Impact of metformin treatment during pregnancy on maternal outcomes: a systematic review/meta-analysis

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Abstract

Objective: We systematically assessed the impact of metformin treatment on maternal pregnancy outcomes.

Data Sources: PubMed, Ovid Embase, Medline, Web of Science, ClinicalTrials.gov and Cochrane databases were systematically searched (inception-19th November 2020).

Methods of Study Selection: Randomized controlled trials reporting pregnancy outcomes in women randomized to metformin versus any other treatment for any indication were included. Outcomes included gestational weight gain (GWG), pre-eclampsia, pregnancy-induced hypertension, preterm birth, gestational age at delivery, cesarean section, gestational diabetes, glycemic control, and gastrointestinal side-effects. Two independent reviewers conducted screening, with a third available to evaluate disagreements. Risk-of-bias and GRADE assessments were conducted using Cochrane Risk-of-Bias and GRADE-pro software.

Tabulation, integration and results: Thirty-five studies (n=8033 pregnancies) met eligibility criteria. GWG was lower in pregnancies randomized to metformin versus other treatments (1.57kg±0.60kg; I_2=86%, p<0.0001), as was likelihood of pre-eclampsia (OR 0.65, 95%CI:0.47-0.91; I_2=52%, p=0.01). The risk of gastrointestinal side-effects was greater in metformin-exposed versus other treatment groups (OR 2.43, 95%CI:1.53-3.84; I_2=76%, p=0.0002). The risk of other maternal outcomes assessed was not significantly different between metformin-exposed versus other treatment groups.

Conclusions: Metformin for any indication during pregnancy is associated with lower GWG and a reduced risk of pre-eclampsia, but increased gastrointestinal side-effects compared to other treatments.

Introduction

Metformin, an oral insulin-sensitizing and glucose-lowering drug, is widely prescribed during pregnancy. Guidelines from several global contexts, including the UK [1,2], New Zealand [3], US [4] and Canada [5] endorse metformin for the treatment of gestational diabetes mellitus (GDM). Metformin is also used in pregnancy for other conditions, including pre-existing diabetes [6] and polycystic ovarian syndrome (PCOS) [7], and has been trialled in the context of maternal obesity [8]. However, despite the widespread prescription of metformin during pregnancy, data regarding maternal pregnancy outcomes are relatively sparse, leading some clinicians to adopt a more cautious approach [9].

In the context of GDM, metformin is a practical alternative to insulin that maintains blood glucose concentrations within the normal range in a substantial proportion of patients [10]. Advantages of metformin include oral administration, cost-effectiveness, and suitability for use in low-resource settings [11]. Previous meta-analyses have raised concerns about the impacts of metformin on fetal and post-natal growth in the context of GDM [12,13]. However maternal pregnancy outcomes are less well-studied, particularly in women treated for conditions other than GDM [14-16]. Randomized trials have reported

potential maternal benefits associated with metformin treatment, including reduced gestational weight gain (GWG) [14,17]. Furthermore, mixed evidence suggests that pre-eclampsia rates may be reduced in women randomized to metformin treatment [18,19].

We evaluated the impact of metformin treatment in pregnancy on the mother, by synthesizing all available randomised trial data pertaining to common maternal outcomes (including gestational weight gain, pre-eclampsia, pregnancy-induced hypertension, pre-term birth, gestational age at delivery, ceserean-section, glycemic control, adverse events and GDM). These were investigated across the range of indications for which metformin is currently prescribed or trialled in pregnancy.

Materials And Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. The systematic review protocol was registered prospectively in PROSPERO CRD42020167692 (Supplementary Text S1) prior to data collection. Ethical approval was not required for this meta-analysis.

Literature searches, search strategies and eligibility criteria

Systematic literature searches using pre-specified terms (Supplementary Text S2) were performed on PubMed (June 1997 to 19th November 2020), Ovid EMBASE (1974 to 19th November 2020), Ovid Medline (1946 to 19th November 2020), Cochrane library (database inception to 19th November 2020), Clinicaltrials.gov (database inception to 19th November 2020), and Web of Science (1900 to 19th November 2020). No language or location restrictions were applied. Studies that randomized pregnant women to metformin (not in combination with any other drug) versus any other drug treatment, placebo, or no treatment were included. Studies were included if they randomized pregnant women for any indication (including GDM, pre-existing diabetes, PCOS, or maternal obesity). All treatment indications were screened for and diagnosed according to local criteria in each study, and we did not apply exclusions with respect to this. Studies were excluded if they included participants with multiple pregnancies or if they randomized fewer than 50 women in total. Data reported only in meeting abstracts would have been included if the abstract contained sufficient information for assessment, but none fulfilled the criteria. Where insufficient information for assessment was available, authors were contacted for further information. One study provided insufficient information for assessment, however the authors did not respond to contact and therefore this study could not be included in the analysis. This Methodology is taken from our previous meta-analysis; [12].

Study selection and data extraction

Two reviewers (JLA and CEA) independently assessed each study using pre-determined inclusion/exclusion criteria (Supplementary Table 1). A third reviewer (SEO) was available to resolve cases where eligibility was unclear. An initial screen of titles and abstracts was performed, followed by a detailed full paper screen (Supplementary Fig. S1).

Data extraction from eligible studies was conducted independently using a standardized proforma by two authors (JLA and CEA). Maternal outcome measures were: gestational weight gain (GWG, throughout pregnancy; kg), pre-eclampsia, pregnancy-induced hypertension (PIH), preterm birth (divided into spontaneous and iatrogenic), gestational age at delivery (weeks), cesarean section rates (divided into elective and emergency), glycemic control (fasting blood glucose, FBG; mg/dL and random blood glucose, RBG; mg/dL), new GDM incidence, maternal hypoglycaemia, and any reported side-effects. All outcome measures were defined as per the original study criteria, and we did not apply any exclusion with respect to these.

Quality assessment (risk of bias)

Each study was independently assessed by two authors (JLA and CEA) for quality and validity using the Cochrane Collaboration tool for assessing risk of bias. Seven risk of bias domains were systematically assessed for each study and each domain was given a rating of low risk, unknown risk or high risk of bias (Supplementary Table S2). All risk of bias analysis was conducted at the study level. (Methodology is taken from our previous meta-analysis; [12]).

The principle summary measures were unadjusted odds ratios (OR) (for dichotomous data) or differences in means (for continuous data). Meta-analysis was performed using Review Manager (RevMan) Version 5.3, Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) and the '*metafor*' package in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Funnel plots were constructed to assess publication bias. Meta-analyses with 5 or more studies included were also subjected to Egger's test. Heterogeneity between studies was assessed using the I-squared statistic. Any outcomes demonstrating significant inter-study heterogeneity (heterogeneity p value <0.05) were analysed using a random-effects model. Sensitivity analyses were performed using 'leave-one-out' sensitivity testing for individual studies. All outcomes were subjected to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis (GRADEpro Guideline Development Tool, McMaster University, USA). Sub-group analyses were performed for each treatment indication. Where the indication for randomization was diabetes in pregnancy, the included studies all compared metformin to either insulin or glyburide, hence further sub-group analyses were performed by comparator group. Where the indication for randomization was PCOS or obesity, all included studies compared metformin to placebo, therefore no further sub-group analyses were performed. A further sensitivity analysis excluding studies in which analysis was not performed on an intention-to-treat basis was also conducted. Where p values are reported, an alpha level <0.05 was considered statistically significant.

Results

Study selection and study characteristics

The PRISMA flow chart (Supplementary Fig. S1) demonstrates the screening procedure involved to attain 35 studies (8033 participants) for this meta-analysis. The majority of these studies (27 studies; 5319 participants) investigated metformin treatment for diabetes in pregnancy. A total of 8 studies (2714

participants) investigated maternal obesity (4 studies; n=1485) or PCOS (3 studies; n=930) or pre-gestational insulin resistance (1 study; n=299). No studies investigated randomisation of metformin compared to diet/lifestyle intervention alone, however these were commonly implemented alongside other treatments. Eligible studies were identified comparing metformin to insulin, glyburide, and placebo. For all indications and comparisons, the studies varied with respect to quality and design (Supplementary Table S3). The included studies demonstrated considerable heterogeneity with respect to the dosage of pharmacological agents (Supplementary Table S3). Heterogeneity also existed in the diagnostic criteria used for GDM and PCOS (Supplementary Table S4). The included studies came from a variety of geographical locations: Australasia (Australia and New Zealand), Europe (the UK, Norway and Finland), North Africa/Middle East (Egypt, Iran and Israel) and the North America/Latin America (Canada, Mexico, Brazil and Chile).

Risk of bias and sensitivity analyses

The risk of bias was moderate-to-low in the majority of included studies, however six studies were considered to have a high risk of bias (Supplementary Table 2). We performed sub-group meta-analyses, excluding the studies assessed as having a high risk of bias (Supplementary Fig. S2), which showed that removal of studies with a high risk of bias did not materially alter the outcome of the meta-analyses for any of the outcomes, therefore all studies were included. Most studies reported non-significant differences in maternal baseline characteristics between groups (including maternal age, BMI and glycemic control) (Supplementary Table S3).

We assessed the likelihood of single studies significantly influencing the overall results using leave-one-out (LOO) analysis. For the primary comparison of metformin vs. any other treatment across all indications, meta-analyses were robust to the omission of single studies (Supplementary Fig. S3), with the exception of cesarean section, RBS, and maternal hypoglycaemia, decreasing our confidence in the robustness of these findings. Funnel plots for all outcomes were assessed visually (Supplementary Fig. S4); there were no obvious asymmetries in the plots for any study outcomes. Eggers testing demonstrated a low likelihood of publication bias with respect to the primary comparisons (Supplementary Table S5).

GRADE analysis (certainty of evidence)

The majority of outcomes were classified as having a moderate certainty of evidence (Supplementary Fig. S5; primary outcomes and Supplementary Fig. S6; secondary outcomes), with one outcome having a high certainty of evidence (pregnancy-induced hypertension).

Synthesis of results

Gestational weight gain

Pregnant women randomized to metformin versus any other treatment had on average 1.57kg less gestational weight gain; (95%CI: 0.97kg to 2.17kg; I_2=86%, p<0.00001) (Figure 1) based on 14 studies including 3004 pregnancies. In the sub-group where the indication for randomization was maternal obesity, there was on average 0.89kg less GWG (p=0.04) in metformin-treated women compared to those randomized to placebo (2 studies [21,22] n=813) (Table 1). In the sub-group where the indication for randomization was PCOS, there was significantly less GWG (p<0.0001) in metformin-treated women compared to those randomised to placebo (1 study [23] n=398) (Table 1). In the sub-group of women with diabetes in pregnancy (11 studies [24-34] n=1793), randomization to metformin also resulted in significantly less GWG (p<0.0001), an effect that remained significant and of similar magnitude when further analysed by treatment type (Table 2).

Table 1: Effect of metformin intervention in women with maternal obesity/PCOS.

Effects size estimate (95% CI) or odds ratio (95% CI). GDM=gestational diabetes mellitus; GWG=gestational weight gain; Het=heterogeneity; PCOS=polycystic ovary syndrome; PIH=pregnancy-induced hypertension.

Outcome		Effect size estimate (95% CI) or OR (95% CI)	P value	Studies	N	Het I_2	Het. P value
GWG (kg)	maternal obesity	-0.89 (-0.04 - -1.75)	.04	2	813	0%	.42
	PCOS	-2.40 (-3.38- -1.42)	<.0001	1	398	N/A	N/A
PIH	maternal obesity	1.22 (0.80-1.84)	.36	3	1354	0%	.65
	PCOS	1.26 (0.59-2.68)	.55	1	478	N/A	N/A
Pre-eclampsia	maternal obesity	0.60 (0.21-1.76)	.34	4	1620	79%	.002
	PCOS	0.76 (0.43-1.39)	.37	3	818	59%	.09
Gestational age (weeks)	maternal obesity	0.08 (-0.16-0.31)	.53	2	948	28%	.24
	PCOS	NO STUDIES	-	-	-	-	-
Preterm birth	maternal obesity	1.17 (0.80-1.71)	.42	4	1620	0%	.43
	PCOS	0.45 (0.24-0.83)	.01	3	818	0%	.95
Cesarean section	maternal obesity	0.78 (0.63-0.98)	.03	3	1352	0%	.58
	PCOS	1.06 (0.74-1.52)	.75	2	748	0%	.74
Nausea	maternal obesity	1.43 (1.11-1.84)	.006	3	1201	36%	.21
	PCOS	1.60 (0.75-3.45)	.23	1	240	N/A	N/A
Vomiting	maternal obesity	1.41 (1.08-1.83)	.01	3	1201	35%	.22
	PCOS	1.85 (0.45-7.58)	.39	1	240	N/A	N/A
Diarrhoea	maternal obesity	2.34 (1.39-3.94)	.001	3	1201	67%	.05
	PCOS	6.47 (2.17-19.29)	.0008	1	240	N/A	N/A
Abdominal pain	maternal obesity	0.98 (0.66-1.44)	.91	3	1201	0%	.99
	PCOS	0.50 (0.19-1.32)	.16	1	240	62%	.11
Bloating	maternal obesity	NO STUDIES	-	-	-	-	-

	PCOS	1.32 (0.73-2.38)	.36	1	240	N/A	N/A
Constipation	maternal obesity	1.11 (0.76-1.63)	.59	3	797	15%	.28
	PCOS	NO STUDIES	-	-	-	-	
Headache	maternal obesity	1.17 (0.82-1.69)	.39	2	797	69%	.07
	PCOS	NO STUDIES	-	-	-	-	-
GDM	maternal obesity	1.16 (0.68-1.96)	.59	2	1208	68%	.08
	PCOS	1.00 (0.71-1.42)	.99	3	746	0%	.54

Table 2: Effect of metformin intervention in women with maternal obesity/PCOS.

Effects size estimate (95% CI) or odds ratio (95% CI). Het; heterogeneity, GWG; gestational weight gain, PIH; pregnancy-induced hypertension, FBS; fasting blood glucose, RBS; random blood glucose.

Outcome		Effect size estimate (95% CI) or OR (95% CI)	P value	Studies	N	Het. I_2	Het. P value
GWG (kg)	All treatments	-1.58 (-2.28- 0.87)	<.0001	11	1793	89%	<.00001
	Glyburide only	-1.67 (-3.07- -0.26)	.02	3	376	0%	0.45
	Insulin only	-1.57 (-2.44- -0.71)	.0004	7	935	93%	<.00001
Pre-eclampsia	All treatments	0.65 (0.45-0.94)	.02	14	3301	40%	0.06
	Glyburide only	0.50 (0.15-1.70)	.26	2	253	0%	0.67
	Insulin only	0.67 (0.44-1.00)	.05	12	3048	49%	0.03
PIH	All treatments	0.82 (0.61-1.11)	.20	10	2806	0%	0.71
	Glyburide only	1.16 (0.42-3.17)	.78	1	159	N/A	N/A
	Insulin only	0.79 (0.56-1.12)	.18	8	1716	0%	0.66
Preterm birth	All treatments	1.07 (0.67-1.70)	.55	19	4443	66%	<.00001
	Glyburide only	1.16 (0.50-2.69)	.73	3	463	0%	0.48
	Insulin only	0.93 (0.56-1.54)	.78	15	3519	71%	<.0001
Gestational age (weeks)	All treatments	-0.12 (-0.26-0.01)	.08	16	2870	47%	0.02
	Glyburide only	-0.17 (-0.40-0.07)	.16	4	525	0%	0.51
	Insulin only	-0.16 (-0.30- -0.01)	.03	12	2345	53%	0.01
Caesarean section	All treatments	0.97 (0.83-1.12)	.33	22	3708	30%	0.10
	Glyburide only	1.17 (0.83-1.64)	.38	5	684	30%	0.22
	Insulin	0.89 (0.76-1.04)	.14	17	2832	33%	0.09

	only						
FBS	All treatments	0.02 (-1.74-1.79)	.98	19	3673	92%	<.00001
	Glyburide only	-1.27 (-6.37-3.84)	.63	4	525	85%	.0002
	Insulin only	-0.13 (-2.21-1.95)	.90	14	3008	94%	<.00001
RBS	All treatments	-0.89 (-2.22-0.43)	.19	18	3610	74%	<.00001
	Glyburide only	-0.90 (-3.86-2.07)	.55	4	525	0%	0.41
	Insulin only	-0.92 (-2.39-0.54)	.22	12	2895	80%	<.00001
Maternal hypo.	All treatments	0.47 (0.28-0.80)	.005	6	1149	17%	.31
	Glyburide only	2.00 (0.18, 22.54)	.57	1	149	N/A	N/A
	Insulin only	0.31 (0.16-0.60)	.0005	4	530	0%	.95

Pre-eclampsia

Pregnant women randomized to metformin had a significant reduction in the likelihood of pre-eclampsia compared to those randomised to any other treatment (OR 0.65, 95%CI: 0.47 to 0.91; I_2=52%, p=0.01) (Figure 2); based on 21 studies including 5979 pregnancies. There were no significant differences in the risk of pre-eclampsia in the sub-group analyses where the indication for randomization was maternal obesity (4 studies [21,22,35,36] n=1620) or PCOS (3 studies [23,37,38] n=818) (Table 1). However, in the sub-group of women with diabetes in pregnancy, randomization to metformin resulted in significantly decreased likelihood (p=0.02) of pre-eclampsia (14 studies [24-26,28,29,31,39,40-46] n=3301) (Table 2). Effect sizes were similar across all diabetes in pregnancy groups, although these failed to reach statistical significance in sub-groups (Table 2).

Pregnancy-induced hypertension

There was no difference in the likelihood of pregnancy-induced hypertension (PIH) between women randomized to metformin versus any other treatment (OR 0.97, 95%CI: 0.77 to 1.22; I_2=0%, p=0.81) (Figure 3) based on 14 studies including 4189 pregnancies. There were no significant differences in the risk of PIH in any of the sub-group analyses where the indication for randomization was maternal obesity (3 studies [21,22,35] n=1354), PCOS (1 study [23] n=478) (Table 1) or diabetes in pregnancy (10 studies [24,26,29,30,34,39,41,45,46,47] n=2806) (Table 2).

Preterm birth (all-cause, spontaneous and iatrogenic)

There was no difference in the overall likelihood of preterm birth between women randomized to metformin versus other interventions (OR 0.91, 95%CI: 0.67 to 1.22; I_2=58%, p=0.52) (Figure 4 a) based on 27 studies including 6959 pregnancies. When sub-group analysis was performed separating spontaneous and iatrogenic preterm birth, there was no significant effect of randomization to metformin versus other treatments on likelihood of either type of preterm birth (Figures 4 b & 4 c).

In women with maternal obesity (4 studies [21,22,35,36] n=1620) (Table 1) or diabetes in pregnancy (19 studies [26,29-31,33,34,39-45,47-52] n=4443) (Table 2), the likelihood of preterm birth was not different between women randomized to metformin versus other treatments. However, in the sub-group where the indication for randomization was PCOS (3 studies [23,37,38] n=827), randomization to metformin was associated with reduced likelihood of preterm birth (p=0.01) (Table 1).

Gestational age at delivery

Randomization to metformin vs. any other treatment did not significantly influence gestational age at delivery (-0.08 weeks, 95%CI: -0.21 weeks to 0.04 weeks; I_2=48%, p=0.19) (Figure 5), based on 18 studies including 3818 pregnancies. There was no significant difference in gestational age at delivery where the indication for randomization was maternal obesity (2 studies [21,22] n=948) (Table 1) or diabetes in pregnancy (16 studies [24,25,26,27,28,29,31,32,33,41,43,44,45,46,53,54] n=2870) (Table 2). No studies reported gestational age at delivery in the sub-group of women with PCOS (Table 1).

Cesarean section (all cause, emergency and elective)

There was a trend to suggest lower likelihood of delivery by cesarean section in women randomized to metformin versus other treatments (OR 0.86, 95%CI: 0.73 to 1.01; I_2=46%, p=0.06) (Figure 6 a) based on 29 studies including 6122 pregnancies. When sub-group analysis was performed separating emergency and elective cesarean section, there was no significant effect of randomization to metformin versus other treatments on likelihood of either type of cesarean section (Figures 6 b & 6 c).

In the sub-group where the indication for randomization was maternal obesity (3 studies [21,22,35] n=1352), randomization to metformin (vs. placebo) was associated with reduced likelihood (p=0.03) of cesarean section (Table 1). Where the indication for randomisation was PCOS (2 studies [23,38] n=1352) (Table 1) or diabetes in pregnancy (22 studies [24-33,39,40,42,44-50,53,54] n=3516) (Table 2) randomization to metformin versus other treatments did not alter likelihood of cesarean section.

Side effects

Randomisation to metformin versus placebo was associated with increased likelihood of nausea, vomiting and diarrhoea, but not abdominal pain or non-gastrointestinal side-effects (Supplementary Table 6). Nausea, vomiting, and diarrhoea were all significantly increased when the indication for metformin randomization was maternal obesity (Table 1). However, when the indication for

randomization was PCOS, fewer studies were available for analysis and only the likelihood of diarrhoea was significantly increased with metformin versus placebo (Table 1). Trials involving women with diabetes in pregnancy either did not report gastrointestinal side effects in the insulin arm, or reported zero values. Between 2-46% of women randomised to metformin for treatment of diabetes in pregnancy reported gastrointestinal side-effects (weighted average incidence 12.5%; Appendix 15) and 0-6% of women stopped medication due to these side effects (weighted average incidence 14.3%), (Supplementary Table S7).

GDM in participants randomised for indications other than diabetes

Randomization to metformin vs. any other treatment did not alter the likelihood of subsequent GDM diagnosis (OR 1.07, 95%CI: 0.87 to 1.33; I_2=0%, (p=0.52) (Supplementary Fig. S7), based on 7 studies including 2063 pregnancies. Whether the indication for randomization was maternal obesity (3 studies [21,22,35] n=1206) or PCOS (3 studies [23,37,38] n=746) (Table 1), randomisation to metformin did not alter likelihood of GDM.

Glycemic control in diabetes in pregnancy

There was no significant difference in FBS (19 studies, n=3673) or RBS (18 studies, n=3610) measurements in women with diabetes in pregnancy randomised to metformin versus other treatments (Table 2). Maternal hypoglycemia was significantly (p=0.005) less likely in women randomized to metformin vs. other treatments (Supplementary Fig. S8), based on 6 studies including 1149 pregnancies [30,34,45,46,49,53], however this effect is driven entirely by studies where insulin was the comparator group (Table 2).

Discussion

Our results demonstrate that exposure to metformin versus other treatments during pregnancy reduced GWG, an effect consistently observed across all sub-group and sensitivity analyses. The likelihood of developing pre-eclampsia was also significantly reduced in women randomized to metformin compared to other treatments, although this effect was driven by trials involving women with diabetes in pregnancy. Randomization to metformin was associated with a borderline significant reduction (p=0.06) in the likelihood of cesarean section in women randomized to metformin compared to other treatments, an effect which was driven by women with obesity compared to placebo. Significantly reduced likelihood of preterm birth was only observed in women with PCOS, randomized to metformin compared with placebo. Women randomised to metformin versus insulin for treatment of diabetes in pregnancy had a significantly lower likelihood of experiencing hypoglycemia. However the likelihood of gastrointestinal symptoms (nausea, vomiting and diarrhoea) was significantly increased in women randomised to metformin versus other treatments. Other maternal outcomes including pregnancy-induced hypertension, gestational age at delivery, incidence of GDM and glycemic control were not significantly different in metformin-treated compared to other treatment groups.

A major strength of this study is the breadth of outcomes affecting women during pregnancy that have been included. Our focus on maternal outcomes complements our previous work performed on fetal and childhood outcomes [12,13]. We also performed extensive sub-group and sensitivity evaluation of our conclusions.

The drawing of definitive conclusions from our meta-analysis is limited by both the quantity and quality of the studies available. In particular, there was a paucity of trials randomizing women with PCOS (3 studies, n=930 women) or maternal obesity (4 studies, n=1485 women), limiting our confidence in conclusions relating specifically to treatment for these indications and therefore we urge a conservative view with regard to interpretation of this sub-group analyses. No randomized trials were found that compared metformin specifically with dietary/lifestyle intervention, although several studies included these interventions for both trial arms. Our search results highlight the need for more high-quality studies investigating metformin use during pregnancy. A further reason for caution in interpretation is the high heterogeneity in dose and starting gestation of metformin treatment between the various included studies.

Overall, metformin use during pregnancy is associated with a greater risk of experiencing gastrointestinal side-effects than placebo or other treatments. Gastrointestinal symptoms are reported in 20-30% of patients treated with metformin outside of pregnancy [56]. A variety of mechanisms are proposed including bile-salt malabsorption, gut serotonin secretion, and alterations to glucose and incretin metabolism [56]. These symptoms may be more common in women [58] and more difficult to tolerate during pregnancy due to concomitant pregnancy-related nausea, vomiting, and food aversions [57,58].

Clear evidence of benefit from randomisation to metformin across all sub-groups is limited to a reduction in GWG, which may be related to direct actions of metformin which can inhibit food intake, via increased concentration of growth/differentiation-factor-15 (GDF15) [59]. Excessive GWG is associated with perinatal complications including increased risk of fetal growth anomalies, risk of GDM, cesarean birth and pre-eclampsia [34,60]. Moreover, increased GWG is associated with long-term (later in life) health risks to the mother including post-partum weight retention, obesity [61,62] and increased risk of developing type 2 diabetes [63] and cardiovascular disease [64]. Limiting GWG may also improve outcomes for future pregnancies [65]. The average weight gain observed in pregnancies affected by GDM is approximately 9kg [60] therefore a reduction of 1.55kg (17%, as observed here) constitutes a potentially clinically significant reduction in total GWG.

The likelihood of pre-eclampsia was reduced in women with diabetes in pregnancy randomized to metformin versus other treatments. Several studies have reported a higher incidence of pre-eclampsia in women with GDM compared to those with normal glucose tolerance [66]; it is thus possible that the impact of metformin in reducing the likelihood of pre-eclampsia may only be detectable in populations with higher baseline risk. Mechanistically, metformin may prevent pre-eclampsia via reduction of anti-angiogenic factors, improvements of endothelial function via actions on the mitochondria and/or via actions through the mammalian target of rapamycin (mTOR) pathway by modification of cellular

homeostasis and energy deposition [67]. Previous meta-analyses have explored the impact of metformin on pre-eclampsia risk, with mixed results [18,19,68]. At least one previous meta-analysis that included both GDM and non-GDM pregnancies and analysed both randomized and observational data [68] found no significant effect of metformin on pre-eclampsia risk, which is in keeping with our observation that pre-eclampsia risk is not reduced in euglycemic pregnancies.

Our finding that metformin reduces the rate of cesarean section in obese women may relate to our previous finding of lower birth weight associated with randomization to metformin, [12] as there is increased likelihood of vaginal delivery with smaller fetuses. Maternal obesity is associated with increased birth weight [69] hence the impact of metformin in reducing fetal size and thus decreasing the risk of cesarean section may be amplified in this sub-group.

In weighing the risks and benefits of metformin treatment in pregnancy to the materno-fetal dyad, our meta-analysis highlights largely neutral or positive maternal outcomes, with the notable exception of increased likelihood of gastrointestinal side effects. From the fetal point of view however, it has previously been demonstrated that randomisation to metformin treatment for GDM is associated with increased risk of low birth-weight followed by accelerated growth in childhood [12,13], independent of maternal glycemic control [13]. It is particularly important to carefully consider the impacts of metformin treatment on both mother and baby as there are other suitable alternative treatments for GDM and no necessity for drug treatment for PCOS or maternal obesity in pregnancy. Moreover, there are other methods of controlling GWG, for example diet and lifestyle modification. Individual pregnant women may weigh the importance of limiting gestational weight gain or of avoiding gastrointestinal symptoms differently, and these findings may thus influence decision-making around metformin treatment in pregnancy.

Data availability

The data for this meta-analysis are freely available. The PROSPERO protocol can be found at https://www.crd.york.ac.uk/prospero CRD ID: CRD42020167692.

Declarations

Author contributions

JLT-A collected the data, contributed data or analysis tools, performed the analysis and wrote the paper. SEO conceived and designed the analysis and wrote the paper. CEA conceived and designed the analysis, contributed data or analysis tools, performed the analysis and wrote the paper.

Additional information

Competing interests: The author(s) declare no competing interests.

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Figures

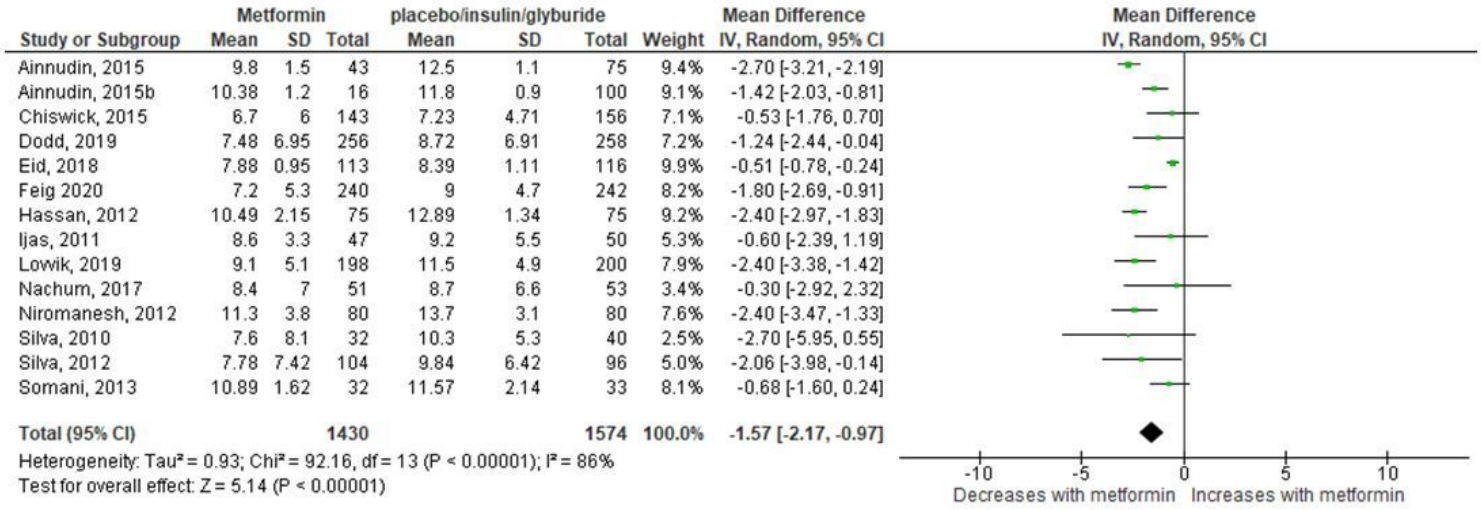

Figure 1

Effect of metformin randomization upon gestational weight gain (throughout pregnancy); (all indications). Mean difference IV, random-effects model, 95% CI.

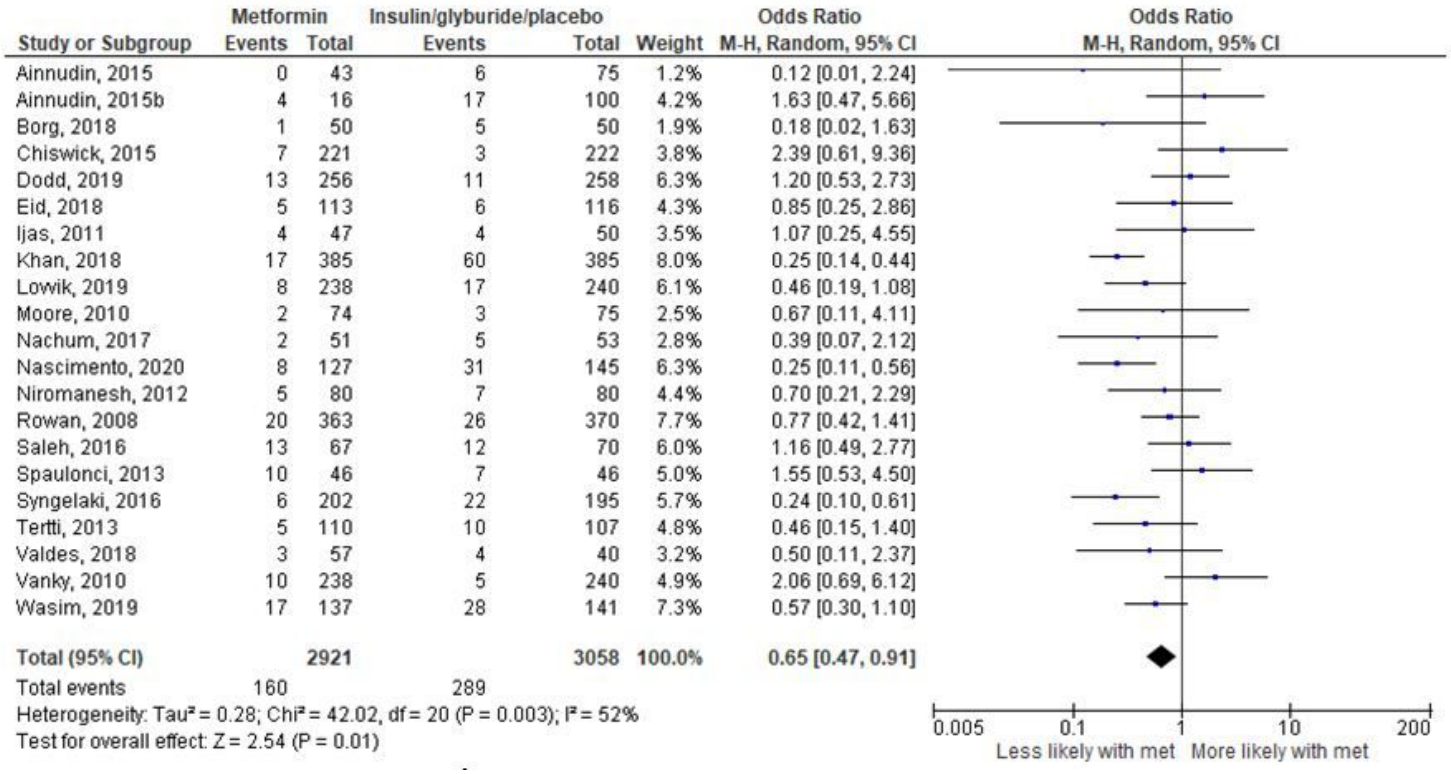

Figure 2

Effect of metformin randomization upon pre-eclampsia (all indications). Odds Ratio, random-effects model, 95% CI.

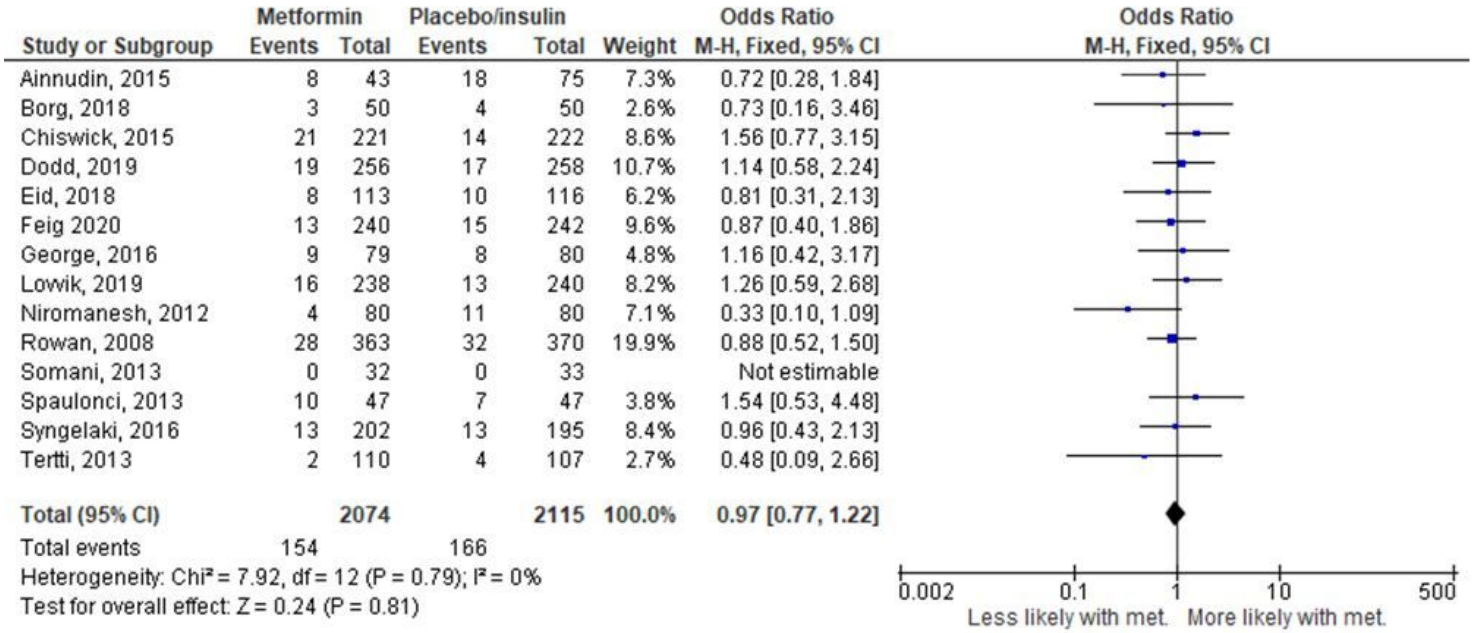

Figure 3

Effect of metformin randomization upon pregnancy-induced hypertension (all indications). Odds Ratio, fixed-effects model, 95% CI.

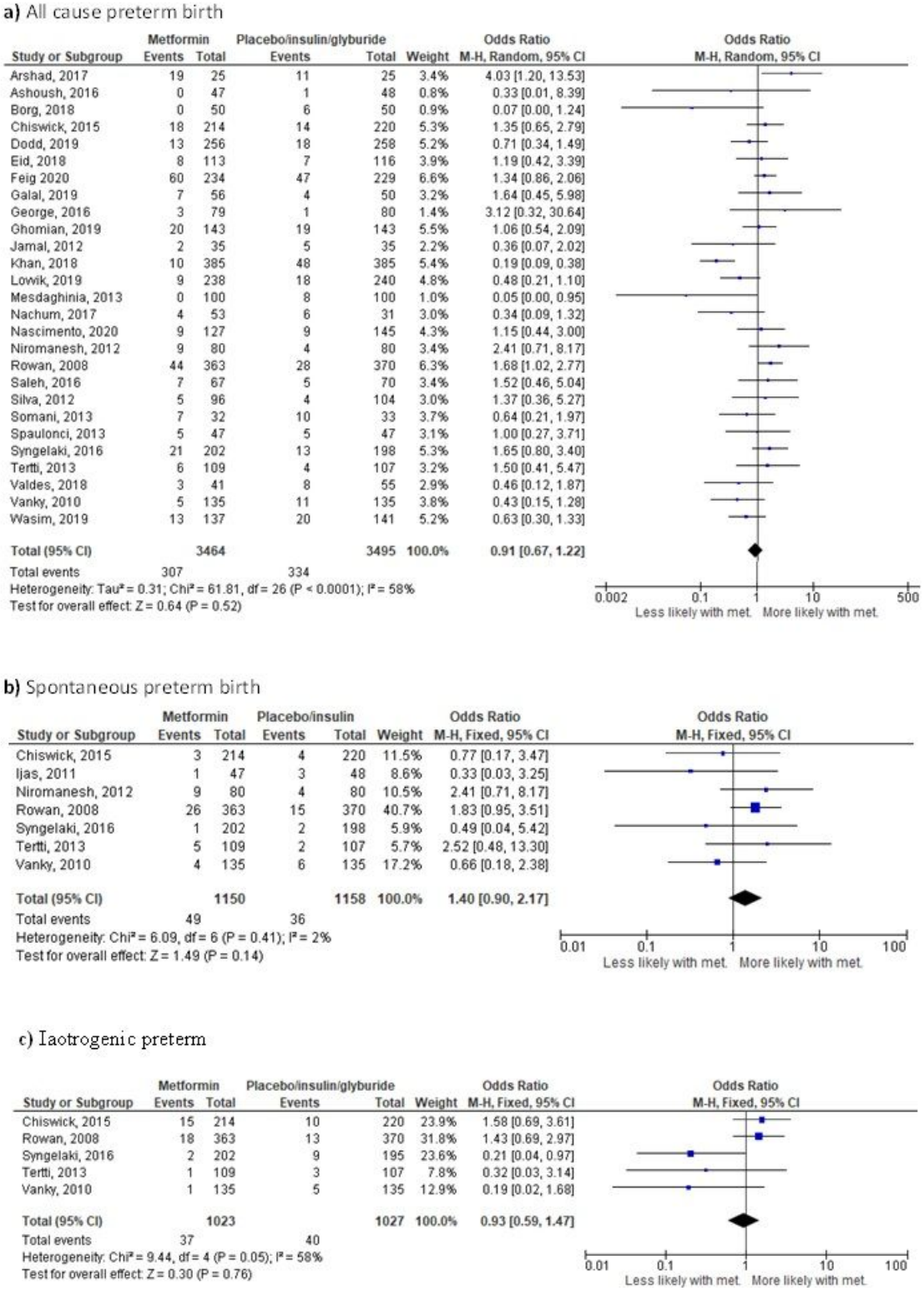

Figure 4

Effect of metformin randomization upon pre-term birth (all indications) a) All-cause, b) Spontaneous and c) Iaotrogenic. Odds Ratio, (95% CI). Fixed-effects model for a) and b), random-effects model for c).

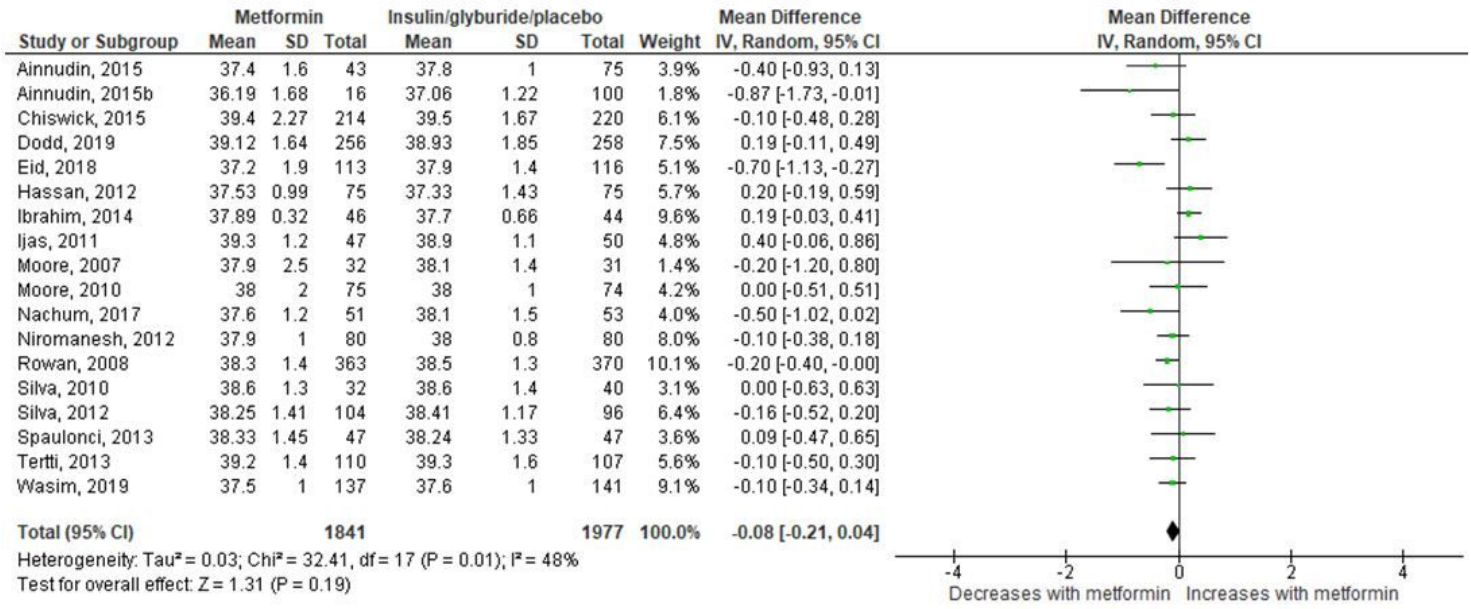

Figure 5

Effect of metformin randomization upon pregnancy-induced hypertension (all indications). Odds Ratio (95% CI), random-effects model.

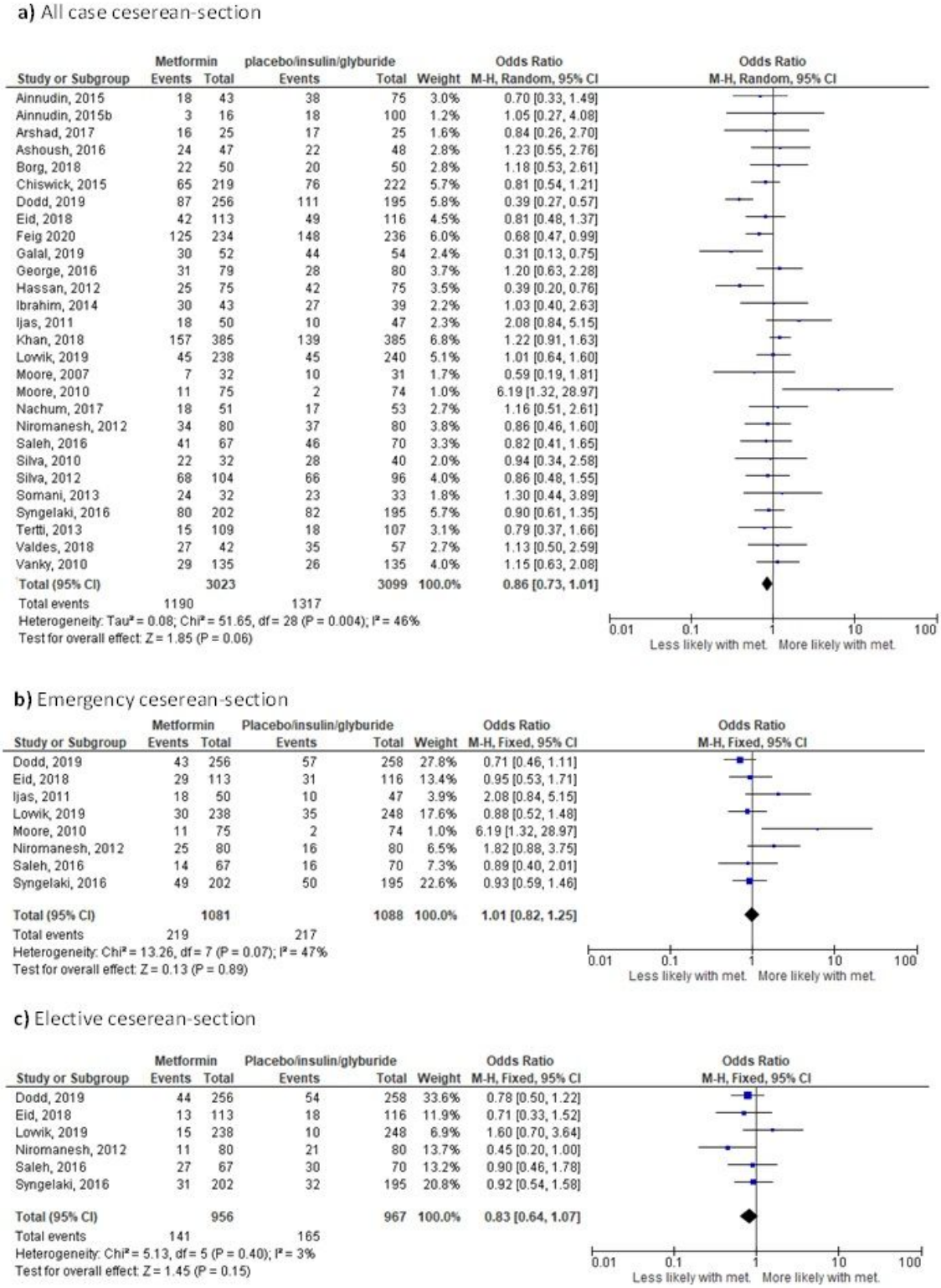

Figure 6

Effect of metformin randomization upon cesarean section (all indications). Odds Ratio (95% CI). Random-effects model for a) and fixed-effects model for b) and c).

Supplementary Files

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