. | 2262207 |
| 21 | (birth adj3 (cohort\* or onwards or follow-up or "through" or (age\*1 adj3 year\*) or until or since)).tw. | 34036 |
| 22 | ((two or three or four or five or six or nine or twelve or fifteen or eightteen or "2" or "3" or "4" or "5" or "6" or "9" or "12" or "15" or "18" or "24") adj3 month\* adj2 (old\* or age or ages or aged)).tw. | 149758 |
| 23 | ((age or ages or aged) adj3 (two or three or four or five or six or nine or twelve or fifteen or eightteen or "2" or "3" or "4" or "5" or "6" or "9" or "12" or "15" or "18" or "24") adj3 month\*).tw. | 102260 |
| 24 | (("one" or two or three or four or five or six or seven or eight or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8") adj3 (yr or yrs or year\*) adj2 (old\* or age or ages or aged)).tw. | 433523 |
| 25 | ((age or ages or aged) adj3 ("one" or two or three or four or five or six or seven or eight or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8") adj3 (yr or yrs or year\*)).tw. | 341112 |
| 26 | (next generation not Next Generation FlexPen).tw,kw. | 58676 |
| 27 | ((long-term or longterm or follow-up) adj6 (neonat\* or neo-nat\* or postnat\* or post-nat\* or perinat\* or newborn\* or birth\* or childbirth)).tw,kw. | 13162 |
| 28 | ((long-term or longterm) adj2 (adverse effect\* or side effect\* or harm or safety or risk\*)).tw,kw. | 33528 |
| 29 | child development/ or motor development/ or child growth/ or language development/ or cognition/ | 277573 |
| 30 | behavior disorder/ or attention deficit disorder/ or exp developmental language disorder/ or developmental disorder/ | 131821 |
| 31 | (learning or memory or (language not (language adj2 restriction\*)) or linguistic or Bayley).tw,kw. | 675570 |
| 32 | programming.tw,kw. | 39275 |
| 33 | (develop\* adj3 (long-term or longterm or postnatal\* or post-natal\* or brain or hippocamp\* or mesolimb\* or neurologic\* or growth or problem\* or motor or social)).tw,kw. | 189390 |
| 34 | (neurodevelopment\* or neurobehavio?r\* or behavio?r\* or ADHD or "ADD" or attention deficit\* or hyperactivit\* or neurocognit\* or cogniti\* or motor skill\*).tw,kw. | 1758762 |
| **35** | **or/18-34 [child - offspring -development]** | **5479943** |
| **36** | **17 and 35 [prenatal & child II ]** | **490620** |
| **37** | **12 or 36 [prenatal exposure I II ]** | **543877** |
| **38** | **6 and 37 [prenatal exposure to hypoglycemic agents]** | **1581** |
| 39 | exp controlled clinical trial/ or ((randomization/ or double blind procedure/ or single blind procedure/ or (randomi?ed or placebo or randomly or (random adj3 allocat\*) or ((random\* or controlled) adj2 (study or trial)) or ((singl\* or doubl\* or treb\* or tripl\*) adj (blind\*3 or mask\*3))).tw,kw.) not (review/ or editorial/ or (review or editorial).pt.)) or trial.ti. [RCT filter] | 1477735 |
| **40** | **38 and 39 [RCTs on prenatal exposure to oral hypoglycemics]** | **185** |
| 41 | ((animal/ or animal experiment/ or animal model/ or nonhuman/ or rat/ or mouse/) not human/) or (animal or tilapia or primate\* or monkey\* or cow or cowes or calf or calves or bovine or sheep or lamb or lambs or ovine or pig or pigs or porcine or cat or cats or feline or dog or dogs or bitch\* or canine or rodent\* or rabbit\* or rat or rats or mouse or mice or murine or chicken\* or dam or dams or pup or pups).ti. | 6778884 |
| **42** | **40 not 41 [human RCTs on prenatal exposure to oral hypoglycemics]** | **181** |
| **43** | **remove duplicates from 42** | **172** |

**CENTRAL 2018-04-27**

|  |  |  |
| --- | --- | --- |
| **ID** | **Search** | **Hits** |
| #1 | metformin\* or sulfonylure\* or acetohexamid\* or carbutamid\* or gl?butamid\* or clorpropamid\* or gl?clazid\* or gl?pizid\* or gl?diazinamid\* or gl?pidizine or gl?diazinamide or gl?burid\* or gl?benclamid\* or tolbutamid\* or glimepirid\* or tolazamid\* or acarbos\*  | 8212 |
| #2 | (antihyperglyc\*em\* or anti-hyperglyc\*em\* or antidiabetic\* or anti-diabetic\* or hypoglyc\*em\*) near/3 (agent\* or drug\* or medicat\* or oral\*)  | 10543 |
| #3 | antihyperglyc\*emics or anti-hyperglyc\*emics or antidiabetics or anti-diabetics or hypoglyc\*emics  | 175 |
| **#4** | **{or #1-#3}**  | **14687** |
| #5 | (prenat\* or pre-nat\* or antenat\* or ante-nat\* or intra-uterine or intrauterine or "in utero") near/6 (expos\* or metformin\* or sulfonylure\* or acetohexamid\* or carbutamid\* or gl?butamid\* or clorpropamid\* or gl?clazid\* or gl?pizid\* or gl?diazinamid\* or gl?pidizine or gl?diazinamide or gl?burid\* or gl?benclamid\* or tolbutamid\* or glimepirid\* or tolazamid\* or acarbos\* or ((antihyperglyc\*em\* or anti-hyperglyc\*em\* or antidiabetic\* or anti-diabetic\* or hypoglyc\*em\*) near/3 (agent\* or drug\* or medicat\* or oral\*)))  | 885 |
| #6 | (f\*etus\* or f\*etal) near/3 (expos\* or metformin\* or sulfonylure\* or acetohexamid\* or carbutamid\* or gl?butamid\* or clorpropamid\* or gl?clazid\* or gl?pizid\* or gl?diazinamid\* or gl?pidizine or gl?diazinamide or gl?burid\* or gl?benclamid\* or tolbutamid\* or glimepirid\* or tolazamid\* or acarbos\* or ((antihyperglyc\*em\* or anti-hyperglyc\*em\* or antidiabetic\* or anti-diabetic\* or hypoglyc\*em\*) near/3 (agent\* or drug\* or medicat\* or oral\*)))  | 246 |
| #7 | ((born or child\* or infant\*) near/6 mother\*):ti,ab  | 5627 |
| #8 | (born near/3 women):ti,ab  | 297 |
| **#9** | **{or #5-#8}**  | **6576** |
| #10 | [mh ^"maternal exposure"] or [mh ^"pregnant women "] or [mh ^pregnancy] or [mh "pregnancy trimesters"] or [mh ^"pregnancy outcome"] or [mh ^"pregnancy complications"] or [mh ^"Pregnancy in Diabetics"] or [mh ^"Diabetes, Gestational"]  | 6342 |
| #11 | [mh "embryonic and fetal development"] or [mh ^fertilization]  | 401 |
| #12 | (pregnan\* or gestat\* or gravidit\* or trimester\* or GDM or prenat\* or pre-nat\* or antenat\* or ante-nat\* or intra-uterine or intrauterine or "in utero" or f\*etus\* or f\*etal or maternal):ti,ab  | 42362 |
| #13 | (preconcept\* or conception or periconcept\* or postconcept\* or prepregnan\* or pregestat\* or perigestat\* or pregravid\* or perigravid\* or fertili?at\*):ti,ab  | 4825 |
| **#14** | **{or #10-#13}**  | **44894** |
| #15 | [mh child] or [mh ^infant]  | 336 |
| #16 | (child\* or infant\* or offspring\* or progeny or progenies or toddler\* or kid or kids or (boys and girls) or schoolage\* or school-age\* or preteen\* or teen\* or puber\* or youth\* or juveniles or minors or menarch\* or adrenarch\*):ti,ab  | 105410 |
| #17 | (birth near/3 (cohort\* or onwards or follow-up or "through" or (age\*1 near/3 year\*) or until or since)):ti,ab  | 703 |
| #18 | ((two or three or four or five or six or nine or twelve or fifteen or eightteen or "2" or "3" or "4" or "5" or "6" or "9" or "12" or "15" or "18" or "24") near/3 month\* near/2 (old\* or age or ages or aged)):ti,ab  | 6026 |
| #19 | ((age or ages or aged) near/3 (two or three or four or five or six or nine or twelve or fifteen or eightteen or "2" or "3" or "4" or "5" or "6" or "9" or "12" or "15" or "18" or "24") near/3 month\*):ti,ab  | 8513 |
| #20 | (("one" or two or three or four or five or six or seven or eight or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8") near/3 (yr or yrs or year\*) near/2 (old\* or age or ages or aged)):ti,ab  | 19204 |
| #21 | ((age or ages or aged) near/3 ("one" or two or three or four or five or six or seven or eight or "1" or "2" or "3" or "4" or "5" or "6" or "7" or "8") near/3 (yr or yrs or year\*)):ti,ab  | 48036 |
| #22 | ("next generation" not "Next Generation FlexPen"):ti,ab  | 952 |
| #23 | ((long-term or longterm or follow-up) near/6 (neonat\* or neo-nat\* or postnat\* or post-nat\* or perinat\* or newborn\* or birth\* or childbirth)):ti,ab  | 666 |
| #24 | ((long-term or longterm) near/2 (adverse effect\* or side effect\* or harm or safety or risk\*)):ti,ab  | 3830 |
| #25 | (learning or memory or (language not (language near/2 restriction\*)) or linguistic or Bayley):ti,ab  | 34959 |
| #26 | [mh ^"child development"] or [mh ^"language development"] or [mh ^"child language"] or [mh learning] or [mh ^cognition]  | 21788 |
| #27 | [mh ^"neurobehavioral manifestations"] or [mh ^"memory disorders"] [mh "neurodevelopmental disorders"] or [mh "neurocognitive disorders"]  | 8524 |
| #28 | programming:ti,ab  | 1075 |
| #29 | (develop\* near/3 (long-term or longterm or postnatal\* or post-natal\* or brain or hippocamp\* or mesolimb\* or neurologic\* or growth or problem\* or motor or social))  | 7838 |
| #30 | (neurodevelopment\* or neurobehavio\*r\* or behavio\*r\* or ADHD or "ADD" or attention deficit\* or hyperactivit\* or neurocognit\* or cogniti\* or motor skill\*):ti,ab  | 93435 |
| **#31** | **{or #15-#30}**  | **244635** |
| **#32** | **#14 and #31**  | **16986** |
| **#33** | **#9 or #32**  | **19395** |
| **#34** | **#4 and #33**  | **253** |
| **#35** | **#4 and #33 in Trials** | **169** |

**SR Search 2018-06-29**

|  |  |
| --- | --- |
| **Database and hits** | **Methodological Search Filter used in combination with topic search to find systematic reviews** |
| **MEDLINE****88 hits** | meta-analysis/ or (meta analy\* or metaanaly\* or meta?analy\*).tw,kw. or ((systematic\* adj3 (review or literature or evidence or search\*)) or ((summari\* or review) adj3 evidence) or ((search\* adj12 (literature\* or ((electronic or medical or biomedical) adj3 database\*) or exhaustive)) or medline or pubmed or embase or psychinfo or (CENTRAL and cochrane) or "Central Register of Controlled Trials")).tw. or (cochrane or clinical evidence or EBM).jw. [SR-Filter] |
| **EMBASE****131 hits** | meta analysis/ or "systematic review"/ or (meta analy\* or metaanaly\* or meta?analy\*).tw,kw. or ((systematic\* adj3 (review or literature or evidence or search\*)) or ((summari\* or review) adj3 evidence) or ((search\* adj12 (literature\* or ((electronic or medical or biomedical) adj3 database\*) or exhaustiv\*)) or medline or pubmed or embase or psychinfo or (CENTRAL and cochrane) or "Central Register of Controlled Trials")).tw. or (cochrane or clinical evidence or EBM).jw. [SR-Filter] |

**Trial registry search (last assessed 2018-07-19)**

|  |  |
| --- | --- |
| **www.clinicaltrial.gov****53 hits** | ((oral antidiabetic) OR metformin OR Glybenclamide OR Gliclazide OR Glimepiride OR Glipizide OR Tolbutamide OR Acarbose) AND (pregnancy OR gravidity OR gestation) AND (follow-up OR child OR infant OR progeny OR offspring OR longterm OR long-term) [Interventional studies-Filter].  |

**Appendix 3. Data extraction form and quality assessment form**
The following data was extracted: first author; year of publication; country of publication; publication type; language; aim of the study; trial in- and exclusion criteria; method of recruitment; duration of study; ethical approval; population description; indication for antidiabetic treatment; gestational age at start of intervention; duration of intervention; drug prescription; number of randomised participants; withdrawals and exclusions; age; race; outcomes evaluated; results of outcomes; funding sources; conflicts of interest and key conclusions of the study.

# Data extraction form Systematic review: antidiabetic drugs

**Study Title:**

**PubMed ID:**

**Reviewer:** [ ]  W. van Weelden
[ ]  V. Wekker
[ ]  **Data extraction form and quality assessment completed**, date: .. / .. / ….

**Notes:**

**General information**

|  |  |
| --- | --- |
| First author |  |
| Year of publication  |  |
| Country of publication |  |
| Publication type | [ ] Journal [ ] Abstract [ ] other (specify) |
| Language study | [ ] English [ ] other (specify)  |

**Study Eligibility/Characteristics**

|  |  |  |
| --- | --- | --- |
|  | **Review Inclusion Criteria** | **Eligibility criteria met? (circle)**  |
| Type of study | 1. RCT, human study
 | [ ]  Yes[ ]  No [ ]  Unclear [ ]  Not reported Notes:  |
| Participants | 1. Pregnant women
 | [ ]  Yes[ ]  No [ ]  Unclear [ ]  Not reported Notes:  |
| Types of intervention | 1. Maternal oral antidiabetic drugs treatment during pregnancy
 | [ ]  Yes, specify: [ ]  No [ ]  Unclear [ ]  Not reported  |
| Type of comparison  | 1. [ ]  Other oral antidiabetic drugs, specify:
2. [ ]  Insulin
3. [ ]  Placebo
4. [ ]  Non-treatment
 | [ ]  Yes[ ]  No [ ]  Unclear [ ]  Not reported  |
| Types of outcome measures | 1. Development, e.g.:[ ]  Somatic growth (head / waist circumference)[ ]  Weight [ ]  Length growth[ ]  Childhood growth milestones[ ]  Secondary sexual development [ ]  Social development [ ]  Integration and neurodevelopment
2. Mental health, e.g.:[ ]  IQ[ ]  Level of education[ ]  Anxiety disorder[ ]  Depression[ ]  Attention deficit disorder
3. Cardiometabolic health, e.g.:[ ]  BMI[ ]  Body composition[ ]  Fat distribution [ ]  Body fat percentageLipid profile:  [ ]  LDL [ ]  HDL [ ]  Total cholesterol  [ ]  Triglycerides [ ]  Glucose tolerance (fasting)  glucose[ ]  HbA1c[ ]  Oral glucose tolerance test (OGTT)[ ]  Homeostasis model assessment (HOMA)[ ]  Insulin-to-glucose ratio[ ]  Insulin resistance[ ]  Diabetes mellitus type 2[ ]  Blood pressure[ ]  hs-CRP[ ]  Heart function
 | [ ]  Yes[ ]  No [ ]  Unclear [ ]  Not reported Other outcomes? Specify:  |

Include [ ]  Exclude [ ]

Reason for exclusion (for ‘Table of excluded studies’):

 **DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW**

**Methods**

|  |  |  |
| --- | --- | --- |
|  | Study | Location in text *(pg & ¶/fig/table/other)* |
| Aim of the study |  |  |
| Trail inclusion criteria |  |  |
| Trail exclusion criteria |  |  |
| Setting |  |  |
| Method of recruitment of pregnant women (e.g. phone, mail, etc.) |  |  |
| Method of recruitment of offspring (e.g. phone, mail, etc.) |  |  |
| Duration of original RCT |  |  |
| Duration of (follow-up) RCT (age the measurements were conducted on the offspring) |  |  |
| Start date  |  |  |
| End date |  |  |
| Ethical approval? |  Yes [ ]  No [ ]  Unclear [ ]  |  |
| Notes: |  |

## Participants (pregnant women)

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Oral antidiabetic drug group* | *Comparison group* | Location in text *(pg & ¶/fig/table/other)* |
| Population description and setting (e.g. social context and location)  |  |  |
| Trial inclusion criteria |  |  |
| Trial exclusion criteria |  |  |
| Indication for use antidiabetic drug (disease; e.g. PCOS, DM etc.) |  |  |
| Gestational age (weeks) at time of start intervention |  |  |
| Type of intervention |  |  |  |
| Duration of intervention (oral antidiabetic drug or comparison) |  |  |
| Description drugs given (dose, frequency and mechanism of delivery) |  |   |  |
| Total no. randomised |  |  |
| Total no. randomised per group |  |  |  |
| Withdrawals and exclusions n; (%) | Withdrawals:Exclusions: | Withdrawals:Exclusions: |  |
| Age (median, mean, range) |  |  |  |
| Race/ethnicity n; (%) |   |  |  |
| Other relevant characteristics or sociodemographics, specify: |  |  |  |
| Notes: |  |

## Offspring

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Oral antidiabetic drug group* | *Comparison group* | Location in text *(pg & ¶/fig/table/other)* |
| Population description and setting |  |  |
| Indication for use antidiabetic drugs during pregnancy by the mother (disease; e.g. PCOS, DM etc.) |  |  |
| Total no. randomised |  |  |
| Total no. randomised per group |  |  |  |
| Withdrawals and exclusions n; (%) | Withdrawals:Exclusions: | Withdrawals:Exclusions: |  |
| Age (median, mean, range) |  |  |
| Gender n; (%) |  |  |  |
| Race/ethnicity n; (%) |  |  |  |
| Gestational age |  |  |  |
| Other relevant characteristics or sociodemographics, specify: |  |  |  |

## Results Dichotomous outcome

|  | **Description as stated in report/paper** | Location in text *(pg & ¶/fig/table/other)* |
| --- | --- | --- |
| Outcome name |  |  |
| Subgroup |  |  |
| Outcome definition *(with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious)* |  |  |
| Time point*(specify whether from start or end of intervention)* |  |  |
| Results | **Intervention** |  |  |
| No. events |  |  | No. participants |  |
|  |  |  |  |  |
| Baseline data  | **Intervention** | **Comparison** |  |
| No. events | No. participants |  | No. participants |  |
|  |  |  |  |  |
| No. excluded participants and reasons  |  |  |  |
| No. missing participants and reasons |  |  |  |
| No. participants moved from other group and reasons |  |  |  |
| Statistical methods used and appropriateness of these methods*(e.g. adjustment for correlation)**Note whether:**post-intervention OR**change from baseline* *And whether**Adjusted OR**Unadjusted* |  |  |
| Imputation of missing data (e.g. assumptions made for intention to treat analysis) |  |  |

## Outcome 3 Continuous outcome

|  | **Description as stated in report/paper** | Location in text *(pg & ¶/fig/table/other)* |
| --- | --- | --- |
| Outcome name |  |  |
| Subgroup |  |  |
| Outcome definition *(with diagnostic criteria if relevant and note whether the outcome is desirable or undesirable if this is not obvious)* |  |  |
| Time point*(specify whether from start or end of intervention)* |  |  |
| Results | **Intervention** | **Comparison** |  |
| Mean | SD (or other variance)  |  | Mean | SD (or other variance) | No. participants |  |
|  |  |  |  |  |  |  |
| Baseline data | **Intervention** | **Comparison** |  |
| Mean | SD (or other variance)  |  | Mean | SD (or other variance) | No. participants |  |
|  |  |  |  |  |  |  |
| No. excluded participants and reasons  |  |  |  |
| No. missing participants and reasons |  |  |  |
| No. participants moved from other group and reasons |  |  |  |
| Statistical methods used and appropriateness of these methods*(e.g. adjustment for correlation)Note whether:**post-intervention OR**change from baseline* *And whether**Adjusted OR**Unadjuste* |  |  |
| Imputation of missing data (e.g. assumptions made for intention to treat analysis) |  |  |

## Other

|  |  |  |
| --- | --- | --- |
|  |  | Location in text *(pg & ¶/fig/table/other)* |
| Study funding sources (including role of funders) |  |  |
| Possible conflict of interest (for study authors)  |  |  |
| Contact with primary investigators | 1. Clarify methods
2. Clarify results

   |  |
| References to other relevant studies |  |  |
| Key conclusions of study authors |  |  |
| Notes |  |  |

# Quality Assessment Systematic review: antidiabetic drugs

The Cochrane Collaboration’s tool for assessing risk of bias

-See appendix for descriptions of all domains. Bias is assessed as a judgment (high, low, or unclear) for individual elements.-

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Domain** | **High risk of bias** | **Low risk of bias** | **Unclear risk of bias** | **Review authors’ judgment** |
| *Selection bias***Random sequence generation** | Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence. | Random sequence generation method should produce comparable groups | Not described in sufficient detail  | *Location in article (pg/figure/table/other):* *Outcome:*[ ]  **High** [ ]  **Low** [ ]  **Unclear***Support:*  |
| *Selection bias* **Allocation concealment** | Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment | Intervention allocations likely could not have been foreseen in advance of, or during, enrollment | Not described in sufficient detail | *Location in article (pg/figure/table/other):* *Outcome:*[ ]  **High** [ ]  **Low** [ ]  **Unclear***Support:*  |
| *Reporting bias* **Selective reporting** | Reporting bias due to selective outcome reporting. | Selective outcome reporting bias not detected | Insufficient information to permit judgement (It is likely that the majority of studies will fall into this category.) | *Location in article (pg/figure/table/other):* *Outcome:*[ ]  **High** [ ]  **Low** [ ]  **Unclear***Support:*  |
| *Performance bias***Blinding (participants and personnel)** | Performance bias due to knowledge of the allocated interventions by participants and personnel during the study. | Blinding was likely effective.  | Not described in sufficient detail | *Location in article (pg/figure/table/other):* *Outcome:*[ ]  **High** [ ]  **Low** [ ]  **Unclear***Support:*  |
| *Detection bias***Blinding of outcomes assessors** | Detection bias due to knowledge of the allocated interventions by outcome assessors. | Blinding was likely effective | Not described in sufficient detail | *Location in article (pg/figure/table/other):* *Outcome:*[ ]  **High** [ ]  **Low** [ ]  **Unclear***Support:*  |
| *Attrition bias***Incomplete outcome data**  | Attrition bias due to amount, nature or handling of incomplete outcome data | Handling of incomplete outcome data was complete and unlikely to have produced bias | Insufficient reporting of attrition/exclusions to permit judgment of ‘Low risk’ or ‘High risk’ (e.g. number randomised not stated, no reasons for missing data provided) | *Location in article (pg/figure/table/other):* *Outcome:*[ ]  **High** [ ]  **Low** [ ]  **Unclear***Support:*  |
| *Other bias***Other sources of bias** | Bias due to problems not covered elsewhere in the table. | No other bias detected | There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias. | *Location in article (pg/figure/table/other):* *Outcome:*[ ]  **High** [ ]  **Low** [ ]  **Unclear***Support:*  |

**Appendix 4. Supplementary Tables and Figures.**

**Supplementary Tables:**

**Table S1**. Summary of offspring body weight and height.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study**  |  | **Age** | **Outcome**  | **N** | **Metformin group (mean ± SD)** | **N** | **Control group(mean ± SD)** | **P-value** |
| Ijäs 2014 [29] |  | 6 months | Weight in kg  | 45 | 8.281 ± 0.99 | 48 | 7.925 ± 0.99 | 0.071 |
| 12 months | 10.466 ± 1.49 | 9.847 ± 1.26 | 0.038 |
| 18 months | 12.051 ± 1.87 | 11.318 ± 1.45 | 0.040 |
| 6 months | Height in cm  | 45 | 68.1 ± 3.8 | 48 | 67.4 ± 2.7 | 0.286 |
| 12 months | 76.9 ± 3.3 | 75.6 ± 3.1 | 0.062 |
| 18 months | 83.9 ± 3.6 | 82.2 ± 3.1 | 0.023 |
| Carlsen 2012 [28] |  | 12 months | Weight in kg  | 102 | 10.2 ± 1.2 | 94 | 9.7 ± 1.1 | 0.003 |
| Rowan 2011 [25] |  | 2 years | Weight in kg  | 154 | 14.3 ± 2.1 | 164 | 14.0 ± 2.2  | 0.18 |
| Height in cm  | 90.7 ± 4.9 | 91 ± 4.8 | 0.68 |
| Leg length in cm | 37.9 ± 3.1 | 38.1 ± 3.3 | 0.61 |
| Hanem 2018 [34] |  | 4 years | Weight in kg | 81 | 18.3 (17.8 – 18.8) b | 79 | 17.5 (17.0 – 18.0) b | 0.020 |
| Weight (SDS a) | 0.44 (0.22 – 0.66) b | 0.06 (-0.16 – 0.28) b | 0.017 |
| Height in cm | 82 | 104.9 (104.0 – 105.7) b | 104.7 (103.8 – 105.5) b | 0.705 |
| Height (SDS a) | 0.18 (-0.03 – 0.38) b | 0.11 (-0.10 – 0.32) b | 0.651 |
| Overweight/obesity, % | 81 | 26 (32) b | 14 (18) b | 0.038 |
| Tertti 2016 [31]c |  | 5 years | Weight in kg | 25 | 21.2 ± 5.2 | 27 | 20.2 ± 4.9 | 0.61 |
| Height in cm |  | 112.5 ± 10.1 |  | 112.3 ± 10.4 | 0.95 |
| Rø 2012 [32] |  | 8 years | Weight in kg  | 12 | 32.3 ± 5.2 | 13 | 32.8 ± 7.9 | 0.85 |
| Weight (SDS a) | 1.15 ± 0.87 | 1.10 ± 0.92 | 0.89 |
| Height (SDS a) | * 1. ± 0.77
 | 0.65 ± 0.56 | 0.79 |
| Rowan 2018 [33] | Australia | 7 years | Weight in kg | 58 | 26.9 ± 5.2 | 51 | 26.3 ± 4.9 | 0.59 |
| Height in cm | 124.5 ± 5.2 | 124.5 ± 5.0 | 0.99 |
| Leg length in cm | 55.8 ± 7.7 | 57.5 ± 3.1 | 0.13 |
| New Zealand | 9 years | Weight in kg | 45 | 37.0 ± 12.6 | 54 | 32.7 ± 7.7 | 0.049 |
| Height in cm | 137.5 ± 7.4 | 135.4 ± 6.6 | 0.13 |
| Leg length in cm | 63.6 ± 4.2 | 63.9 ± 4.1 | 0.70 |

a Standard deviation score; b means (95% CI) or numbers (%); c only male offspring.

**Table S2**. Summary of offspring body composition

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Age** | **Outcome**  |  | **N** | **Metformin group (mean ± SD)** | **N** | **Control group(mean ± SD)** | **P-value** |
| Ijäs 2014 [29] | 6 months | Head circumference in cm  |  | 45 | 43.8 ± 1.3 | 48 | 43.8 ± 1.5 | 0.865 |
| 12 months | 46.9 ± 1.6 | 46.8 ± 1.7 | 0.979 |
| 18 months | 48.3 ± 1.5 | 48.4 ± 1.7 | 0.856 |
| 6 months | BMI (SDS a) b |  | 43 | 0.15 ± 1.14 | 48 | 0.25 ± 0.94 | 0.65 |
| 12 months | 42 | 0.53 ± 1.16 | 0.51 ± 0.96 | 0.91 |
| 18 months | 42 | 0.61 ± 1.16 | 0.61 ± 0.97 | 0.99 |
| 6 months | Ponderal index in kg/m3  |  | 45 | 26.8 ± 8.0  | 48 | 25.8 ± 2.4 | 0.827 |
| 12 months | 23.0 ± 2.5 | 22.8 ± 2.0 | 0.617 |
| 18 months | 20.4 ± 2.1 | 20.3 ± 1.7 | 0.895 |
| Rowan 2011 [25] | 2 years | Mid-upper arm circumferences in cm |  | 154 | 17.2 ± 1.5 | 164 | 16.7 ± 1.5 | 0.003 c |
| Head circumferences in cm |  | 49.4 ± 1.8 | 49.3 ± 1.7 | 0.52 |
| Chest circumferences in cm |  | 52.1 ± 3.0 | 51.6 ± 3.0 | 0.12 |
| Waist circumferences in cm |  | 50.5 ± 3.5 | 50.1 ± 4 | 0.33 |
| Hip circumferences in cm |  | 52.1 ± 4.0 | 51.6 ± 4.0 | 0.28 |
| Biceps skinfold in mm |  | 6.0 ± 1.9 | 5.6 ± 1.7 | 0.05 c |
| Subscapular skinfolds in mm |  | 6.3 ± 1.9 | 6.0 ± 1.7  | 0.14 c |
| Triceps skinfolds in mm |  | 10.1 ± 2.0 | 9.9 ± 2.4 | 0.50 |
| DEXA scan d | Total fat (g) | 57 | 2.421 ± 1.002 | 57 | 2.274 ± 711 | 0.37 |
| Abdominal fat (g) | 132 ± 73 | 131 ± 60 | 0.92 |
| Thigh fat (g) | 266 ± 96 | 262 ± 86 | 0.83 |
| Arm fat (g) | 196 ± 104 | 181 ± 74 | 0.36 |
| Abdominal-to-thigh fat ratio | 0.48 ± 0.1 | 0.50 ± 0.1 | 0.33 |
| Lean body mass (g) | 10.756 ± 1.283 | 10.736 ± 1.401 | 0.94 |
| Bone mineral content (g) | 389 ± 69 | 390 ± 70 | 0.95 |
| Fat free mass | 11.095 ± 1.293 | 11.126 ± 1.458 | 0.91 |
| Total fat (%) | 16.4 ± 4.9 | 16.9 ± 4 | 0.34 |
| Abdominal fat (% of fat mass) | 5.3 ± 1.3 | 5.6 ± 1.3 | 0.20 |
| Thigh fat (% of fat mass) | 11.3 ± 2.5 | 11.4 ± 2.5 | 0.73 |
| Arm fat (% of fat mass) | 7.82 ± 1.7 | 7.75 ± 1.6 | 0.81 |
| Bioimpedance  | Fat free mass (kg) | 103 | 11.8 ± 1.89 | 118 | 11.4 ± 1.45 | 0.13 |
| Total fat (%) | 16.5 ± 9.07 | 17.1 ± 6.99 | 0.58 |
| Hanem 2018 [34] | 1 year | Head circumference in cm |  | 78 | 47.0 (46.7 – 47.2) e | 76 | 46.5 (46.3 – 46.8) e | 0.026 |
| Head circumference (SDS a) |  | 0.62 (0.40 – 0.85) e | 0.36 (0.13 – 0.58) e | 0.093 |
| 4 years | BMI in kg/m2 |  | 81 | 16.6 (16.3 – 16.9) e | 79 | 15.9 (15.6 – 16.3) e | 0.005 |
| BMI (SDS a) |  | 0.49 (0.25 – 0.72) e | 0.04 (-0.20 – 0.28) e | 0.010 |
| Tertti 2016 [31]f | 5 years | Waist-to-hip circumference ratio  |  | 25 | 0.92 ± 0.05 | 27 | 0.91 ± 0.08 | 0.32 |
| BMI in kg/m2 |  | 16.4 ± 2.1 | 15.5 ± 1.5 | 0.11 |
| BMI (SDS a) |  | 0.25 ± 1.5 | -0.22 ± 1.3 | 0.16 |
| Rø 2012 [32] | 8 years | Waist-to-height circumference ratio (SDS a) |  | 12 | 0.88 ± 0.03 | 13 | 0.89 ± 0.05 | 0.53 |
| BMI (SDS a) |  | 1.09 ± 0.91 | 1.05 ± 1.06 | 0.92 |
| DEXA scan d | Total fat mass (kg) | 9.0 ± 3.2 | 10.6 ± 4.6 | 0.33 |
| Total fat mass (%) | 26.9 ± 5.5 | 30.7 ± 6.7 | 0.14 |
| Total lean mass (kg) | 22.7 ± 2.4 | 21.7 ± 3.5 | 0.40 |
| Truncal fat mass (kg) | 3.1 ± 1.7 | 3.9 ± 2.1 | 0.33 |
| Truncal fat mass (%) | 21.5 ± 7.0 | 26.0 ± 7.8 | 0.14 |
| Bone mineral density (SDS a) | 12 | 0.33 ± 0.96 | 12 | 0.66 ± 1.24 | 0.48 |
| Rowan 2018 [33] | Australia | 7 years | Mid-upper arm circumferences in cm |  | 58 | 19.7 ± 2.4 | 51 | 19.5 ± 2.3 | 0.54 |
| Head circumferences in cm |  | 52.2 ± 1.2 | 51.9 ± 1.5 | 0.24 |
| Chest circumferences in cm |  | 63.5 ± 6.0 | 63.1 ± 5.0 | 0.66 |
| Waist circumferences in cm |  | 60.2 ± 6.7 | 59.5 ± 6.1 | 0.57 |
| Hip circumferences in cm |  | 67.6 ± 6.4 | 67.7 ± 5.7 | 0.90 |
| Waist:height ratio |  | 0.48 ± 0.05 | 0.48 ± 0.04 | 0.54 |
| Biceps skinfold in mm |  | 6.9 ± 3.8 | 6.7 ± 2.8 | 0.72 |
| Subscapular skinfolds in mm |  | 8.0 ± 5.6 | 7.5 ± 5.3 | 0.65 |
| Triceps skinfolds in mm |  | 11.4 ± 4.3 | 11.4 ± 4.0 | 0.997 |
| BMI in kg/m2 |  | 17.2 ± 2.5 | 16.9 ± 2.5 | 0.48 |
| DEXA scan d | Fat-free mass (g) | 32 | 19702 ± 2564 | 29 | 19271 ± 2532 | 0.51 |
| Total fat (g) | 7651 ± 3906 | 7987 ± 3339 | 0.72 |
| Abdominal fat (g) | 423 ± 384 | 430 ± 315 | 0.93 |
| Thigh fat (g) | 1252 ± 618 | 1323 ± 618 | 0.63 |
| Arm fat (g) | 1079 ± 492 | 1103 ± 422 | 0.84 |
| Abdominal fat:thigh fat ratio | 0.30 ± 0.11 | 0.30 ± 0.10 | 0.99 |
| Total fat (%) | 26.8 ± 7.6 | 28.5 ± 6.8 | 0.37 |
| Abdominal fat % of abdominal mass | 21.3 ± 11.8 | 22.4 ± 10.5 | 0.71 |
| Bioimpedance | Fat-free mass (kg) | 56 | 21.5 ± 2.8 | 51 | 20.7 ± 3.0 | 0.34 |
| Total fat % | 18.8 ± 7.9 | 20.8 ± 5.4 | 0.13 |
| MRI- abdomen | Abdominal fat volume (cm3) | 7 | 2720 ± 1786 | 5 | 1843 ± 724 | 0.27 |
| Abdominal fat % of abdominal volume | 27.6 ± 11.2 | 23.5 ± 9.5 | 0.50 |
| Abdominal subcutaneous fat volume (cm3) | 1807 ± 1468 | 1092 ± 618 | 0.28 |
| Abdominal subcutaneous fat % | 17.5 ± 9.6 | 14.1 ± 8.6 | 0.54 |
| Abdominal visceral fat volume (cm3) | 913 ± 610 | 752 ± 221 | 0.54 |
| Abdominal visceral fat % | 10.1 ± 4.8 | 9.3 ± 1.2 | 0.69 |
| VAT:SAT | 0.74 ± 0.41 | 0.88 ± 0.48 | 0.60 |
| New Zealand | 9 years | Mid-upper arm circumferences in cm |  | 45 | 23.0 ± 4.3 | 54 | 21.2 ± 2.9 | 0.02 |
| Head circumferences in cm |  | 53.6 ± 2.2 | 53.1 ± 1.8 | 0.23 |
| Chest circumferences in cm |  | 70.4 ± 10.2 | 67.7 ± 8.0 | 0.16 |
| Waist circumferences in cm |  | 69.1 ± 12.2 | 64.2 ± 8.4 | 0.04 |
| Hip circumferences in cm |  | 77.6 ± 11.1 | 74.7 ± 7.1 | 0.16 |
| Waist:height ratio |  | 0.51 ± 0.08 | 0.47 ± 0.05 | 0.02 |
| Biceps skinfold in mm |  | 13.9 ± 7.5 | 11.8 ± 5.9 | 0.14 |
| Subscapular skinfolds in mm |  | 13.1 ± 9.6 | 10.5 ± 6.8 | 0.14 |
| Triceps skinfolds in mm |  | 19.5 ± 9.0 | 16.2 ± 6.7 | 0.05 |
| BMI in kg/m2 |  | 19.3 ± 4.6 | 17.7 ± 3.0 | 0.051 |
| DEXA scan d | Fat-free mass (g) | 45 | 24385 ± 5894 | 53 | 22511 ± 3689 | 0.07 |
| Total fat (g) | 12550 ± 7214 | 10281 ± 4450 | 0.07 |
| Abdominal fat (g) | 774 ± 681 | 548 ± 413 | 0.056 |
| Thigh fat (g) | 1983 ± 1122 | 1655 ± 710 | 0.10 |
| Arm fat (g) | 1568 ± 801 | 1285 ± 534 | 0.047 |
| Abdominal fat:thigh fat ratio | 0.34 ± 0.13 | 0.30 ± 0.09 | 0.15 |
| Total fat (%) | 32.0 ± 8.5 | 30.3 ± 6.6 | 0.28 |
| Abdominal fat % of abdominal mass | 29.7 ± 14.4 | 26.6 ± 10.5 | 0.24 |
| Bioimpedance | Fat-free mass (kg) | 45 | 27.7 ± 7.7 | 54 | 25.1 ± 5.2 | 0.065 |
| Total fat % | 23.6 ± 8.1 | 22.3 ± 8.9 | 0.43 |
| MRI- abdomen | Abdominal fat volume (cm3) | 42 | 4172 ± 2964 | 50 | 3120 ± 1898 | 0.051 |
| Abdominal fat % of abdominal volume | 36.0 ± 14.4 | 32.2 ± 10.9 | 0.16 |
| Abdominal subcutaneous fat volume (cm3) | 3231 ± 2412 | 2398 ± 1566 | 0.059 |
| Abdominal subcutaneous fat % | 27.6 ± 12.3 | 24.4 ± 9.7 | 0.18 |
| Abdominal visceral fat volume (cm3) | 941 ± 629 | 722 ± 365 | 0.051 |
| Abdominal visceral fat % | 8.5 ± 3.1 | 7.7 ± 1.9 | 0.19 |
| VAT:SAT | 0.35 ± 0.15 | 0.37 ± 0.18 | 0.57 |
| Liver fat % (MRS) | 2.5 (1.1 – 6.1) e | 1.8 (1.3 – 2.6) e | 0.10 |

a Standard deviation score; b Unpublished data provided by author; c based on our own analysis using Review Manager; d bioimpedance analysis and Dual Energy X-ray Absorptiometry (DEXA); e means (95% CI); f Only male offspring.

**Table S3**. Summary of offspring cardiometabolic health

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Age** | **Outcome**  |  | **N** | **Metformin group (mean ± SD)** | **N** | **Control group(mean ± SD)** | **P-value** |
| Rø 2012 [32] | 8 years | Fasting glucose levels in mmol/L |  | 11 | 4.93 ± 0.31 | 12 | 4.60 ± 0.35 | 0.02 a |
| LDL cholesterol in mmol/L |  | 2.42 ± 0.69 | 2.99 ± 0.46 | 0.02 a  |
| Blood pressure in mmHg | Systolic | 12 | 106 ± 6 | 13 | 101 ± 7 | 0.05 a |
| Diastolic | 66 ± 7 | 65 ± 3 | 0.65 a |
| Glucagon levels in pmol/L |  | 26.4 ± 20.7  | 12 | 55.7 ± 111.1 | 0.67 |
| Insulin in pmol/L |  | 22.2 ± 14.2 | 23.0 ± 25.2 | 0.29 |
| C-peptide in pmol/L |  | 267 ± 65 | 246 ± 146 | 0.24 |
| HDL cholesterol in mmol/L |  | 11 | 1.70 ± 0.27 | 1.55 ± 0.31 | 0.35 |
| Total cholesterol in mmol/L |  | 4.36 ± 0.89 | 4.81 ± 0.53 | 0.26 |
| Triglycerides in mmol/L |  | 0.52 ± 0.18 | 0.59 ± 0.18 | 0.38 |
| Leptin in pmol/L |  | 12 | 126 ± 75 | 214 ± 213 | 0.80 |
| Ghrelin in pmol/L |  | 241 ± 100 | 270 ± 79 | 0.41 |
| PAI-1 b in pmol/L |  | 1282 ± 297 | 1190 ± 455 | 0.20 |
| Resistin in pmol/L |  | 317 ± 86 | 340 ± 136 | 0.89 |
| Visfatin in pmol/L |  | 41.3 ± 17.4 | 51.8 ± 38.7 | 0.76 |
| HOMA-IR c |  | 11 | 0.82 ± 0.58 | 11 | 0.61 ± 0.63 | 0.12 |
| HOMA-ß c |  | 51.8 ± 30.2 | 54.6 ± 51.2 | 0.44 |
| QUICKI d |  | 0.38 ± 0.13 | 0.43 ± 0.16 | 0.16 |
| Rowan 2018 [33] | 7 years | Australia | Fasting plasma glucose in mg/dL | 58 | 85 ± 7  | 51 | 86 ± 7 | 0.14 |
| Fasting plasma glucose in mmol/L | 4.7 ± 0.4 | 4.8 ± 0.4 | 0.14 |
| 9 years | New Zealand | Fasting plasma glucose in mg/dL | 45 | 85 ± 7.0 | 54 | 87 ± 5.7 | 0.10 |
| Fasting plasma glucose in mmol/L | 4.7 ± 0.4 | 4.8 ± 0.3 | 0.10 |
| HbA1c in mmol/mol | 35 ± 2.5 | 35 ± 2.5 | 0.84 |
| Hemoglobin in mg/dL | 134 .6 ± 5.4  | 133.7 ± 7.8 | 0.50 |
| Ferritin in µg/L | 52 (40 – 70) e | 40 (28 – 59) e | 0.009 |
| Fasting insulin in mlU/L | 6.5 (4.6 – 12.4) e | 8.6 (5.9 – 12.2) e | 0.24 |
| Insulin resistance | 1.0 (0.6 – 1.6) e | 1.1 (0.8 – 1.6) e | 0.31 |
| Fasting triglycerides in mmol/L | 0.59 (0.47 – 0.88) e | 0.70 (0.55 – 0.82) e | 0.31 |
| LDL cholesterol in mmol/L | 2.7 ± 0.5 | 2.6 ± 0.6 | 0.81 |
| HDL cholesterol in mmol/L | 1.6 ± 0.4 | 1.6 ± 0.3 | 0.42 |
| AST in IU/L | 36 ± 10 | 33 ± 5 | 0.10 |
| ALT in IU/L | 19 ± 9 | 17 ± 6 | 0.18 |
| Leptin in ng/mL | 1.5 (0.5 – 3.6) e | 1.4 (0.5 – 2.7) e | 0.69 |
| Adiponectin in µg/mL | 13.2 (5.2 – 33.5) e | 14.0 (5.6 – 54.4) e | 0.53 |

a based on our own analysis using Review Manager; b plasminogen activator inhibitor-1; c Homeostatic model assessment; d Quantitative insulin sensitivity check index; e means (95% CI).

**Table S4**. Summary of offspring social-, motor- and neurodevelopment

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Age** | **Outcome**  |  | **N** | **Metformin group** | **N** | **Control group** | **P-value** |
| Ijäs 2014 [29] | 18 months | Motor-, social- and linguistic development at 18 months (mean ± SD) | Standing without support in months | 45 | 11.0 ± 2.0 | 48 | 11.1 ± 2.0 | 0.786 |
| Walking without support in months | 13.3 ± 2.3 | 13.0 ± 1.9 | 0.841 |
| Not walking unaided | 1 (2.2) | 2 (4.3) | 0.999 |
| Absent key pinch grip | 0 (0) | 0 (0) |  |
| Speech delay | 4 (9.1) | 3 (6.4) | 0.708 |
| Any mild developmental delay | 5 (11.1) | 5 (10.4) | 1.000 |
| Strabismus | 3 (6.7) | 1 (2.0) | 0.356 |
| Hearing impairment | 1 (2.2) | 0 (0) | 0.484 |
| Tertti 2015 [30] | 2 years | Bayley-III (mean ± SD) | Cognitive scale | 75 | 63.6 ± 3.6 | 71 | 64.3 ± 3.6 | 0.12 |
| Language scale: Receptive communication | 75 | 27.9 ± 4.3 | 69 | 28.9 ± 3.9 | 0.14 |
| Language scale: Expressive communication | 75 | 28.8 ± 4.9 | 69 | 28.7 ± 4.5 | 0.75 |
| Fine motor scale | 74 | 39.1 ± 2.4 | 71 | 39.8 ± 2.6 | 0.10 |
| Gross motor scale | 73 | 60.6 ± 2.5 | 70 | 60.2 ± 2.6 | 0.13 |
| Hammersmith Infant Neurological Examination (mean ± SD) |  | 73 | 74.2 ± 2.0 | 69 | 74.6 ± 2.0 | 0.14 |
| Wouldes 2016 [27] | 2 years | BSID- IIa outcome |  | MDI (mean ± SD) |  |  |  |  |  | 0.87 |
|  | Australia | 39 | 102.5 ± 16.5 | 44 | 98.4 ± 16.6 |  |
| New Zealand | 64 | 83.6 ± 15.2 | 64 | 86.9 ± 16.0 |  |
| MDI range | Australia | 39 | 64 – 129 | 44 | 50 – 116 |  |
| New Zealand | 64 | 50 – 114 | 64 | 54 – 126 |  |
| PDI (mean ± SD) |  |  |  |  |  | 0.38 |
|  | Australia | 39 | 105.6 ± 11.5 | 44 | 99.9 ± 17.2 |  |
| New Zealand | 64 | 83.4 ± 13.8 | 64 | 85.2 ± 14.8 |  |
| PDI range | Australia | 39 | 86 – 136 | 44 | 56 – 125 |  |
| New Zealand | 64 | 50 – 107 | 64 | 52 – 117 |  |
| BRS total non-optimal |  |  |  |  |  | 0.120 |
|  | Australia | 39 | 1 (3%) | 44 | 0 |  |
| New Zealand | 64 | 7 (12%) | 64 | 2 (3%) |  |
| BRS total questionable | Australia | 39 | 3 (8%) | 44 | 6 (14%) |  |
| New Zealand | 64 | 4 (7%) | 64 | 2 (3%) |  |
| BRS total within normal limits | Australia | 39 | 33 (89%) | 44 | 37 (86%) |  |
| New Zealand | 64 | 50 (82%) | 64 | 58 (94%) |  |

a Bayley Scales of Infant Development V.2.

**Table S5.** Summary of offspring testicular size

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Age** | **Outcome a** |  | **N** | **Metformin group****(mean ± SD)**  | **N** | **Control group(mean ± SD)** | **P-value** |
| Tertti 2016 [31]a | 5 years | Testis volume (in ml)Prader’s orchidometer  | Right:Left: | 24 b25 | 1.84 ± 0.61.81 ± 0.4 | 2727 | 1.80 ± 0.41.78 ± 0.3 | 0.860.74 |
| Testis volume (in ml)by US c  | Right: Left: | 24 b25 | 0.89 ± 0.40.93 ± 0.3 | 2727 | 0.87 ± 0.30.86 ± 0.3 | 0.920.40 |
| Testis volume (in ml)by ruler c  | Right:Left: | 24 b25 | 1.74 ± 0.741.72 ± 0.53 | 2727 | 1.67 ± 0.451.60 ± 0.43 | 0.900.50 |

a Only male offspring; b n=24, one boy had an undetectable right testis due to cryptorchidism; c ultrasonography.

**Table S6**. Quality assessment

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Random sequence generation | Allocation concealment | Blinding of participant and personnel  | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other sources of bias |
| Battin 2015 [26] | Low risk | Low risk | Low risk | Low risk | Low risk | High risk, *support:*Lack of reporting the systolic and diastolic blood pressure in numbers separately for both treatment groups. | Low risk |
| Carlsen 2012 [28] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Hanem2018 [34] | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear *support:*Insufficient information to permit judgement. | Low risk |
| Ijäs 2014 [29] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Rowan 2011 [25] | Low risk | Low risk | Low risk | Unclear, s*upport:*Not reported | Low risk | Low risk | Low risk |
| Rowan 2018 [33] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | High risk, *support:*Auckland mothers at enrollment into the trial were not as well matched between treatment groups as the Adelaide cohort and the population was more heterogeneous. |
| Rø 2012 [32] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | High risk, s*upport:*An uneven distribution of gender between the treatment groups. |
| Tertti 2015 [30] | Unclear, s*upport:*No explanation about how randomisation was performed. | Low risk | Low risk | Low risk | Low risk | Low risk | High risk, s*upport:*The article compared the study groups using the crude scores of Bayley- III instead of age-adjusted standard scores. Also, the Finnish national criteria for GDM changed during the original study. |
| Tertti 2016 [31] | Unclear, s*upport:*No explanation about how randomisation was performed. | Low risk | Low risk | Unclear, *support:*Not reported | Low risk | Low risk | High risk, *support:*The Finnish national criteria for GDM changed during the original study. |
| Wouldes 2016 [27] | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |

**Supplementary Figures:**

**Forest plot of meta-analysis on total fat (%) (DEXA scan)** **Forest plot of meta-analysis on LDL cholesterol (mmol/L)
**Rowan 2018: only offspring from New Zealand cohort.

**Forest plot of meta-analysis on glucose level (mmol/L)
**Rowan 2018 A: Australian cohort; Rowan 2018 B: New Zealand cohort.

**Forest plot of meta-analysis on systolic blood pressure (mmHg)****
Forest plot of meta-analysis on diastolic blood pressure (mmHg)** **

**Forest plot of meta-analysis on mid-upper-arm circumference (cm)**

**
Forest plot of meta-analysis on biceps skinfold (mm)

Forest plot of meta-analysis on subscapular skinfold (mm)
**

**Sensitivity analyses for treatment indication:**

**Forest plot of meta-analysis on mean body weight– including only children of mothers with GDM**



**Forest plot of meta-analysis on mean body weight– including only children of mothers with PCOS**



**Forest plot of meta-analysis on mean height – including only children of mothers with GDM**

****

 **Forest plot of meta-analysis on BMI standard deviation scores – including only children of mothers with GDM**



**Appendix 5. Grading of Recommendations Assessment, Development and Evaluation (GRADE)**

**Author(s)**: Vincent Wekker; Wenneke van Weelden

**Date**: 01-06-2018

**Question**: What is the long term effect of fetal exposure to Metformin compared to Placebo or Insulin in offspring?

**Setting**: Follow-up studies of RCT’s in offspring to women that needed Metformin treatment compared to Placebo or Insulin during gestation.

**Bibliography**:

| **Certainty assessment** | **№ of patients** | **Effect** | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Metformine** | **Placebo/Insuline** | **Relative(95% CI)** | **Absolute(95% CI)** |
| BMI z-scores |
| 3  | randomised trials  | not serious  | not serious  | not serious  | serious a | none  | 79  | 88  | -  | Mean SDS difference **0.3 higher**(0.01 lower to 1.24 higher)  | ⨁⨁⨁◯MODERATE  | Important  |
| Body weight |
| 5  | randomised trials  | not serious  | not serious  | not serious  | serious a | none  | 338  | 346  | -  | SMD **0.26 SD higher**(0.11 higher to 0.41 higher)  | ⨁⨁⨁◯MODERATE  | Important |
| Height |
| 4  | randomised trials  | not serious  | not serious  | not serious  | serious a | none  | 306  | 318  | -  | SMD **0.1 SD higher**(0.14 lower to 0.33 higher)  | ⨁⨁⨁◯MODERATE  | Important |

**CI:** Confidence interval; **SMD:** Standardised mean difference

#### Explanations

a Samples sizes are small and lead to wide confidence intervals

**Appendix 6. PRISMA checklist**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **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.  | 3 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | 5 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 6 |
| **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.  | 6 |
| 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.  | 6 |
| 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.  | 6 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | 7 + Appendix 2 |
| 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).  | 7 |
| 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.  | 7 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | 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.  | 7 |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | 8 |
| 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.  | 8 |

Page 1 of 2

|  |  |  |  |
| --- | --- | --- | --- |
| **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).  | 9 |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | - |
| **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.  | 8 |
| 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.  | 8 |
| 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).  | 9 + 14 |
| 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.  | 10 - 14 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | 10 - 12 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | 9 |
| 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).  | 15 |
| 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).  | 16 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | 17 |
| **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.  | 17 |

*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(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Page 2 of 2