



Effects of metformin on pregnancy outcome, metabolic profile, and sex hormone levels in women with polycystic ovary syndrome and their offspring: a systematic review and meta-analysis

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Background: Researches of the efficacy and safety of metformin on long-term pregnancy outcomes remains conflicted. We performed an updated systematic review and meta-analysis to systematically investigate the effect of metformin treatment on pregnancy outcome, metabolic profile, and sex hormone characteristics in women with polycystic ovary syndrome (PCOS) and their offspring.

Methods: The PubMed, Embase, and Cochrane Library databases were searched from inception to July 10, 2021 with the keywords “metformin”, “PCOS”, and “pregnancy”. Randomized controlled studies reported pregnant related outcomes after metformin intervention among PCOS women were included, while abstracts and reviews were excluded. Two authors independently identified trials, extracted data and assessed risk of bias with Cochrane Reviewer’s Handbook 5.0. Random effects models were used to evaluate the pooled risk ratios (RR) and 95% confidence intervals (95% CI) of pregnancy outcome, metabolic profile, and sex hormone levels.

Results: Eighteen studies were included. The majority of trials were in medium methodological quality. In terms of pregnancy complications among women with PCOS, metformin treatment was associated with a significantly reduced risk of preterm delivery (RR =0.37, 95% CI: 0.23–0.61), pregnancy-induced hypertension (PIH) and preeclampsia (RR =0.45, 95% CI: 0.24–0.83) and macrosomia (RR =0.26, 95% CI: 0.11–0.64). In terms of offspring, metformin significantly associated with larger head circumference (MD =0.29, 95% CI: 0.13–0.45) and higher long-term body mass index (BMI) measures (MD =0.37, 95% CI: 0.17–0.56). In terms of metabolic profile and sex hormone characteristics, a significant decrease in homeostatic model assessment for insulin resistance (HOMA2-IR) scores was found in mothers (MD =-0.32, 95% CI: -0.63 to -0.02), whereas a significant increase of sex hormone binding globulin (SHBG) levels was detected in offspring (MD =0.33, 95% CI: 0.01–0.65).

Discussion: Although the relative low quality of randomized controlled trials (RCTs) and limited results made it difficult to draw a definite conclusion, our study showed that metformin treatment during pregnancy can reduce the risk of pregnancy complications but may have impacts on increasing SHBG levels and long-term BMI in offspring.

Keywords: Metformin; polycystic ovary syndrome (PCOS); pregnant outcomes; offspring

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Introduction

Polycystic ovary syndrome (PCOS), which is often accompanied by insulin resistance (IR), is one of the most common hormonal disorders affecting the ovaries during childbearing years, with an estimated prevalence of 5% to 10% (1). Women with PCOS have difficulties conceiving naturally. Even when pregnancy is successfully achieved through medication, surgery, or *in vitro* fertilization, women with PCOS still experience many complications, such as gestational diabetes mellitus (GDM), miscarriage, pregnancy-induced hypertension (PIH) and preeclampsia, preterm birth, and intrauterine growth retardation or malformation (2,3).

Metformin can regulate the menstrual cycle and promote ovulation by improving IR and reducing hyperinsulinemia and weight loss, thereby increasing the pregnancy rate for patients with PCOS. At present, most guidelines for PCOS treatment recommend that metformin treatment should be implemented during the early period of pregnancy. However, studies have shown that metformin can enter the placenta through transport channels such as plasma membrane monoamine transporters and organic cation transporters, resulting in possible exposure of the fetus to the drug (4,5). Evidence for the efficacy, safety, and benefits of continual metformin use during the pregnancy period still remains conflicted, for example, some studies reported use of metformin is significantly associated with reduction in gestational diabetes among PCOS women (6-8), however, several other studies showed that metformin have no significant effect on gestational diabetes (1,9-11). Some studies found metformin had no effect on pregnancy induced hypertension (9,12), whereas others showed that metformin significantly reduced hypertension (8,13). Besides, whether metformin is associated with metabolic profile and sex hormone levels also remain a subject of debate. Recent published studies showed controversial results of fasting glucose and SHGB hormone levels (9,14-16). The small sample size of the studies might contribute to the various and inconsistent results, thus it is necessary to develop a meta-analysis to assess the efficacy of metformin.

Given the controversial results, we conducted the present systematic review and meta-analysis to compare the risks

and benefits of metformin on pregnancy outcome, metabolic profile, and sex hormone levels of PCOS women and their children, with the expectation to give an evidence-based analysis for clinical practice. We present the following article in accordance with the PRISMA reporting checklist (17) (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-909/rc>).

Methods

Search strategy and selection criteria

This protocol was registered on the PROSPERO platform (No. CRD42021266145).

We searched the China National Knowledge Infrastructure (CNKI), Wanfang Databases, PubMed, Embase, and Cochrane Library databases to identify human studies using the following keywords: (“metformin”) AND (“polycystic ovary syndrome” OR “PCOS”) AND (“outcomes” OR “complications” OR “effects”). The detailed search strategies were showed in Supplementary file (Table S1). Studies published from inception to July 10, 2021 were included.

Two researchers (DYZ and YC) independently assessed the articles for eligibility. Randomized controlled trials investigating the effects of continual treatment of metformin during pregnancy on maternal or offspring outcomes were included if they met the following inclusion criteria: (I) the study population were women who were pregnant and diagnosed with PCOS according to the Rotterdam 2003 criteria or offspring whose mother had been diagnosed with PCOS; (II) metformin was used as an intervention on participants during pregnancy; (III) the study included a placebo control group who were not treated with metformin during pregnancy; (IV) the study assessed outcomes relating to pregnancy complications, including PIH and preeclampsia, GDM, and preterm birth, or offspring outcomes, including birth weight, birth length, head circumference at birth, and body mass index (BMI) at longer follow-up; (V) the study was a published randomized controlled trial (RCT) study. We excluded conference abstracts, case reports, systematic reviews and meta-analysis, and studies without control groups or without available

full text or data were excluded. The detailed information regarding to the specific inclusion and exclusion criteria and treatment intervention of each study were summarized in [Table S2](#) and [Table S3](#). When data appeared in more than 1 publication, only the dataset with the most comprehensive data was included.

Data extraction

Working independently, DYZ and YC used detailed information forms to extract the data and conduct the quality assessment. A third researcher (LZX) was responsible for addressing any unresolved disagreements between DYZ and YC concerning the extracted data or its quality. The data extraction included the following information: first author, year of publication, country where the study was conducted, study design, total sample size, survey time, mean or median age with standard deviation (SD) of pregnant women, mean or median BMI with SD of pregnant women, follow-up time, number of events or total participants in the exposure group and control group, mean or median of offspring weight, length, and BMI with SD.

We used the Cochrane Reviewer's Handbook 5.0 to assess the risk of bias for all of the eligible articles. We evaluated the selection, performance, detection, attribution, reporting and other bias of RCT studies and clarified the risk of bias as "low", "high" and "unclear". We defined the articles with 7 low-risk items as "high quality", the articles with 5 or more than 5 high-risk or unclear risk items as "low quality", and the rest as "medium quality".

Statistical analysis

We calculated the pooled risk ratio (RR) or mean difference, each accompanied by the 95% CI. To estimate risks for pregnancy outcomes, we divided the data into two comparative groups: participants treated with metformin versus participants without metformin treatment. We used an I^2 statistic of $\geq 50\%$ as an indicator of large statistical heterogeneity. If substantial heterogeneity was detected, we used a random-effects model to calculate pooled effect size and 95% CIs.

Subgroup analyses and meta-regression analyses were also performed to explore potential sources of heterogeneity. The subgroup analyses were categorized by the following variables: regional income level based on the World Bank standard (18), and quality of the study. Evidence for differences between the subgroups was quantified by the

RRs or mean difference comparing associations in the subgroups and the corresponding P values for interaction. Studies that clearly provided essential information were included in corresponding subgroup analyses. A meta-regression analysis of the relationship between metformin treatment and pregnancy outcomes was conducted for each outcome with high heterogeneity.

We used funnel plots, Egger's test, and Begger's test to assess the possibility of publication bias and small-study effects in each result. In addition, sensitivity analyses were performed to determine the impact of individual studies on the pooled estimates by excluding each of the studies from the pooled estimate. All analyses used the "Meta-Analysis" statistical package in Stata 12 software (StataCorp LLC, College Station, TX, USA).

Results

We conducted the search on July 10, 2021. A total of 3,149 records were included in the initial search, and 2,837 remained after duplicates were removed. After excluding articles that did not meet the inclusion criteria, 48 studies were full-text screened, and finally 18 articles were determined to be eligible and included in this analysis ([Figure 1](#)) (1,9-12,14-16,19-28).

The characteristics of the included studies and their corresponding quality scores are reported in [Table 1](#). These studies covered 6 countries (13 in Norway, and each in China, Egypt, Bangladesh, Finland and a multi-national study). Among the 18 eligible studies, a total of 2,461 women and 1,291 offspring were included in this meta-analysis. Regarding pregnancy complications, 11 studies were included for maternal prenatal outcomes, 4 studies for maternal metabolic profile, and 2 studies for maternal hormone levels. Regarding complications among offspring, 10 studies were included for prenatal outcomes, 2 studies for metabolic profile, and 2 studies for sex hormone levels. One study involved psychiatric and neurological complications among pregnant women and offspring.

The effect of continual use of metformin on pregnancy outcomes

Using a random-effects model, the meta-analysis showed that continual use of metformin during pregnancy can significantly reduce the occurrence of PIH and preeclampsia (RR =0.45, 95% CI: 0.24–0.83, $I^2=12\%$, $P=0.33$); preterm delivery (RR =0.37, 95% CI: 0.23–0.61, $I^2=0\%$, $P=0.52$);

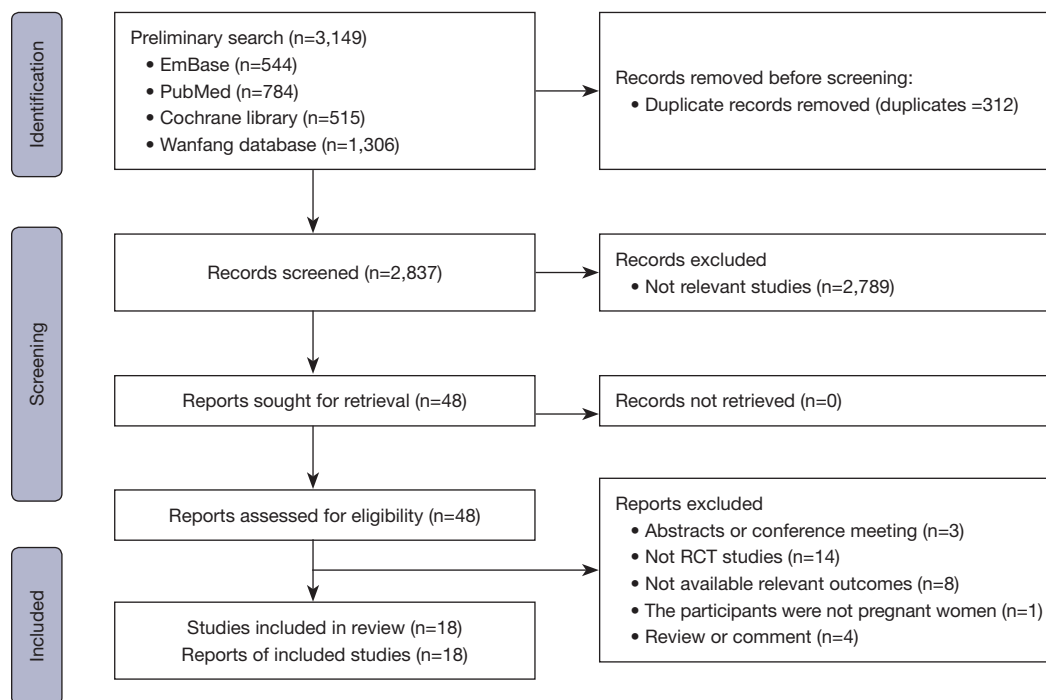


Figure 1 Flow chart of the included studies.

and macrosomia (RR =0.26, 95% CI: 0.11–0.64, $I^2=0\%$, $P=0.83$; *Figure 2*). However, it has no significant efficacy on improving the live birth rate (RR =1.20, 95% CI: 0.98–1.47, $I^2=2\%$, $P=0.36$); or decrease the risk of GDM or miscarriage compared with a placebo, with a pooled RR of 0.86 (95% CI: 0.67–1.12, $I^2=35\%$, $P=0.19$) and (RR =0.53, 95% CI: 0.24–1.21, $I^2=0\%$, $P=0.74$; *Figure 2*), respectively. With respect to other complications, such as persistent nausea and gastrointestinal discomfort, a study conducted by Salvesen (12) reported no difference between the metformin and placebo groups.

With respect to offspring, we found that intrauterine exposure of metformin was significantly associated with increased risk of larger head circumference at birth (MD =0.29, 95% CI: 0.13–0.45, $I^2=56\%$, $P=0.11$) and higher BMI measures in the long term (MD =0.37, 95% CI: 0.17–0.56, $I^2=0\%$, $P=0.82$). Despite these differences, no difference was detected in other offspring outcomes, including birth weight (MD =-0.08, 95% CI: -0.27 to 0.12, $I^2=51\%$, $P=0.04$) or birth length (MD =0.08, 95% CI: -0.09 to 0.24, $I^2=0\%$, $P=0.87$; *Figure 3*). Additionally, no significant difference was found in birth asphyxia (RR =0.62, 95% CI: 0.28–1.36, $I^2=54\%$, $P=0.14$), hypoglycemia (RR =0.59, 95% CI: 0.20–1.75, $I^2=71\%$, $P=0.06$), or malformation (RR

=1.57, 95% CI: 0.26–9.61, $I^2=26\%$, $P=0.25$; *Figure 4*).

Regarding long term cognitive function, a follow-up study of 7.7 years by Greger (10) found no statistically significant difference in IQ scores between metformin and placebo. Moreover, no significant difference was detected in verbal comprehension, working memory, perceptual organization, or processing speed.

The effect of metformin on metabolic profile and sex hormone levels

Our study found that metformin could significantly decrease homeostatic model assessment for insulin resistance (HOMA-IR) scores (MD =-0.32, 95% CI: -0.63 to -0.02, $I^2=0\%$, $P=0.62$) in maternal women, although no effect on fasting glucose (MD =0.10, 95% CI: -0.14 to 0.35, $I^2=63\%$, $P=0.06$) or glycated hemoglobin (HbA1c; MD =-0.20, 95% CI: -0.47 to 0.07, $I^2=71\%$, $P=0.06$) was detected (*Figure 5*). In addition, levels of androstenedione, dehydroepiandrosterone sulfate (DHEAS), sex hormone binding globulin (SHBG), and testosterone were similar in the maternal blood of the metformin group and the placebo group (*Figure 6*).

In the metformin group, offspring of mothers with PCOS

Table 1 Characteristics of the included studies in the meta-analysis

Author [publication year]	Nation	Sample size	Study design	Mean age (SD) in metformin group	Mean age (SD) in control group	Mean BMI (SD) in metformin group	Mean BMI (SD) in control group	Follow-up duration	Main outcomes
Vanky E [2004]	Norway	40	RCT	28.6±4.2	-	30.6±7.3	-	During pregnancy	Severe pregnancy or post partum complications, preterm delivery
Vanky E [2010]	Norway	274	RCT	29.6±4.4	29.2±4.4	29.5±7.0	28.5±7.2	During pregnancy	Preeclampsia, preterm delivery, gestational diabetes mellitus
Underdal MO [2018]	Norway	274	Follow-up study of an RCT	37.5±4.2	-	29.6±6.9	-	7.7 years after pregnancy	Type 2 diabetes mellitus, depression
Salvesen KA [2007]	Norway	40	RCT	28.9 (4.8)	28.3 (3.7)	32.1 (6.1)	29.3 (8.0)	From 6–12 (mean: 8) gestational weeks to birth	Pregnancy complications, cesarean section, persistent nausea and gastrointestinal discomfort, preterm delivery, preeclampsia, postpartum streptococcus sepsis
Levik TS [2019]	Norway, Sweden, and Iceland	468	RCT	29 (24–34)	30 (24–36)	27.5 (18.2–36.5)	26.7 (18.8–34.6)	During pregnancy	Miscarriage, GDM, preterm delivery, PIH
Hjorth-Hansen A [2018]	Norway	258	RCT	29.6 (4.3)	29.3 (4.4)	29.6 (7.3)	28.2 (6.4)	During pregnancy	Birth weight, birth length
Greger HK [2020]	Norway	93	Follow-up of 2 randomized, placebo-controlled trials	29.3 (3.4)	29.0 (4.3)	30.2 (7.0)	27.9 (6.3)	7.7 years	GDM, preeclampsia, preterm delivery
Fougne KJ [2008]	Norway	40	RCT	28.9 (26.5–31.4)	28.3 (26.6–30.0)	29.3 (25.8–32.9)	32.1 (29.1–35.2)	During pregnancy	GDM
Carlsen SM [2012]	Norway	199	Follow-up study of RCT	29.7 (4.4)	29.4 (4.3)	29.5 (7.1)	27.6 (6.1)	1 year after birth	1-year postpartum BMI
Carlsen SM [2010]	Norway	40	Follow-up study of RCT	-	-	-	-	During pregnancy	SHBG levels, dihydrotestosterone
Begum MR [2009]	Bangladesh	59	RCT	28.14 (2.92)	26.13 (3.62)	28.21 (2.37)	27.97 (2.49)	During pregnancy	GDM, miscarriage, preterm labor

Table 1 (continued)

Table 1 (continued)

Author [publication year]	Nation	Sample size	Study design	Mean age (SD) in metformin group	Mean age (SD) in control group	Mean BMI (SD) in metformin group	Mean BMI (SD) in control group	Follow-up duration	Main outcomes
Abdalmagee OS [2019]	Egypt	102	RCT	31.1±3.7	31.89±3.6	33.8±4.4	32.9±6.7	During pregnancy	Miscarriage
Wang Aiping [2018]	China	72	RCT	30.8±3.0	30.0±2.7	–	–	During pregnancy	Fasting glucose, insulin, HbA1c (%)
Rø TB [2012]	Norway	25	Follow-up study of an RCT	8.2 (0.6)	8.1 (0.8)	1.09 (0.91)	1.05 (1.06)	8 years after birth	Birth weight, BMI (SDs) at 8 years old
Morin-Papunen L [2012]	Finland	135	RCT	28.4 (3.9)	27.9 (4.1)	27.1 (6.3)	26.9 (6.2)	During pregnancy	Live birth
Hanem LGE [2019]	Norway	139	Follow-up of randomized, placebo-controlled trials	29.5±3.9	30.2±4.2	29.0±6.9	28.4±6.3	4 years after birth	BMI at 4 years, waist circumference, body fat
Hanem LGE [2018]	Norway	141	Follow-up of randomized, placebo-controlled trials	–	–	17.8 (17.0 to 18.5)	16.8 (16.2 to 17.3)	5–10 years after birth	Birth length, birth weight
Hanem LGE [2021]	Norway	62	Follow-up of randomized, placebo-controlled trials	7.40 ± 1.21	7.46 ± 1.18	–	–	5–10 years after birth	Androstenedione, 11-deoxycortisol

BMI, body mass index; GDM, gestational diabetes mellitus, RCT, randomized controlled trial; BMI SDS, standardized BMI.

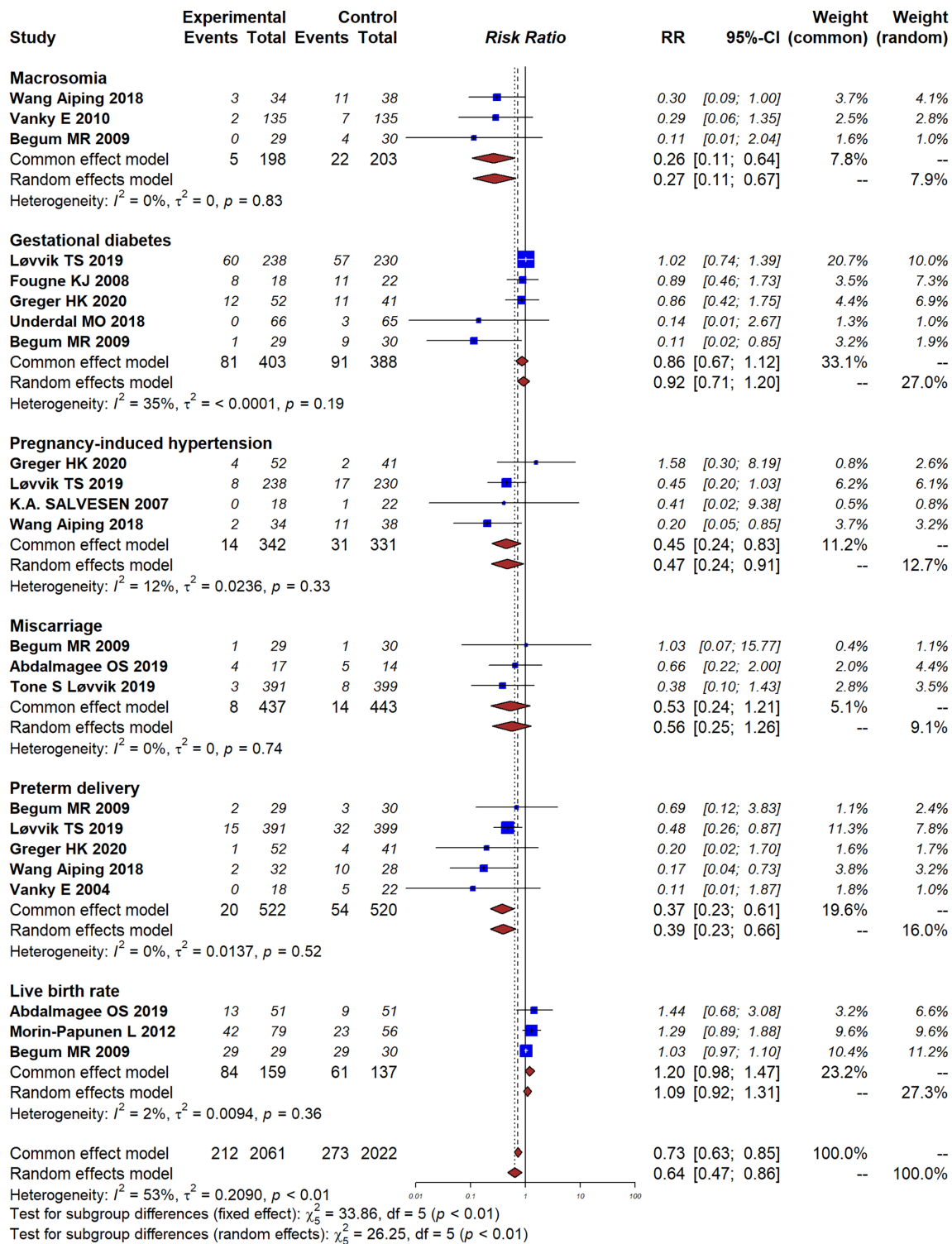


Figure 2 Effect of continual metformin treatment in pregnancy on perinatal outcomes in women with PCOS. PCOS, polycystic ovary syndrome.

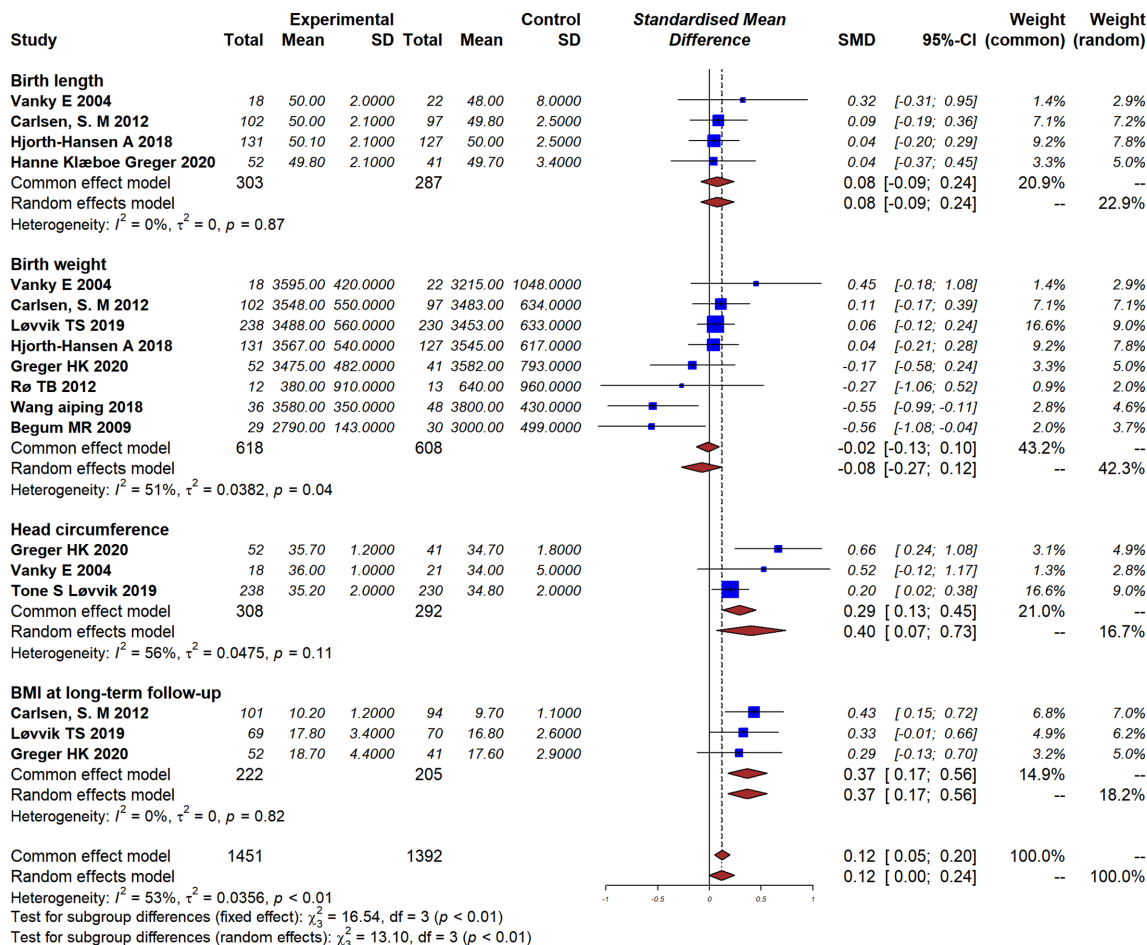


Figure 3 Effect of continual metformin treatment on birth anthropometrics in offspring.

had significantly higher SHGB levels in their blood (MD =0.33, 95% CI: 0.01–0.65, $I^2=69\%$, $P=0.07$). There was a tendency towards higher androstenedione (MD =0.02, 95% CI: -0.30 to 0.34), testosterone (MD =0.13, -0.19 to 0.45), and 11-deoxycortisol (MD =0.27, 95% CI: -0.10 to 0.63), but the difference was not statistically significant (Figure 7).

A study by Rø *et al.* (25) reported higher systolic blood pressure in the metformin group at a follow-up of 8 years (106 vs. 101 mmHg), with a borderline significance of $P=0.05$. Our study found no significant differences in the metabolic health profile of offspring, including fasting glucose, insulin, c-peptide, or HOMA2-IR (Figure 8).

Methodological assessment

The majority of the studies were in medium quality, while 4 of the studies were in low quality. Sixteen (88.9%) studies were in low risk in randomization sequence generation,

while 2 studies were in high risk because they didn't provide appropriate methods of randomization. Fourteen (77.8%) studies reported appropriate methods of allocation concealment, while the rest 4 studies didn't report it. Thirteen (72.2%) studies provided the method of blinding for the participants, while no studies reported blinding of outcome assessment. Eight (45.4%) studies reported incomplete outcome data and in a high risk, the remaining studies were in low risk. There were only 3 (16.7%) studies in low risk of selective reporting of outcomes and none of the studies reported information of other bias. The assessment of risk of bias for the included trials was showed in Figures S1,S2.

Subgroup analysis and meta-regression

To further investigate influential factors with results, we conducted subgroup analyses according to study location

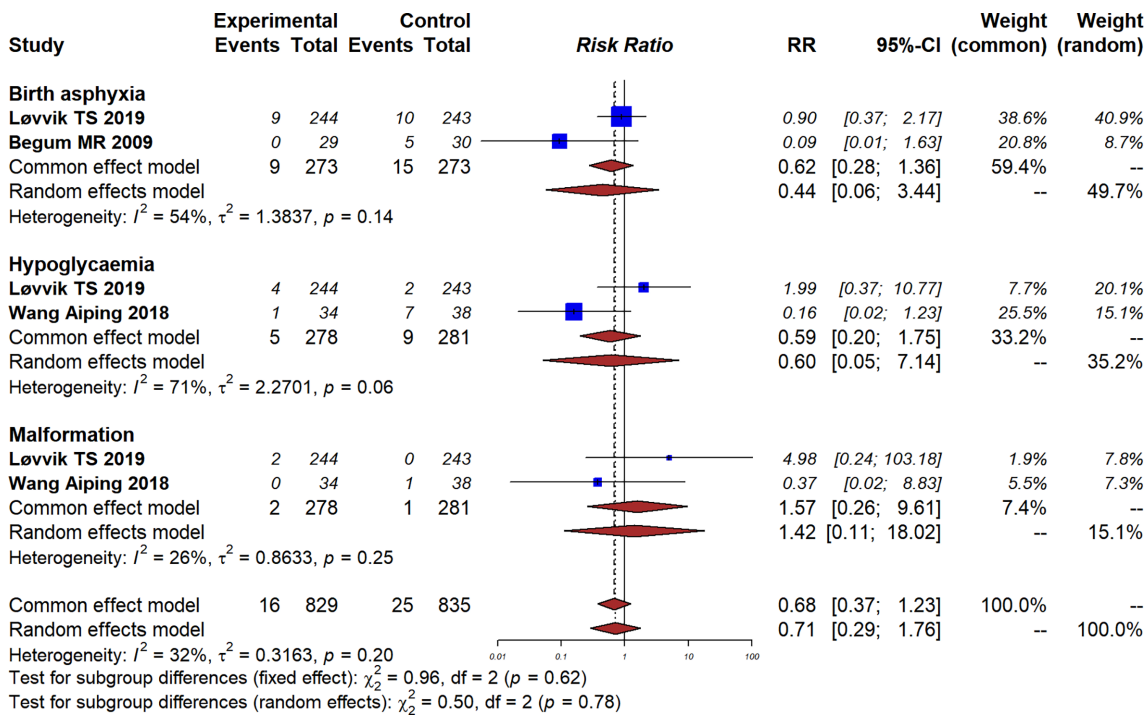


Figure 4 Effect of continual metformin treatment on birth outcomes in offspring.

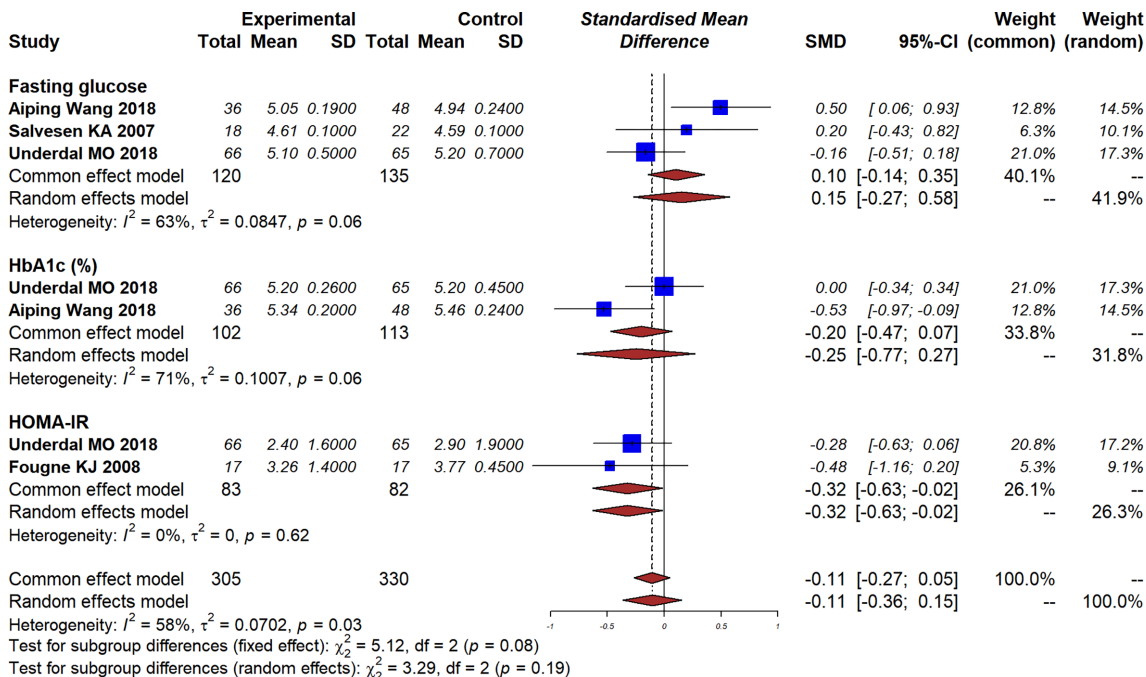


Figure 5 Effect of continual metformin treatment in pregnancy on metabolic health in women with PCOS. PCOS, polycystic ovary syndrome.

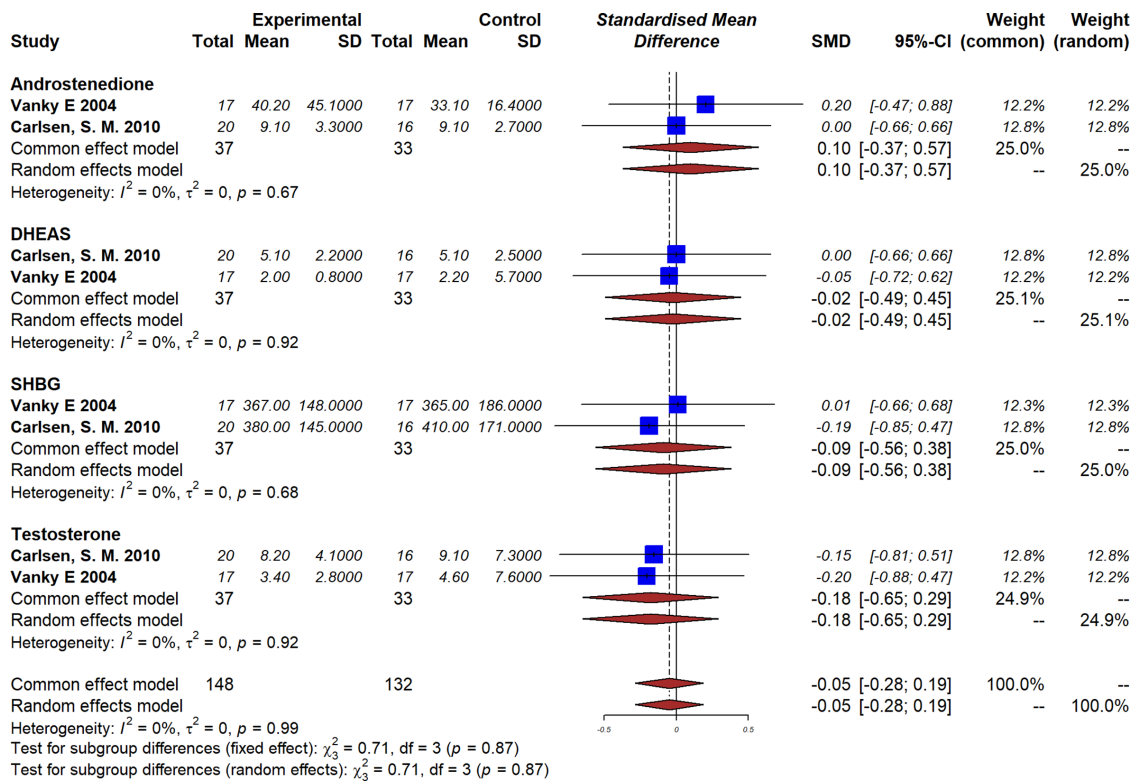


Figure 6 Effect of continual metformin treatment in pregnancy on sex hormone levels in women with PCOS. PCOS, polycystic ovary syndrome.

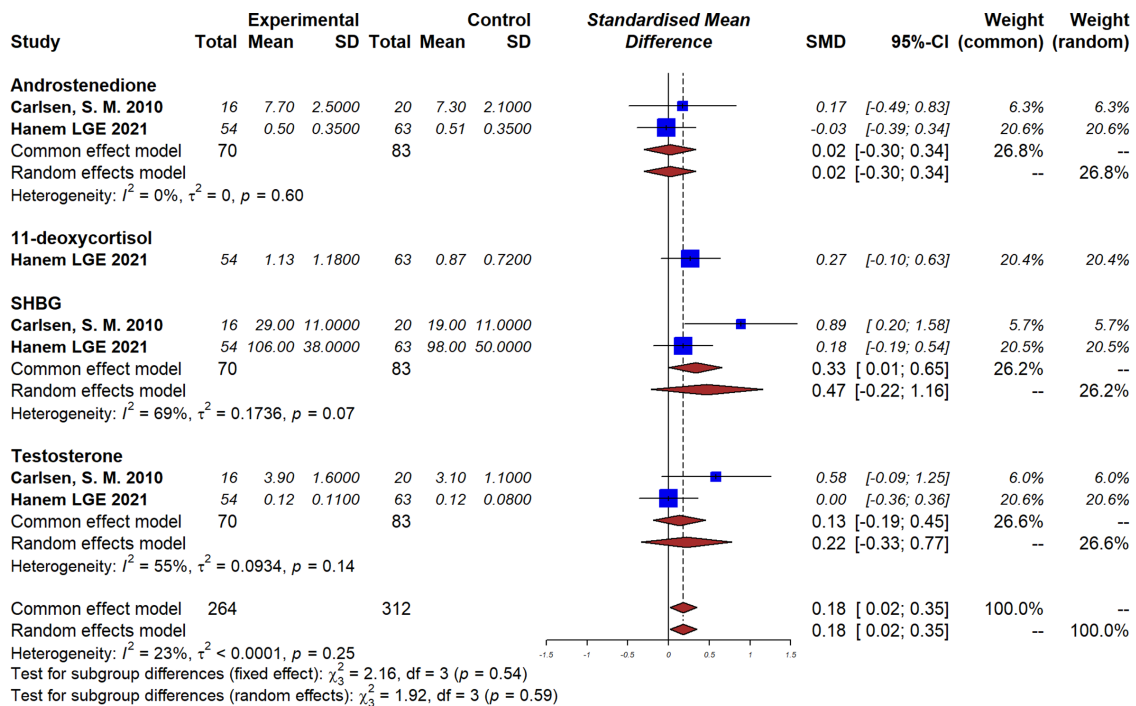


Figure 7 Effect of continual metformin treatment on sex hormone levels in offspring.

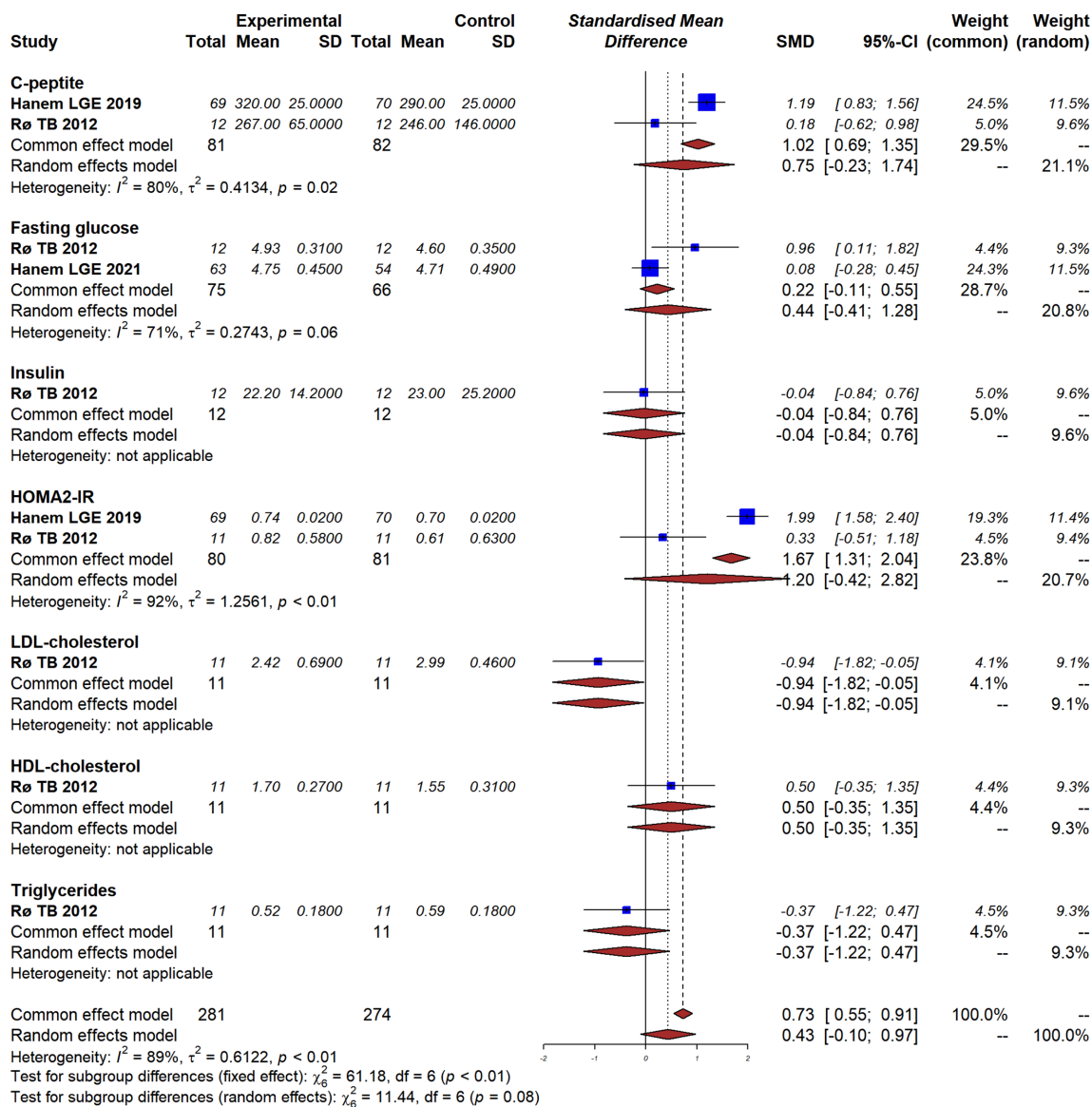


Figure 8 Effect of continual metformin treatment on metabolic health in offspring.

and quality level. The results showed that the effect of metformin on GDM could be influenced by the study region. Metformin significantly reduced the risk of GDM in Middle or low income country compared with high income country, with RRs of 0.11 (95% CI: 0.02–0.85) and 0.94 (95% CI: 0.72–1.23, $I^2=0\%$, $P=0.59$), respectively ($P=0.04$ for subgroup differences). Birth weight was found to be influenced by both study region and study quality. We found that metformin had a significant efficacy on studies conducted in Middle or low income country and studies with low levels of quality ($P<0.01$ for both subgroup

differences). In addition, no difference was found in the regional or quality subgroup analysis concerning preterm delivery (Figures S3–S8). The meta-regression analysis found no effect of either age or BMI on the effect of metformin ($P=0.2949$ and $P=0.2431$).

Publication bias and quality control

The leave-one-out sensitivity analysis showed consistency on all outcomes. Either Egger's test or Begger's test showed no publication bias for either pregnancy or offspring

outcomes ($P>0.05$) (Figures S9-S19; Table S4).

Discussion

To our knowledge, this study is the largest and most wide-ranging systematic review and meta-analysis comprehensively summarizing current evidence on the possible effect of metformin treatment on maternal and offspring pregnancy outcome, metabolic health, and sex hormone levels in women with PCOS and their offspring. Our results showed that metformin treatment during pregnancy could reduce the risk of pregnancy complications, including PIH, macrosomia and preterm delivery. In addition, we found that metformin ameliorated IR in women with PCOS and increased SHBG levels in offspring. Regarding negative impacts, our results showed that metformin might increase the risk of larger head circumference at birth and lead to higher BMI in the long-term.

Individuals with PCOS have an increased risk of developing maternal complications involving GDM, PIH, and miscarriage (29,30). Previous studies have reported that PCOS is associated with severe pregnancy complications, including a threefold increased risk of GDM, a threefold to fourfold increased risk of PIH and preeclampsia, and a twofold increased risk of preterm delivery (28,29,31). In addition, approximately 30% to 50% of patients experience miscarriage (32). Our study demonstrated that metformin treatment decreased the risk of PIH and preeclampsia, and preterm delivery by 55% and 63%, respectively, when compared with the placebo group. Controversy remains regarding the effect of metformin on pregnancy outcome. In 2012, Morin-Papunen *et al.* (24) reported an insignificant difference between the metformin and the placebo group. In 2010, a randomized, placebo-controlled, double-blind, multicenter trial conducted by Vanky *et al.* investigating 257 women with PCOS found that metformin treatment from first trimester to delivery did not reduce pregnancy complications (including preeclampsia and preterm delivery) in patients with PCOS (28). However, our findings are consistent with a number of high-quality studies. In 2019, a multicenter, randomized, controlled trial performed at 14 hospitals revealed that metformin treatment from the late first trimester until delivery reduced the risk of late miscarriage and preterm birth but did not prevent GDM (11). Additionally, our findings are consistent with another meta-analysis which reported that metformin treatment throughout pregnancy can increase the success possibility of full-term delivery and decrease

the risk of preterm labor and pregnancy complications, such as PIH, with no serious side effects.

In terms of offspring, the effect of metformin treatment throughout the pregnancy period remains unknown due to the limited number of studies addressing the issue. Our meta-analysis found that metformin significantly decreased the risk of macrosomia but was associated with significantly increased fetal head circumference. However, there was no evidence that fetal birth weight or length were associated with metformin treatment. Our results showed that metformin had a significant impact on children's long-term growth as measured by BMI, which indicated that metformin-exposed children tended to be larger than placebo-exposed children. This finding is consistent with the 5–10 years follow-up of the PregMet RCT conducted by Hanem *et al.*, which found that metformin treatment in PCOS pregnancies led to children with a higher mean BMI accompanied by central adiposity and an increased prevalence of obesity at 5–10 years of age (9). Another study following the offspring of women with GDM found that metformin-exposed offspring were larger by measures of weight, arm and waist circumference, and BMI at 9 years compared with offspring exposed to insulin treatment during pregnancy (29). Although our study found no difference in the birth weight of offspring, children exposed to metformin appeared to have a higher risk of obesity in childhood.

With respect to metabolic profile, our study found that metformin could help modulate IR in pregnant women with PCOS. A previous study revealed that metformin could reduce plasma insulin levels by promoting weight loss and improving the metabolic health of women (30). Although animal models have suggested that metformin might contribute to improvements in IR in female offspring, the effect of metformin on the offspring of patients with PCOS remains uncertain. A follow-up study of children from the PregMet study found no difference in HOMA2IR scores in offspring between the groups (9). Our results are consistent with these studies; although metformin appeared to improve the HOMA2IR scores in offspring, no significant difference was detected.

We also investigated the effect of metformin on sex hormone levels. Our study found that SHGB levels were significantly increased in offspring of women with PCOS; however, no similar trend was found in mothers. The underlying mechanism might be related to the improvement of the metabolic health of mothers. A previous study has shown that IR can cause decreased SHBG, so taking

metformin during pregnancy might impact SHBG by ameliorating HOMA2IR levels (33). Regarding androgen and testosterone levels, we found that neither was affected by metformin treatment, which is consistent with previous study (14). Although no significant difference in maternal hormone levels was found in this study, the correlation between maternal and offspring hormone levels should be investigated in the future.

This meta-analysis has several limitations. First, there are a limited number of studies addressing the relevant outcomes, especially regarding long-term metabolic profile and sex hormone levels, and so our results should be interpreted cautiously. Second, the qualities of eligible studies were not high. Therefore, a higher quality study with a larger sample size should be established to further investigate the inconsistent situation. Third, although we found no significant difference in maternal sex hormone levels between groups, the impact of maternal sex hormones on the sex hormones of offspring should be further studied in the future.

In conclusion, although the relative low quality of RCTs and limited results made it difficult to draw a definite conclusion, our study showed that metformin treatment during pregnancy can reduce the risk of pregnancy complications but may have impacts on SHBG levels and long-term BMI in offspring.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-909/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-909/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix 1 Search Strategy

Table S1 Search strategy

Database: PubMed July 14th, 2021

#	Searches	Results
	metformin	25,451
	(polycystic ovary syndrome) OR (PCOS)	20,458
	(pregnancy*) OR (reproductive) OR (reproduction)	1,502,781
	#1 AND #2 AND #3	1,015
	Limit to English language AND Humans	784
	((“metformin”[MeSH Terms] OR “metformin”[All Fields] OR “metformine”[All Fields] OR “metformin s”[All Fields] OR “metformins”[All Fields]) AND (“polycystic ovary syndrome”[MeSH Terms] OR (“polycystic”[All Fields] AND “ovary”[All Fields] AND “syndrome”[All Fields]) OR “polycystic ovary syndrome”[All Fields] OR “PCOS”[All Fields]) AND (“pregnancy*”[All Fields] OR (“reproduction”[MeSH Terms] OR “reproduction”[All Fields] OR “reproductions”[All Fields] OR “reproductive”[All Fields] OR “reproductively”[All Fields] OR “reproductives”[All Fields] OR “reproductivity”[All Fields]) OR (“reproduction”[MeSH Terms] OR “reproduction”[All Fields] OR “reproductions”[All Fields] OR “reproductive”[All Fields] OR “reproductively”[All Fields] OR “reproductives”[All Fields] OR “reproductivity”[All Fields]))) AND ((humans[Filter] AND (english[Filter]))	

Database: Embase July 14th, 2021

Search Strategy:

#	Searches	Results
1	metformin:ab,ti	38,978
2	(polycystic ovary syndro'polycystic ovary syndrome':ab,ti OR pcos:ab,time) OR (PCOS)	23,563
3	pregnancy*:ab,ti OR reproductive:ab,ti OR reproduction:ab,ti	739,689
4	#1 AND #2 AND #3	648
5	Limit to English language AND Humans	544

Database: Cochrane library July14th, 2021

#	Searches	Results
1	metformin	11,479
2	(polycystic ovary syndrome) OR (PCOS)	4,168
4	(pregnancy*)or (reproductive) or (reproduction)	70,263
7	#1 AND #2 AND #5 AND #6	515

Table S2 Inclusion and exclusion criteria methods in studies

Study	Inclusion criteria	Exclusion criteria
Hjorth-Hansen, A.(2018)	Inclusion criteria were (I) PCOS diagnosed according to the Rotterdam criteria, (II) age 18 to 45 years, (III) gestational age between 5 and 12 weeks, and (IV) singleton viable fetus shown on ultrasonography	Exclusion criteria were alanine transaminase level 90 IU/L, serum creatinine 1.70 mg/dL, known alcohol abuse, previously diagnosed diabetes mellitus, or fasting serum glucose level 126 mg/dL at the time of inclusion
E.Vanky (2004)	(I) diagnosis of PCOS before the actual pregnancy, (II) age 18–40 years, (III) gestational age between 5 and 12 weeks, and a singleton viable fetus judged by ultrasonography	The exclusion criteria were alanine aminotransferase, higher than 90 international enzyme units per L, serum creatinine concentration higher than 1.70 mg/dL, known alcohol abuse, previously diagnosed diabetes or fasting serum glucose higher than 126 mg/dL at the point of inclusion, treatment with oral glucocorticoids, or use of drugs known to interfere with metformin
Hanne Klæboe Greger (2020)	The present study (CogMet study) is a follow-up study of children whose mothers participated in “the Pilot study” and “the PregMet study”	
K. J. Fougne (2008)	(I) Diagnosis of PCOS before the present pregnancy, (II) aged between 18 and 40 years, (III) gestational age between 5 and 12 weeks, and a singleton viable foetus judged by ultrasonography	The exclusion criteria were known liver disease, s-creatinine >130 mmol/L, known alcohol abuse, previously known diabetes mellitus, fasting plasma Glucose >5.6 mmol/L, treatment with oral glucocorticoids or use of drugs known to interfere with metformin
K.Å. SALVESEN (2007)	(I) Diagnosis of PCOS before the actual pregnancy; (II) age 18–40 years; (III) gestational age 5–12 weeks; and (IV) a single viable fetus.	The exclusion criteria were alanine aminotransferase, higher than 90 international enzyme units per L, serum creatinine concentration higher than 1.70 mg/dL, known alcohol abuse, previously diagnosed diabetes or fasting serum glucose higher than 126 mg/dL at the point of inclusion, treatment with oral glucocorticoids, or use of drugs known to interfere with metformin
Laure Morin-Papunen (2012)	Eligible participants were women aged 18–39 yr at entry, with a body mass index (BMI) greater than 19 kg/m ² and diagnosed with PCOS according to Rotterdam criteria	Exclusion criteria were type 2 diabetes mellitus, active liver disease (alanine aminotransferase >100 IU/liter), history of cardiac or renal failure, hormone medication, alcohol use, and regular smoking
Liv Guro Engen Hanem (2019)	The inclusion criteria were diagnosis of polycystic ovary syndrome according to the Rotterdam criteria, age 18–45 years, gestation between 5 and 12 weeks, and a singleton viable fetus shown on ultra-sonography	The exclusion criteria were alanine aminotransferase, higher than 90 international enzyme units per L, serum creatinine concentration higher than 1.70 mg/dL, known alcohol abuse, previously diagnosed diabetes or fasting serum glucose higher than 126 mg/dL at the point of inclusion, treatment with oral glucocorticoids, or use of drugs known to interfere with metformin
Maria Othelie Underdal (2018)	(I) Diagnosis of PCOS before the actual pregnancy, (II) age 18–40 years, (III) gestational age between 5 and 12 weeks, and a singleton viable fetus judged by ultrasonography	The exclusion criteria were alanine aminotransferase, higher than 90 international enzyme units per L, serum creatinine concentration higher than 1.70 mg/dL, known alcohol abuse, previously diagnosed diabetes or fasting serum glucose higher than 126 mg/dL at the point of inclusion, treatment with oral glucocorticoids, or use of drugs known to interfere with metformin
Mawahib A.S. Al-Biate (2015)	The inclusion criteria of the study were the diagnosis of PCOS before pregnancy, maternal age of 18–40 years, gestational age between 5 weeks and 12 weeks, normal serum thyroid-stimulating hormone and prolactin levels, and pregnancy with singleton fetus	The exclusion criteria were other risk factors for miscarriage such as abnormal serum karyotyping for both parents; antiphospholipid syndrome, which was excluded by anticoagulant antibodies test; uterine anomalies as excluded by transvaginal ultrasound scanning; and diabetes mellitus by oral glucose tolerance test

Table S2 (continued)

Table S2 (continued)

Study	Inclusion criteria	Exclusion criteria
Mosammat Rashida Begum (2009)	Infertile patients having PCOS with clomiphene citrate resistance and insulin resistance were recruited for pretreatment and co-administration of metformin. PCOS were diagnosed using the Rotterdam criteria	N/A
Osama S. Abdalmagee (2018)	We included women with PCOS who were less than 39 years, over-weight, and obese with body mass index (BMI) >24 kg/m ² . They were diagnosed as having PCOS according to Rotterdam criteria, by the finding of at least 2 of the following: basal ultrasound polycystic ovary (12 or more follicles ranging from 2 to 9 mm), hyperandrogenism (clinical and biochemical), and anovulation or oligoovulation (less than 9 ovulatory cycles per year). All patients had normal thyroid-stimulating hormone (TSH), prolactin, and day 3 follicular-stimulating hormone (FSH) levels	Exclusion criteria were diabetes mellitus, renal or liver disease, documented tubal factor or pelvic adhesions, elevated 17 ahydroxyprogesterone level, and FSH more than 10 IU/mL. We also excluded the women who started program or medications to reduce their weight and those whose partners had abnormal semen parameters according to the World Health Organization parameters. Hysterosalpingography or office hysteroscopy was performed to confirm normal uterine cavity, and we excluded the patients with uterine abnormalities
Carlsen, S. M. (2012)	(I) PCOS diagnosed according to The Rotterdam Criteria, (II) age 18 to 45 years, (III) gestational age between 5 and 12 weeks, and (IV) a singleton viable fetus shown on ultrasonography	The exclusion criteria were alanine aminotransferase level >90 IU/L, serum creatinine concentration >130 mmol/L, known alcohol abuse, previously diagnosed diabetes mellitus or fasting serum glucose >7.0 mmol/L at the time point of inclusion, treatment with oral glucocorticoids, or use of drugs known to interfere with metformin
Tone S. Løvvik (2019)	(I) Diagnosis of PCOS before the actual pregnancy, (II) age 18–40 years, (III) gestational age between 5 and 12 weeks, and a singleton viable fetus judged by ultrasonography.	The exclusion criteria were alanine aminotransferase, higher than 90 international enzyme units per L, serum creatinine concentration higher than 1.70 mg/dL, known alcohol abuse, previously diagnosed diabetes or fasting serum glucose higher than 126 mg/dL at the point of inclusion, treatment with oral glucocorticoids, or use of drugs known to interfere with metformin
TORSTEIN B. R Ø (2012)	(I) Diagnosis of PCOS before the actual pregnancy, (II) age 18–40 years, (III) gestational age between 5 and 12 weeks, and a singleton viable fetus judged by ultrasonography	The exclusion criteria were alanine aminotransferase, higher than 90 international enzyme units per L, serum creatinine concentration higher than 1.70 mg/dL, known alcohol abuse, previously diagnosed diabetes or fasting serum glucose higher than 126 mg/dL at the point of inclusion, treatment with oral glucocorticoids, or use of drugs known to interfere with metformin
Wang Aiping (2018)	(I) Pregnant women with PCOS; (II) age between 20–40; (III) Hb A1c between 6.0–7.0%	(I) Refuse to sign the informed consent; (II) diagnosed with gestational diabetes mellitus; (III) diagnosed with adrenal hyperplasia, thyroid disease, hyperprolactinemia, Cushing's syndrome, ovarian, adrenal androgen-secreting tumors and other interfering diseases

Table S3 Intervention treatment summary

Study	Treatment
Anna Hjorth-Hansen (2018)	Treatment with metformin 500 mg (metformin hydrochloride; Weifa AS, Oslo, Norway) or identically coated placebo tablets was initiated
Charles J. Glueck (2002)	The study was prospective from the diagnosis of PCOS through pre-conception therapy with metformin-diet (metformin 2–2.55 g/day, low glycemic index diet), and then on metformin-diet throughout pregnancy. Metformin – low GI diet duration: started before conception and continued throughout pregnancy
E.Vanky (2004)	Treatment with metformin 425 mg (metformin hydrochloride, MetforminH; Weifa AS, Norway) or identical placebo capsules was initiated. All participants took two capsules once daily during the first week and two capsules twice daily for the rest of the study period.
Hanne Klæboe Greger (2020)	Participants in the PregMet study were randomized to metformin (2,000 mg daily) or placebo throughout pregnancy, and 80% had a self-reported intake of > 85% of the tablets; The CogMet study were randomized to metformin (1,700 mg daily) and 22 to placebo throughout pregnancy
K. J. Fougne (2008)	Treatment with metformin 425 mg (metformin hydrochloride, MetforminH; Weifa AS, Norway) or identical placebo capsules was initiated. All participants took two capsules once daily during the first week and two capsules twice daily for the rest of the study period.
K.°A. SALVESEN (2007)	Treatment with metformin 425 mg (metformin hydrochloride, MetforminH; Weifa AS, Norway) or identical placebo capsules was initiated. All participants took two capsules once daily during the first week and two capsules twice daily for the rest of the study period.
Laure Morin-Papunen (2012)	Metformin (metformin hydrochloride depot tablets, Diformin 500 mg; Leiras) or placebo was initiated at a dose of one tablet once a day for the first week and increased thereafter by one tablet daily in weekly steps up to three tablets (one + two daily) in non-obese women and to four tablets (two + two daily) in obese women and was continued up to a maximum of 9 months. If pregnancy occurred, metformin/placebo was continued up to the 12th week
Liv Guro Engen Hanem (2019)	They were randomly assigned to metformin (2,000 mg/day) or placebo from inclusion in the first trimester (average gestational week 10) to birth
Maria Othelie Underdal (2018)	Metformin 2,000 mg daily or placebo from 1st trimester to delivery in the original study
Mawahib A.S. Al-Biate (2015)	The first group who became pregnant while receiving metformin and continued the treatment at a dose of 1,000 mg/d (metformin group) and the second group who discontinued the use of the drug once pregnancy started because they were unwilling to continue its use
Mosammat Rashida Begum (2009)	Metformin was given 1,500 mg daily for BMI <29, 2,000 mg daily for BMI 30–32 and 2,500 mg daily for BMI >32. Patients who conceived were divided into two groups by lottery either for continuation of metformin until delivery or discontinuation at 8 weeks of pregnancy
Osama S. Abdalmagee (2018)	The eligible women were allocated to either group I (metformin group) received 2 tablets of metformin 500 mg (Cidophage, Chemical Industries Development Co, Egypt) or group II (placebo group) received 2 placebo tablets with the same shape, color, and consistency. If pregnancy test was positive, the patient was instructed to continue having the medication during the first 12 weeks of gestation in both groups
Carlsen, S. M. (2012)	The participants took 1 tablet twice daily during the first week and thereafter 2 tablets twice daily until delivery, when study medication was stopped
Tone S Løvvik (2019)	Treatment with metformin 425 mg (metformin hydrochloride, MetforminH; Weifa AS, Norway) or identical placebo capsules was initiated. All participants took two capsules once daily during the first week and two capsules twice daily for the rest of the study period.
TORSTEIN B. R Ø (2012)	Treatment with metformin 425 mg (metformin hydrochloride, MetforminH; Weifa AS, Norway) or identical placebo capsules was initiated. All participants took two capsules once daily during the first week and two capsules twice daily for the rest of the study period
Wang Aiping (2018)	The observation group was treated with metformin combined with insulin, and the control group was treated with insulin alone

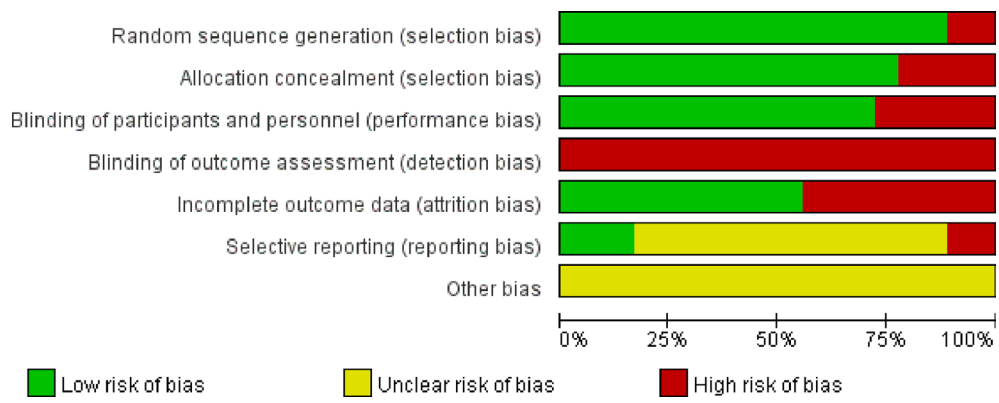


Figure S1 Risk of bias graph.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Abdalmageed,O.S	+	+	-	-	-	?	?
Begum,M.R	-	-	-	-	-	-	?
Calsen,S.M2012	+	+	+	-	+	?	?
Calson, S.M.2010	+	+	+	-	+	?	?
Fougner,K.j	+	-	-	-	+	?	?
Greger,H.K	+	+	+	-	+	?	?
Hanem,L.G.E.2018	+	+	+	-	-	?	?
Hanem,L.G.E.2021	+	+	+	-	-	?	?
Hanem,L.G.E2019	+	+	+	-	+	?	?
Hjorth-Hansen,A	+	+	+	-	-	?	?
Lowik,T.S	+	+	+	-	+	?	?
Morin-Papunen,L	+	-	+	-	+	?	?
Ro,T.B	+	+	+	-	-	-	?
Salvesen,K.A	+	+	-	-	+	?	?
Underdal,M.O	+	+	+	-	-	?	?
Vanke.E2004	+	+	+	-	+	+	?
Vanke.E2010	+	+	+	-	+	+	?
Wang ai ping	-	-	-	-	-	+	?

Figure S2 Risk of bias summary graph.

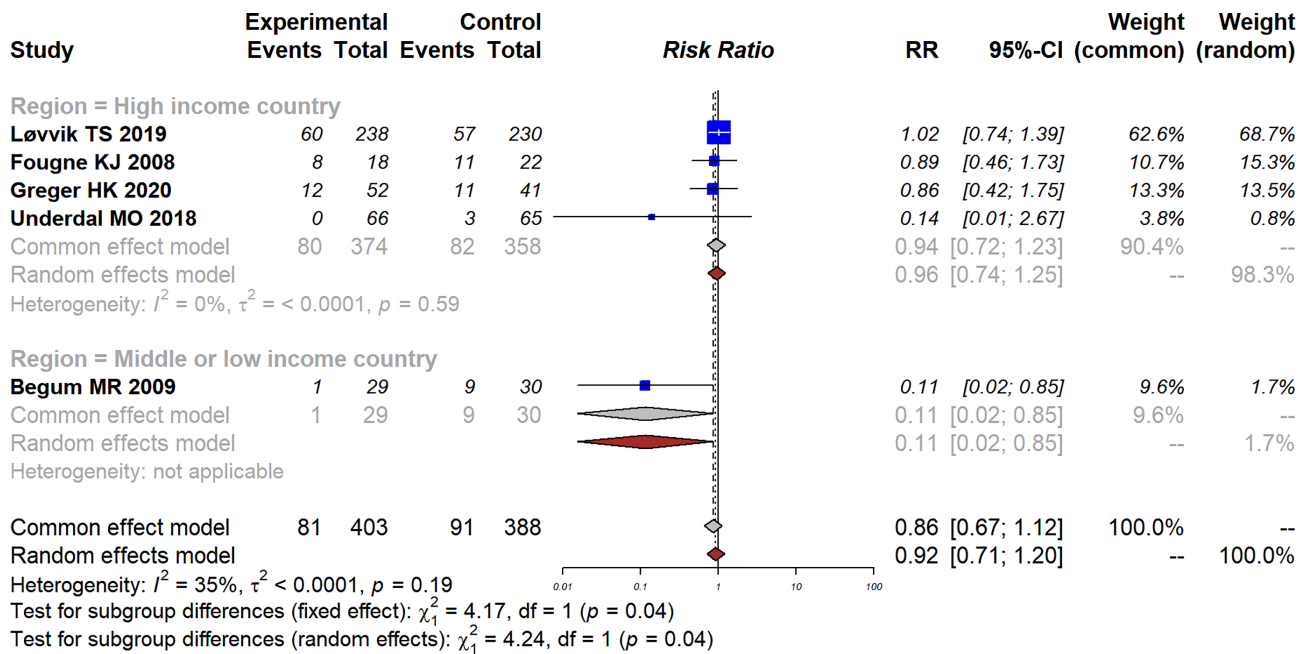


Figure S3 Subgroup analysis of GDM by region.

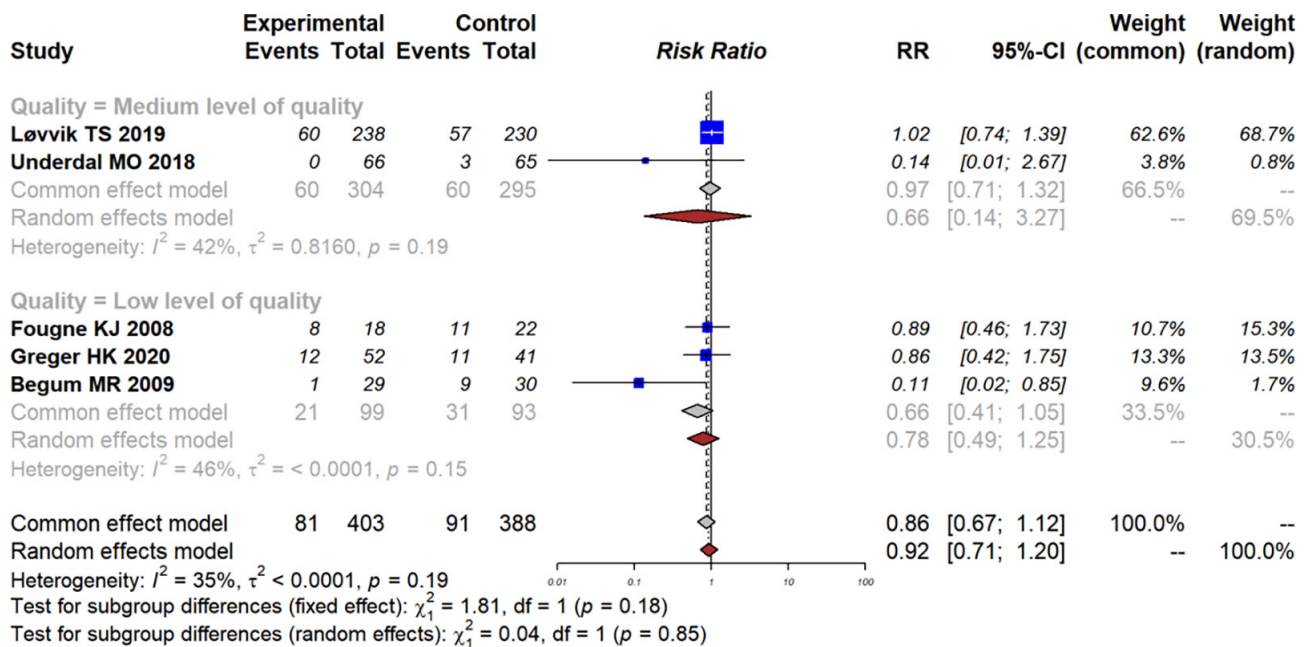


Figure S4 Subgroup analysis of GDM by study quality.

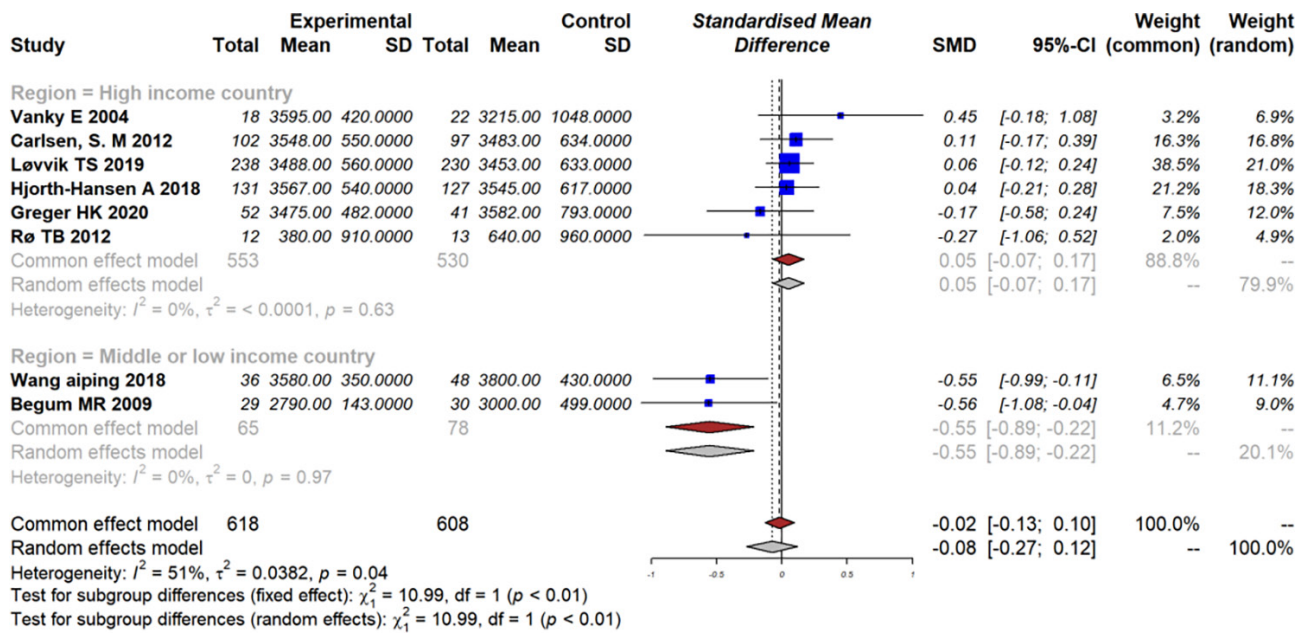


Figure S5 Subgroup analysis of birth weight by region.

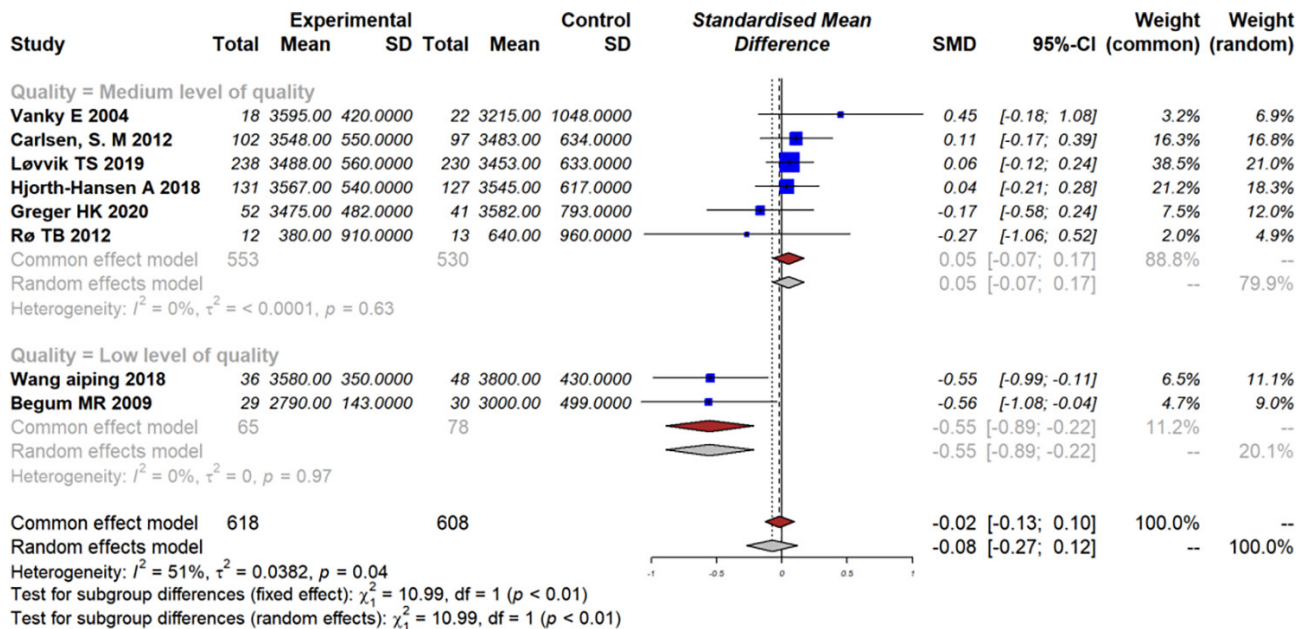


Figure S6 Subgroup analysis of birth weight by study quality.

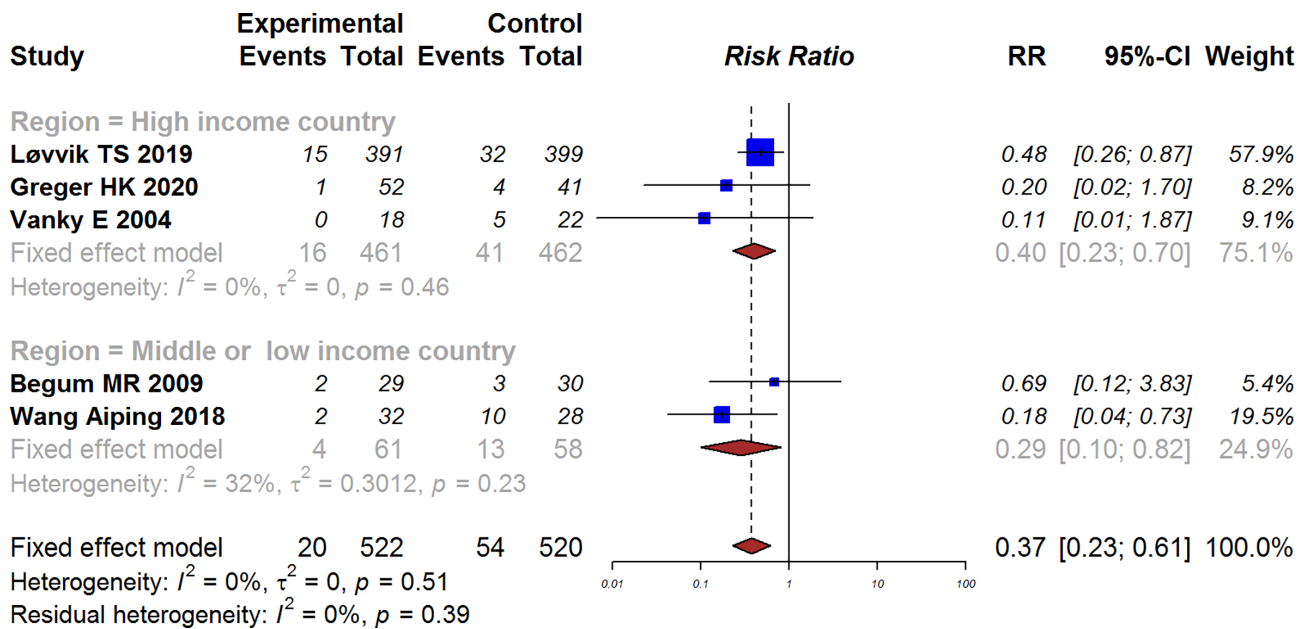


Figure S7 Subgroup analysis of preterm by region.

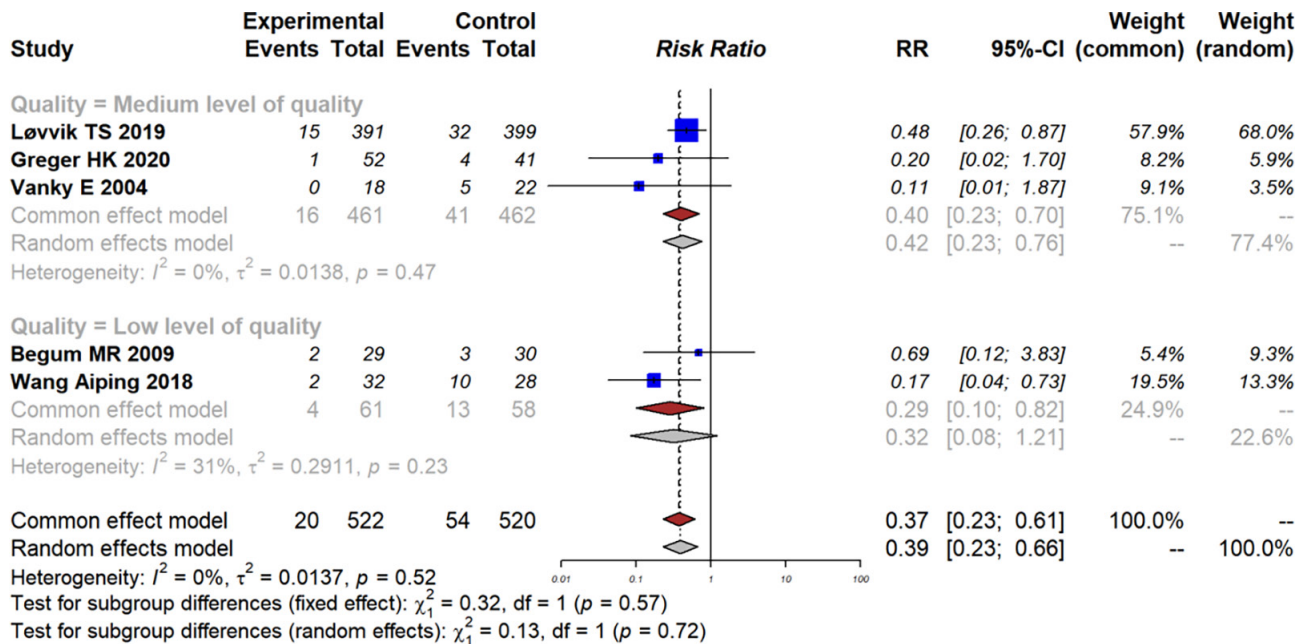


Figure S8 Subgroup analysis of preterm by study quality.

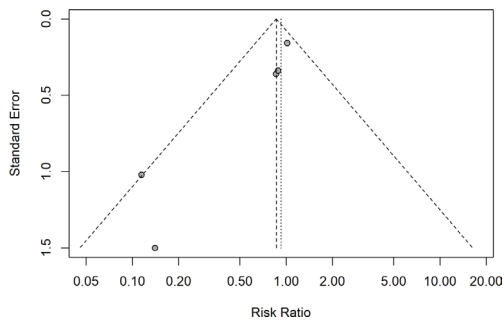


Figure S9 Funnel Plot of gestational diabetes.

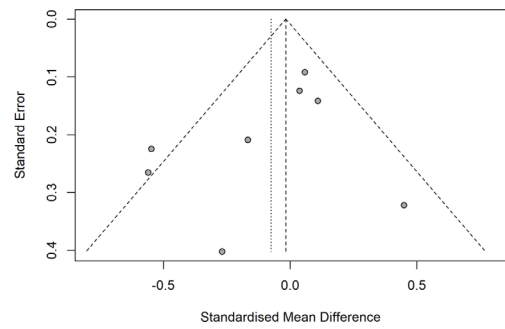


Figure S12 Funnel plot of neonatal birth weight.

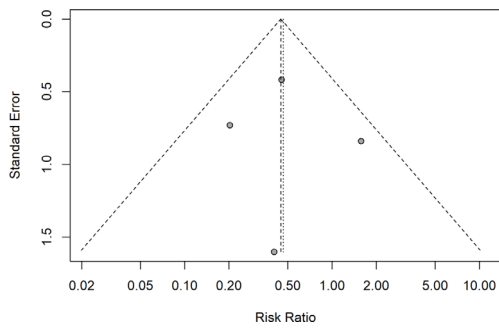


Figure S10 Funnel Plot of maternal hypertension.

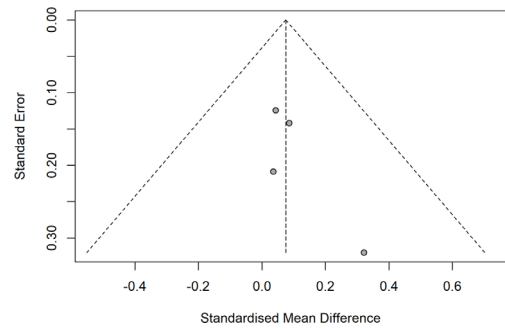


Figure S13 Funnel plot of neonatal birth length.

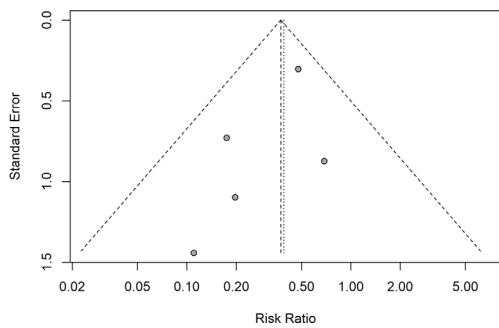


Figure S11 Funnel plot of preterm birth.

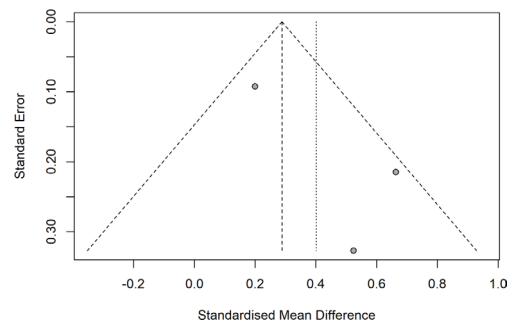


Figure S14 Funnel plot of neonatal head circumference.

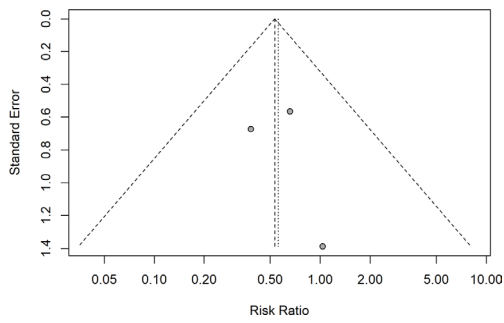


Figure S15 Funnel plot of miscarriage.

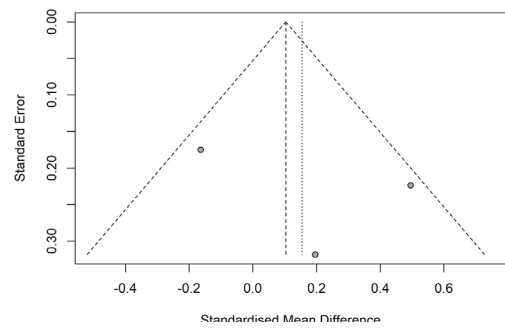


Figure S18 Funnel plot of long term fasting glucose.

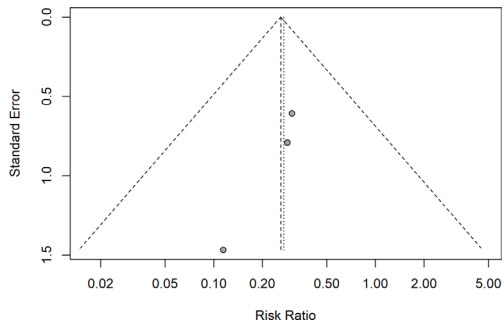


Figure S16 Funnel plot of macrosomia.

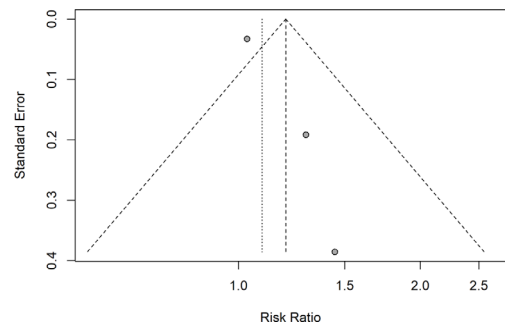


Figure S19 Funnel plot of live birth rate.

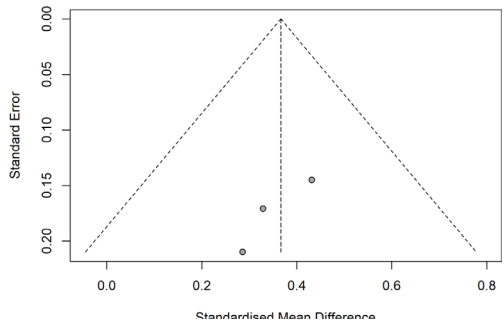


Figure S17 Funnel plot of long term BMI.

Table S4 Publication bias by Egger's test and Begger's test

Outcome	Egger's test		Begger's test	
	t	P value	Z	P value
Birth length	1.67	0.2367	1.36	0.1742
Birth weight	-1.28	0.2477	-0.74	0.4579
Long term BMI	-2.76	0.2215	-1.57	0.1172
Fasting glucose	0.66	0.6302	0.52	0.6015
Head circumference	1.72	0.3349	0.52	0.6015
Live birth rate	4.88	0.1286	0.52	0.6015
Macrosomia	-4.04	0.1545	-1.57	0.1172
Miscarriage	0.45	0.7330	0.52	0.6015
PIH	0.17	0.8816	0	1.000
Preterm	-1.51	0.2288	-0.98	0.3272
Gestational diabetes	-4.12	0.0259	-1.96	0.050