Supplementary

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

https://dx.doi.org/10.21037/atm-22-909

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-creatininew >130 mmol/L, known alcohol abuse, previously known diabetes mellitus, fasting plasma Glucosew >5.6 mmol/L, treatment with oral glucocorticoids or use of drugs known to interfere with metformin
K.˚A. 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*)

https://dx.doi.org/10.21037/atm-22-909

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

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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

https://dx.doi.org/10.21037/atm-22-909

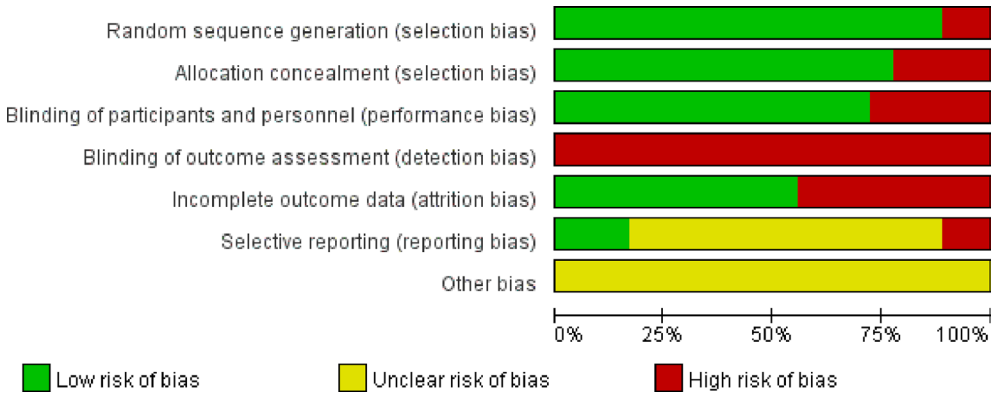

Figure S1 Risk of bias graph.

https://dx.doi.org/10.21037/atm-22-909

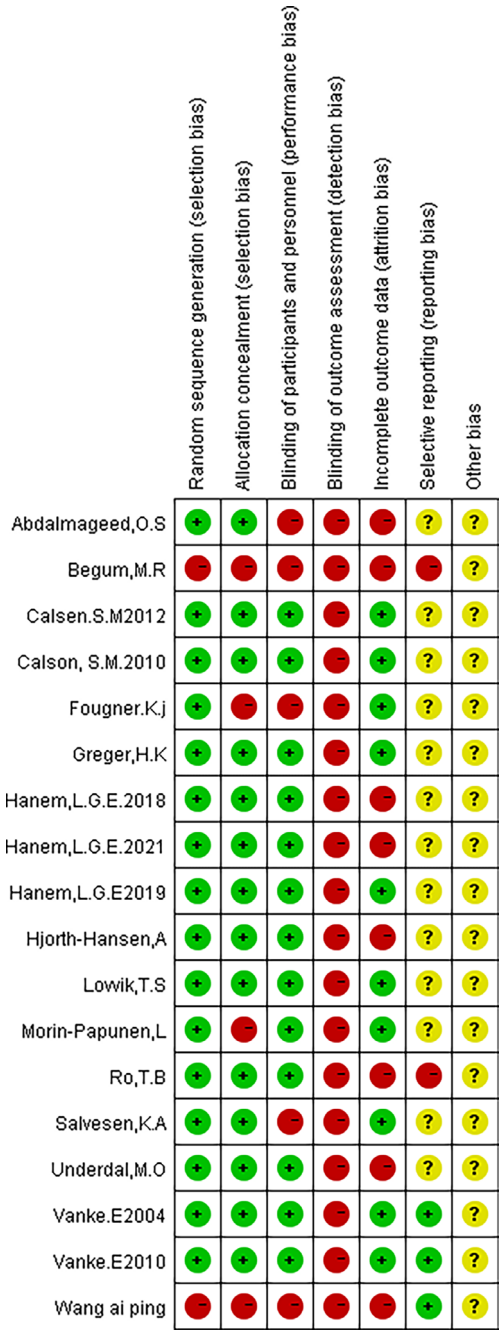

Figure S2 Risk of bias summary graph.

https://dx.doi.org/10.21037/atm-22-909

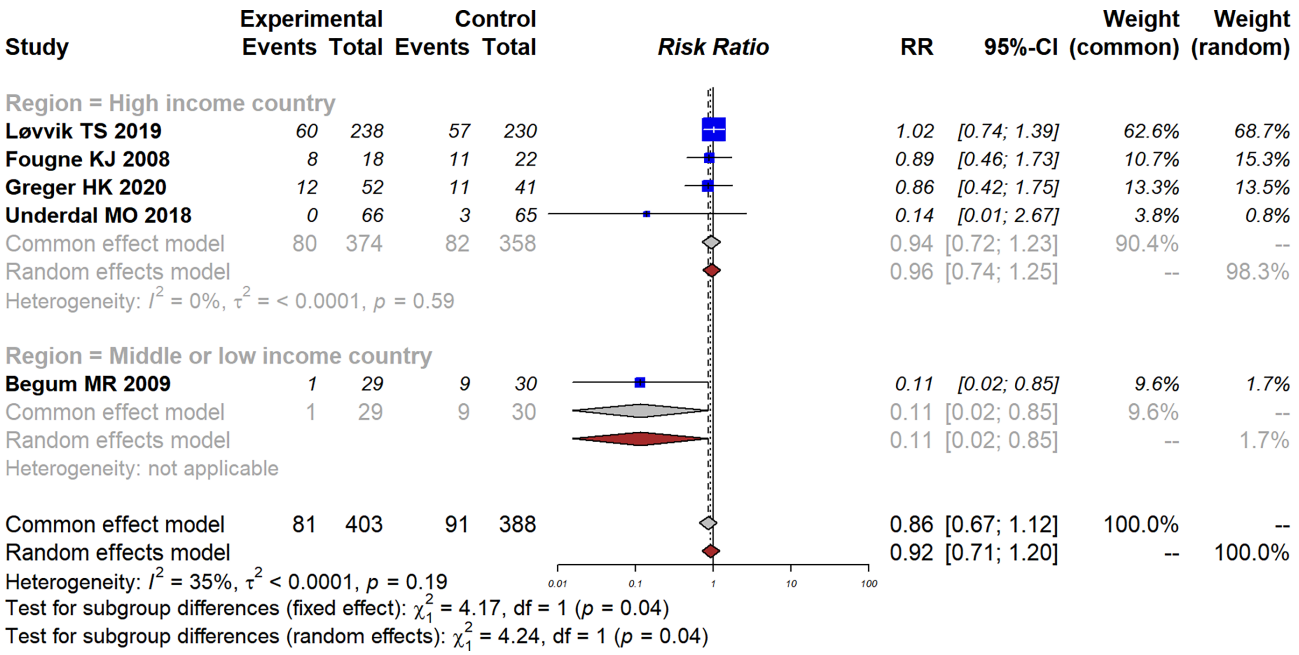

Figure S3 Subgroup analysis of GDM by region.

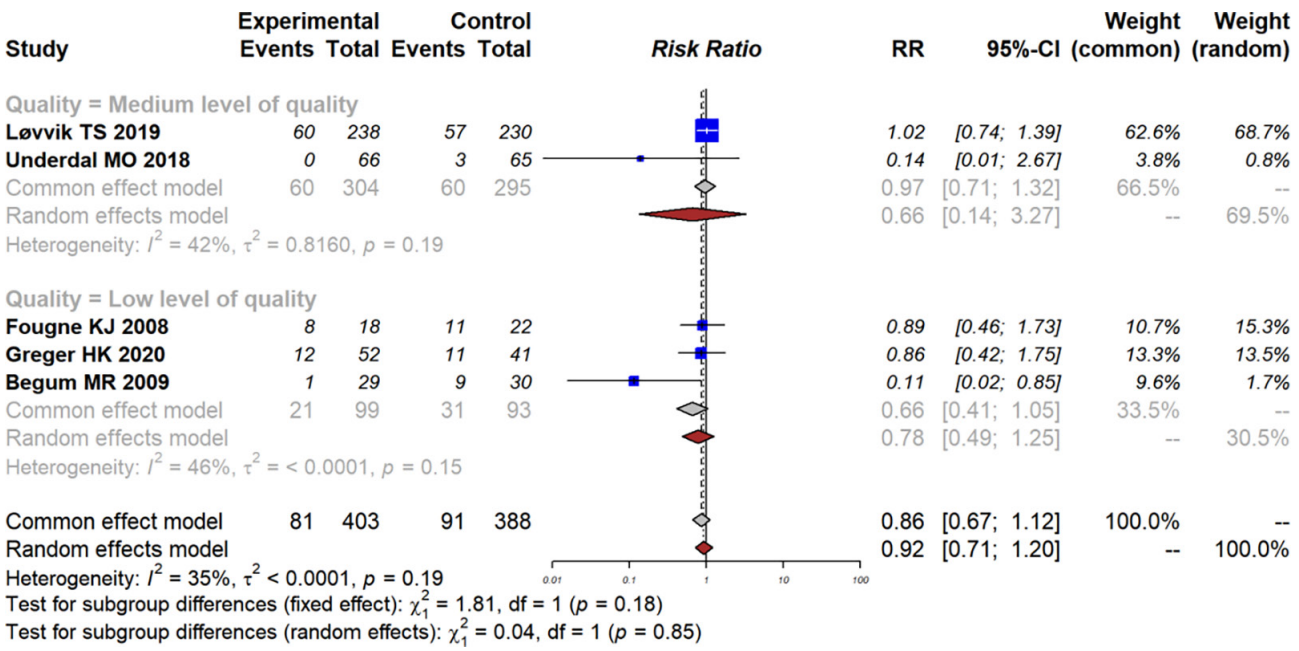

Figure S4 Subgroup analysis of GDM by study quality.

https://dx.doi.org/10.21037/atm-22-909

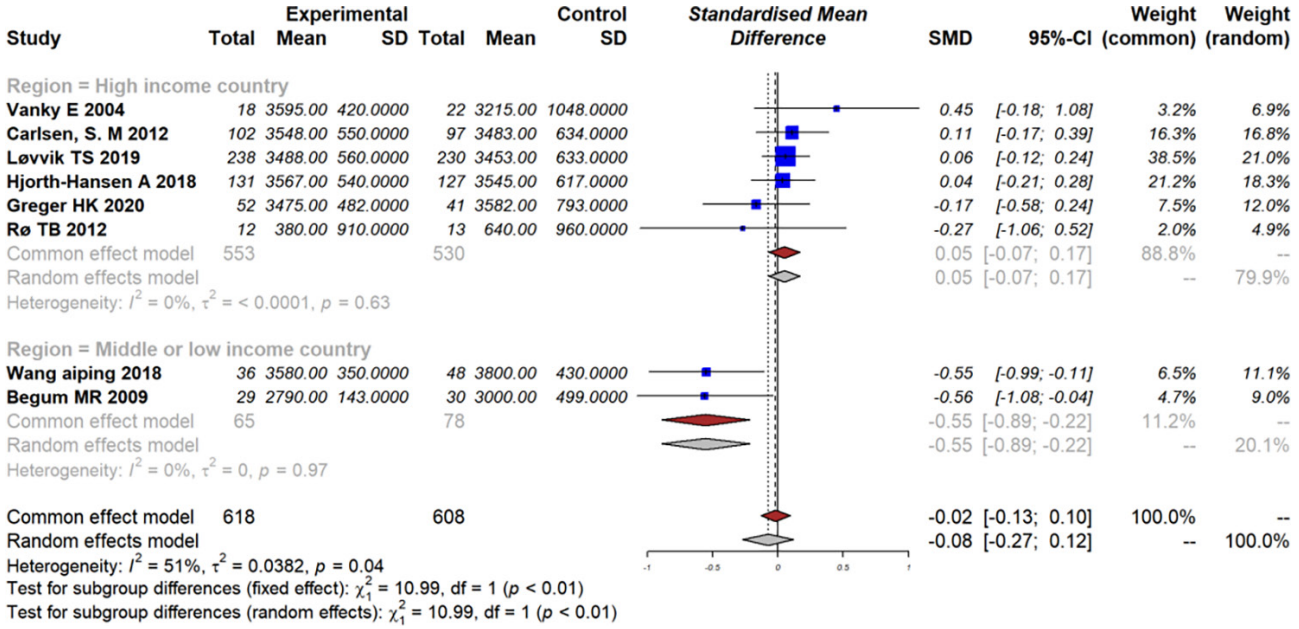

Figure S5 Subgroup analysis of birth weight by region.

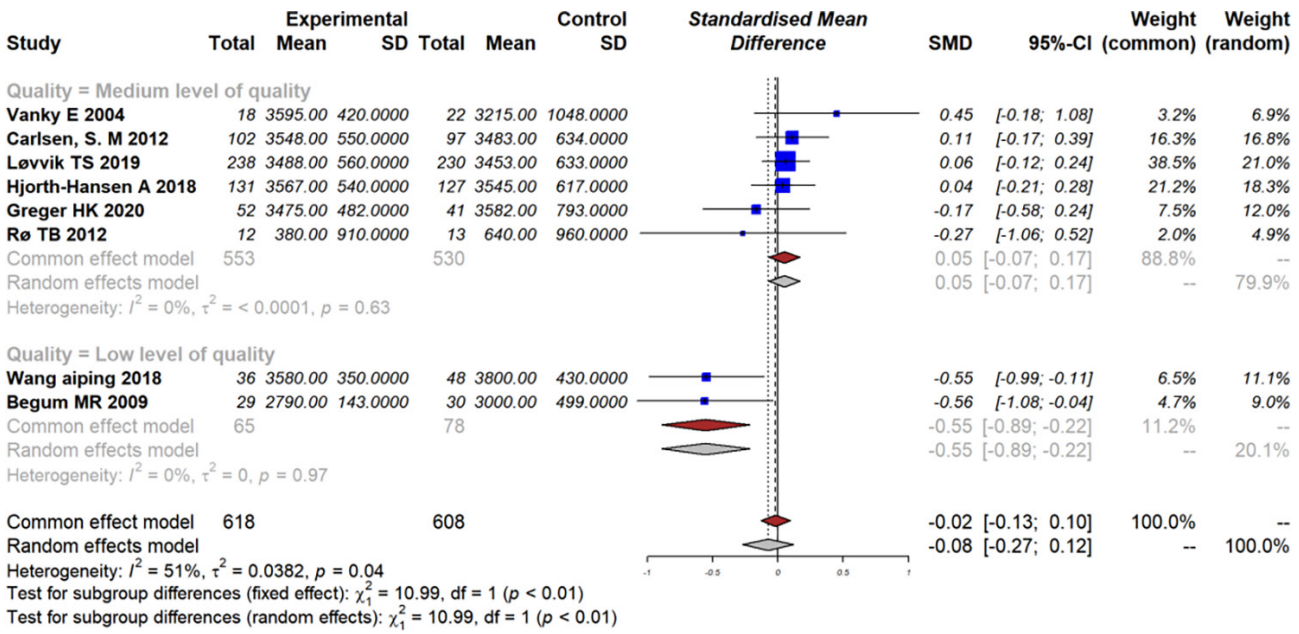

Figure S6 Subgroup analysis of birth weight by study quality.

https://dx.doi.org/10.21037/atm-22-909

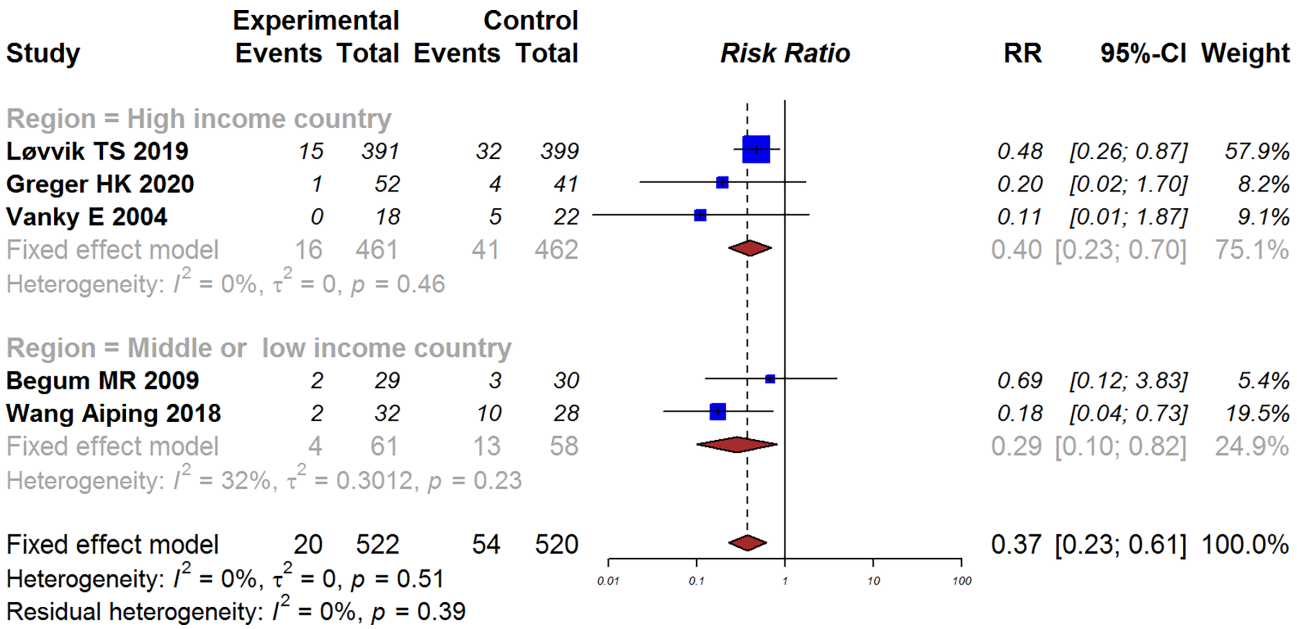

Figure S7 Subgroup analysis of preterm by region.

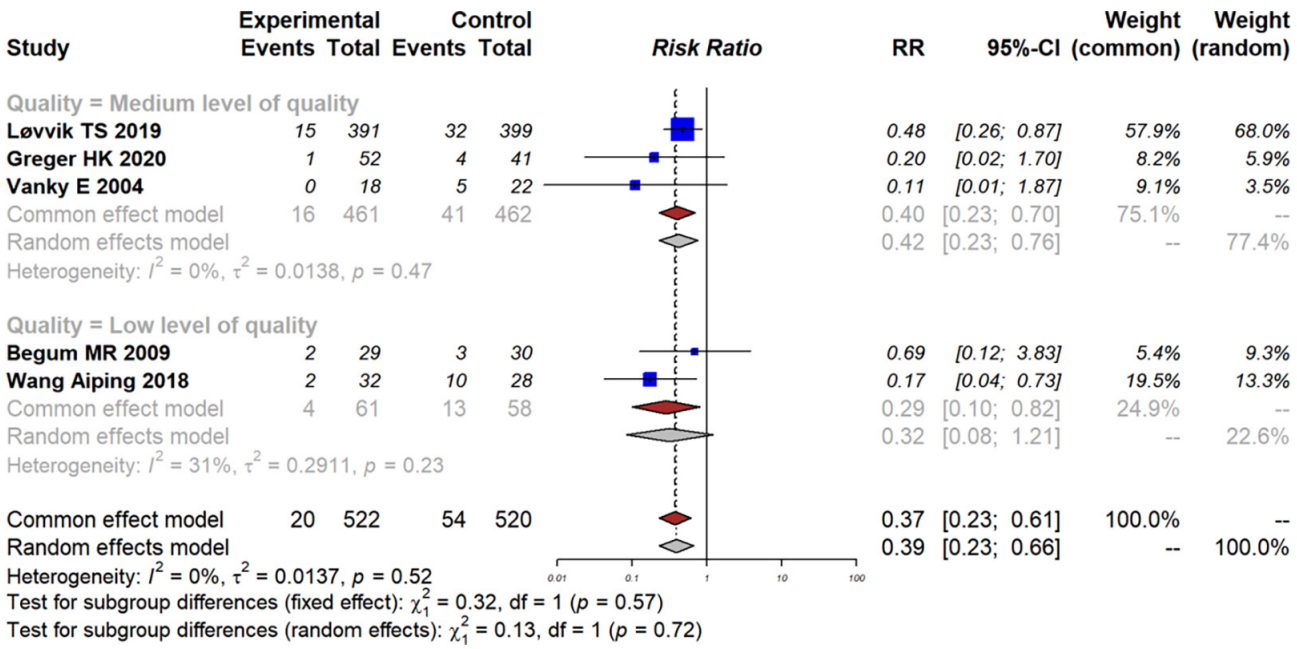

Figure S8 Subgroup analysis of preterm by study quality.

https://dx.doi.org/10.21037/atm-22-909

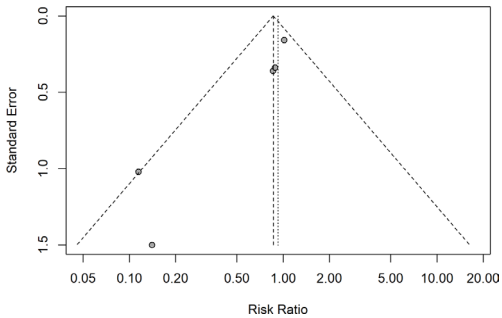

Figure S9 Funnel Plot of gestational diabetes.

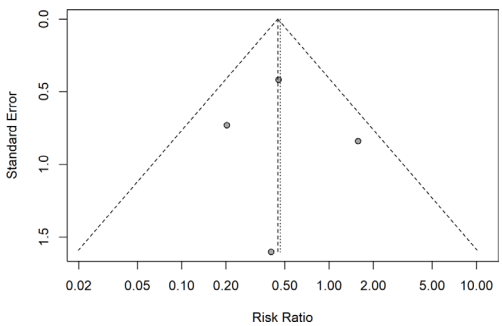

Figure S10 Funnel Plot of maternal hypertention.

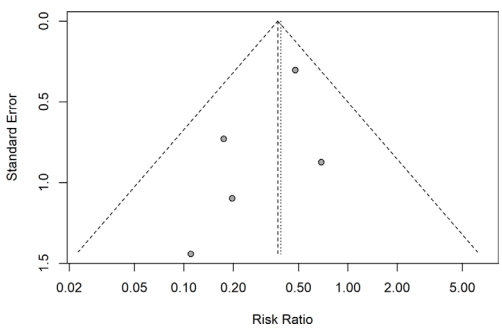

Figure S11 Funnel plot of preterm birth.

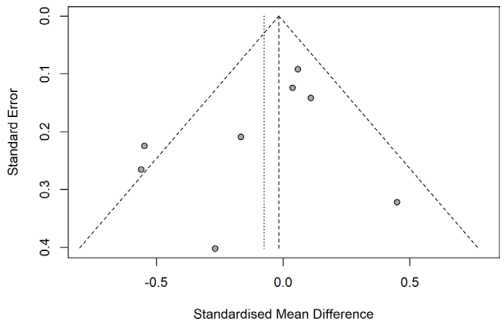

Figure S12 Funnel plot of neonatal birth weight.

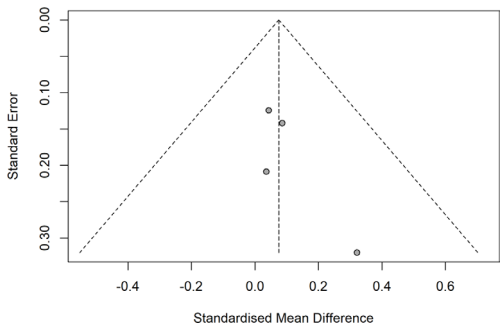

Figure S13 Funnel plot of neonatal birth length.

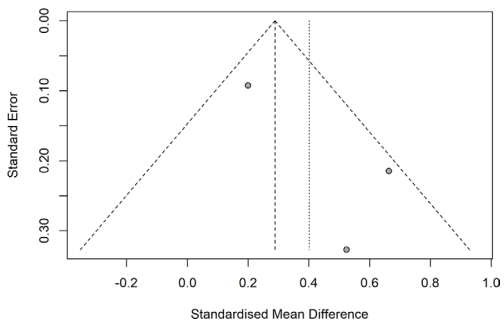

Figure S14 Funnel plot of neonatal head circumference.

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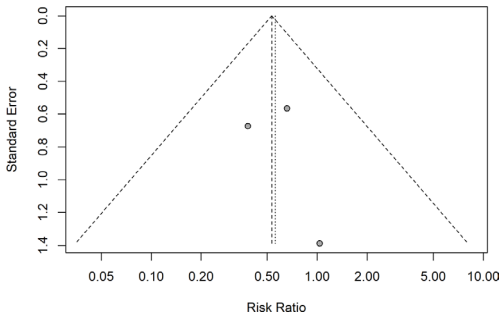

Figure S15 Funnel plot of miscarriage.

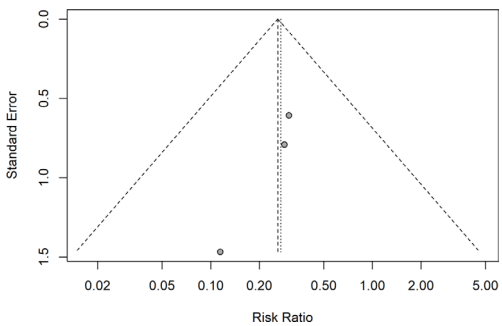

Figure S16 Funnel plot of macrosomia.

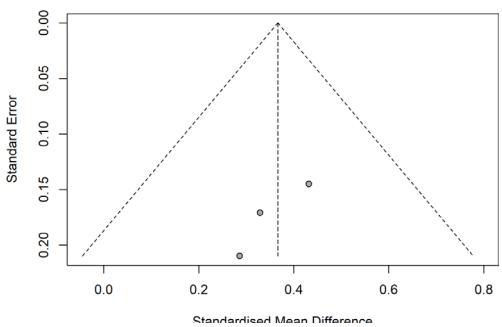

Figure S17 Funnel plot of long term BMI.

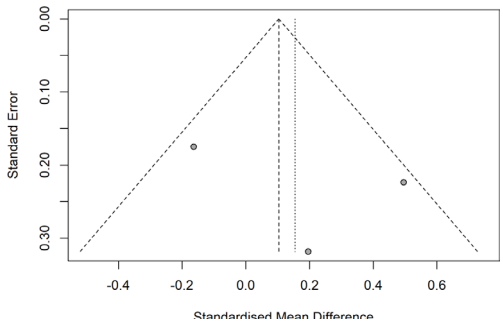

Figure S18 Funnel plot of long term fasting glucose.

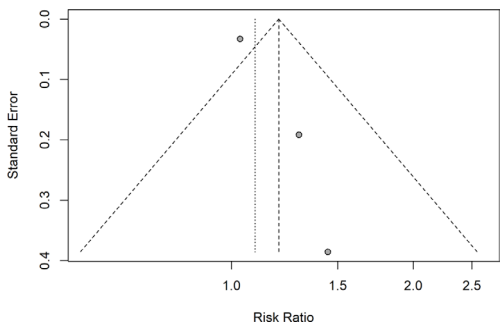

Figure S19 Funnel plot of live birth rate.

https://dx.doi.org/10.21037/atm-22-909

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

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