FETAL OUTCOMES IN PREGNANCIES COMPLICATED BY TYPE 1 DIABETES MELLITUS TREATED WITH MULTIPLE DAILY INJECTIONS OF INSULIN AND INSULIN PUMPS

A SYSTEMATIC REVIEW AND META-ANALYSIS

53rd EASD Annual Meeting of the European Association for the Study of Diabetes
Lisbon, Portugal 11-15 September 2017

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Introduction

Uncontrolled type 1 diabetes mellitus (T1DM) can be a leading cause of congenital malformations, metabolic and functional disorders, respiratory distress syndrome, premature birth, and perinatal mortality and many others. Therefore, an adequate glycemic control in pregnant women with type 1 diabetes mellitus (T1DM) has a potential for minimizing the risk of maternal or fetal complications, thus constituting important issue in diabetes management.

In clinical practice, glycemic control in patients with T1DM is approached either by multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII). Randomized clinical trials have demonstrated superiority of CSII over MDI in the general T1DM population in terms to glycemic control and the reduction of severe hypoglycemic episodes. However, it is not clear whether there are any differences in fetal outcomes in pregnancies complicated by type 1 diabetes (T1DM) that are treated with MDI and those treated with CSII.

Method

Systematic search in databases of scientific literature (MEDLINE, EMBASE, CENTRAL), conference materials (*American Diabetes Association, European Association for the Study of Diabetes*) and registries of clinical trials was performed in order to identify fulfilling following inclusion criteria:

- Population: pregnant women with T1DM who received insulin therapy before pregnancy, according to MDI or CSII scheme;
- Intervention: regular human insulin (RHI) or rapid-acting insulin analogs (RAA) administrated via CSII;
- Comparator: RHI or RAA administrated via MDI;
- Methodology:
  - randomized controlled trials including at least 10 women in each arm;
  - observational studies including at least 10 women in each arm;
- Outcomes: gestational age, Apgar score; premature birth, perinatal mortality, congenital malformation, caesarian section, macrosomia, large for gestational age (LGA), small for gestational age (SGA), shoulder dystocia, respiratory diseases syndrome, hypoglycemia, hypocalcaemia, hiperbilirubinemia, polycythemia;

Two authors independently reviewed the articles at each stage of the selection.

Statistical Analysis

Results of each trial were expressed as relative risk (RR) with 95% confidence intervals (CI).

Heterogeneity between studies was assessed with Cochrane Q test assuming p <0.1 as statistically significant. Heterogeneity was quantitated with I^2 statistics.

Meta-analyses were performed according to Mantel-Haenszel fixed effect model in case of homogenous data or with DerSimonian random effect model if hetero¬geneity was significant. Results were considered significant when p for overall effect <0.05.

Results

Study flow

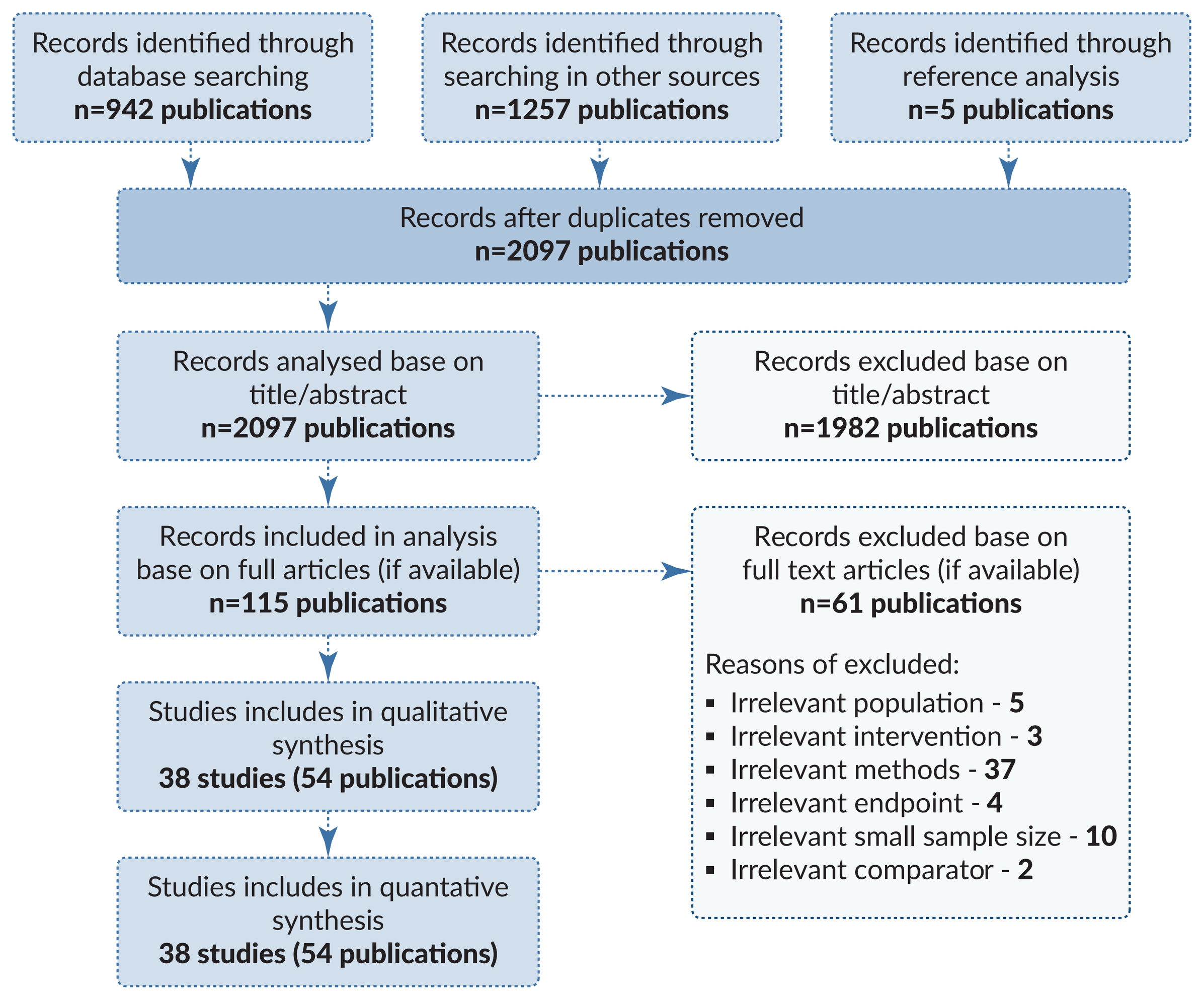
The systematic search resulted in 2097 unduplicated records. Following screening of abstracts and titles a total number of 115 papers were selected for the assessment of eligibility based on full texts. Finally, 38 RCTs reported in 54 publications were considered relevant and were included in both quantitative and qualitative analysis (**Figure 1**).

Study characteristic

The systematic search retrieved 38 original papers meeting the eligibility criteria, including 23 full text articles [1–23] and 15 conference abstracts [24–38]. Only 4 studies were RCTs, while remaining 34 positions were carried out according to observational design.

Studies were conducted in 17 countries, most often in USA (5), Great Britain (5), Italy (4) and Poland (3). Sample size of respective positions ranged from 22 to 688 patients and the total number of patients was 4499, of whom 1847 and 2509 received insulin therapy via CSII and MDI schemes, respectively. Methodological quality of RCTs ranged from 1 to 3 points, according to the 5-point Jadad score and was downgraded mainly due to open-label design. Credibility of non-randomized studies was assessed using The Newcastle-Ottawa Scale and granted from 4 to 9 points.

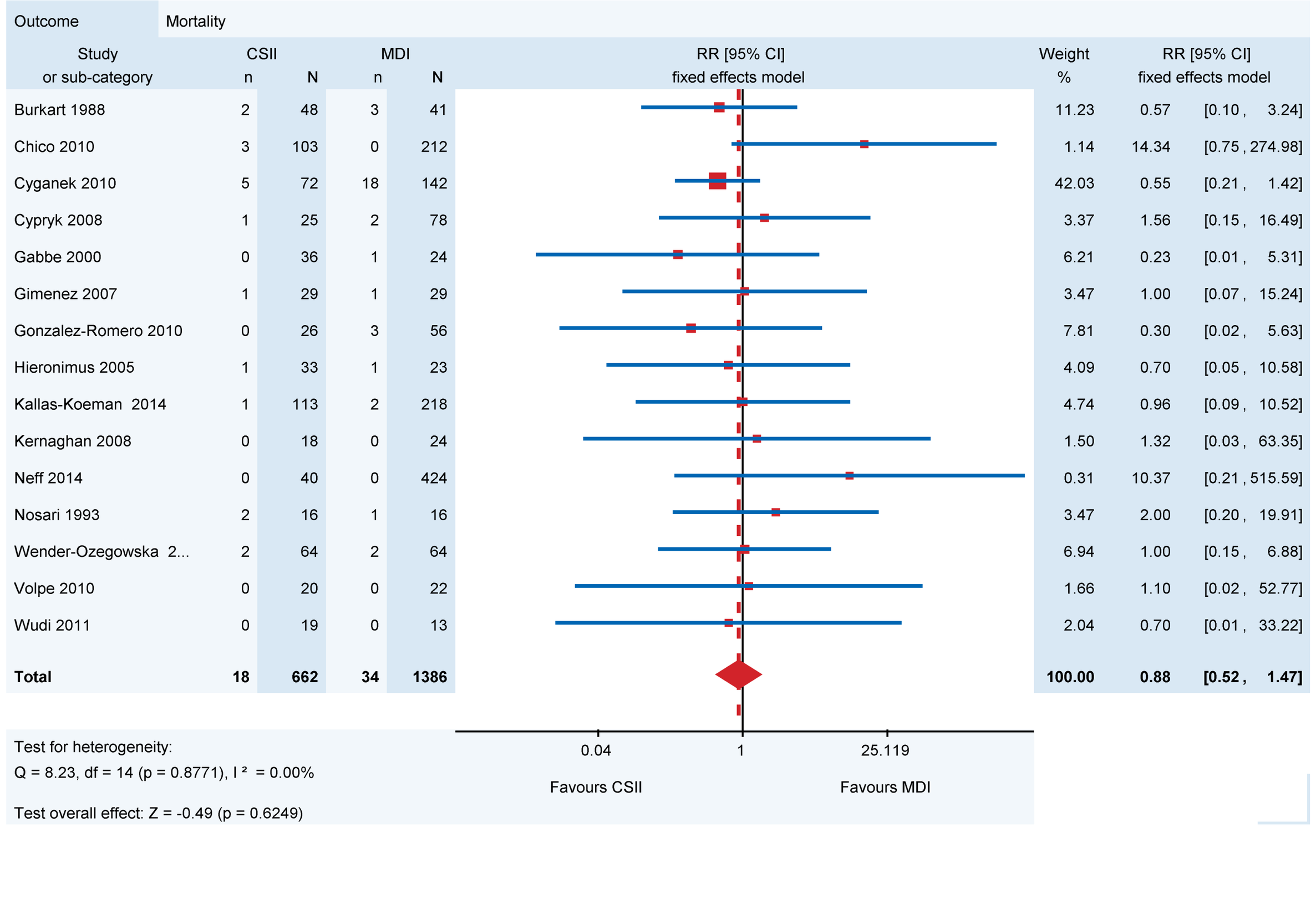
Figure 1. PRISMA diagram for publication flow



Perinatal mortality

Perinatal mortality was reported in 15 studies, which enrolled a total number of 2048 pregnant women.[2,4,6,7,9–14,19,20,22,23,38] Although some differences in reporting of fatal cases were noted between respective studies, most papers presented data regarding both intrauterine and neonatal deaths. Meta-analysis of all studies did not reveal statistically significant difference between CSII and MDI (RR = 0.88 [0.52, 1.47]) (**Figure 2**).

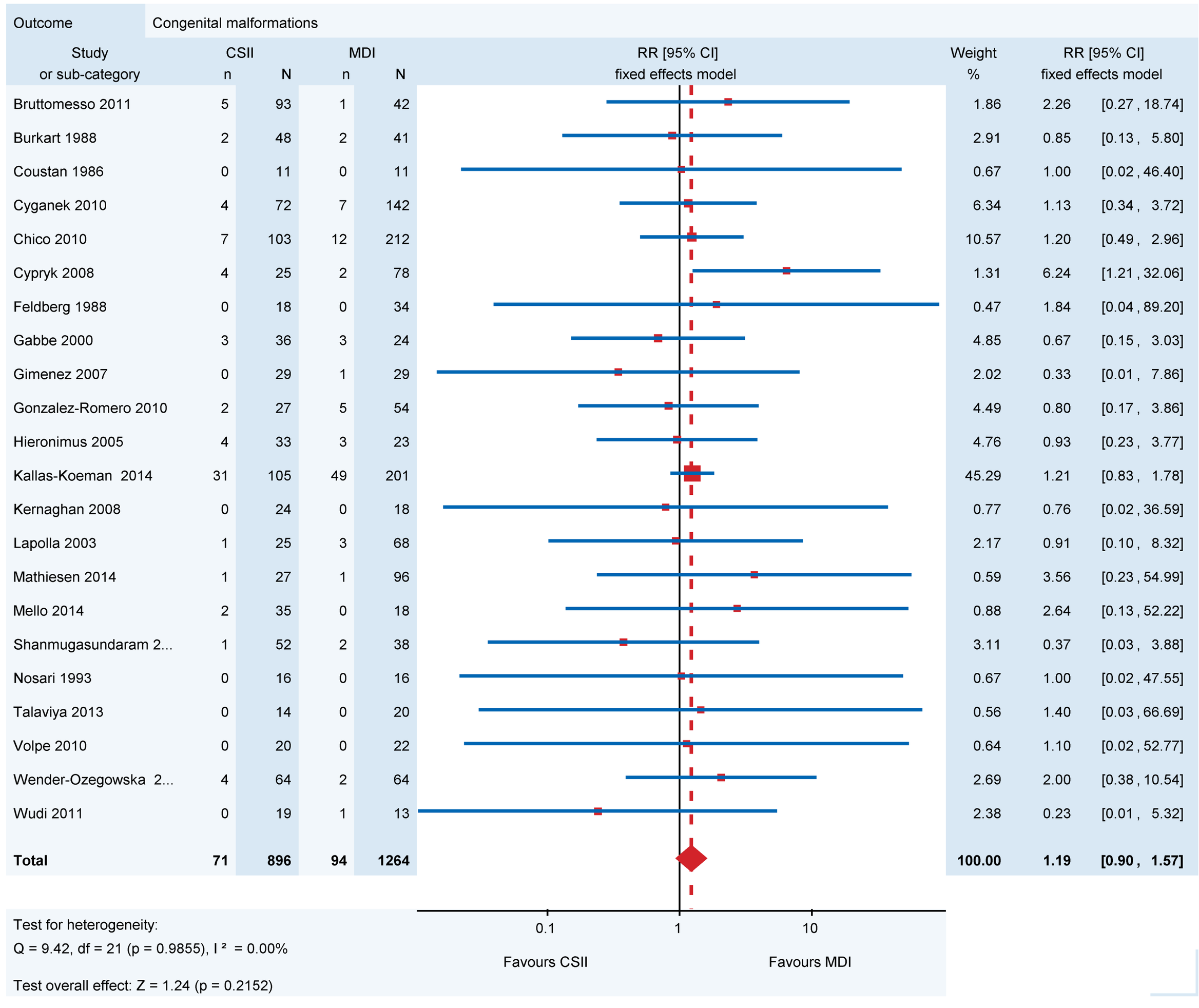
Figure 2. Risk of perinatal death for the comparison between CSII and MDI



Congenital malformation

The risk of congenital malformations was reported in 22 studies, which enrolled 2160 pregnancies.[1,2,4–14,16–18,20–23,34,38] Majority of studies reported malformations regardless of their severity or did not precisely described their definition. Single studies reported solely severe (Chico 2010, Mathiesen 2014) or mild cases (Gimenez 2007). One study (Kallas-Koeman 2014) reported the risk of both overall and severe malformations separately. No apparent between-study heterogeneity was revealed, therefore fixed-effect meta-analysis was preformed, which did not reveal statistically significant differences between both strategies of insulin administration (RR = 1.19 [0.90, 1.57]) (**Figure 3**).

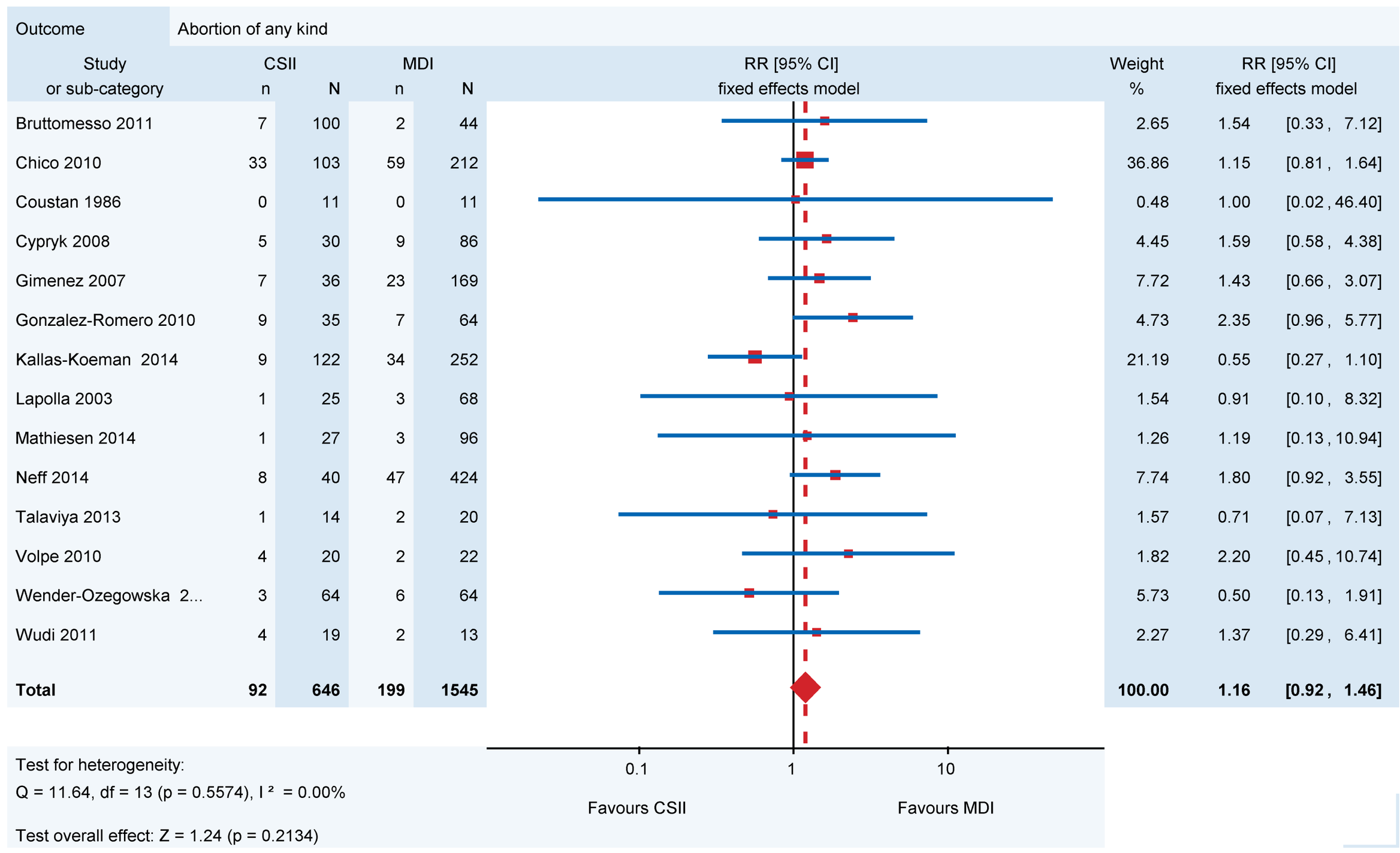
Figure 3. Risk of congenital malformations for the comparison between CSII and MDI



Abortions

The risk of any kind of abortion was reported in 14 studies including 2191 pregnancies, which did not reveal statistically significant differences between strategies of insulin administration (RR = 1.16 [0.92, 1.46], **Figure 4**). However, spontaneous abortions were observed more frequently in the CSII group (RR = 1.54 [1.05, 2.25]), which could be due to reporting bias as women in the MDI group booked later (8–9 vs 6 week) to antenatal clinics and therefore early cases probably were detected less often in the CSII group.

Figure 4. Risk of abortion of any kind for comparison between CSII and MDI

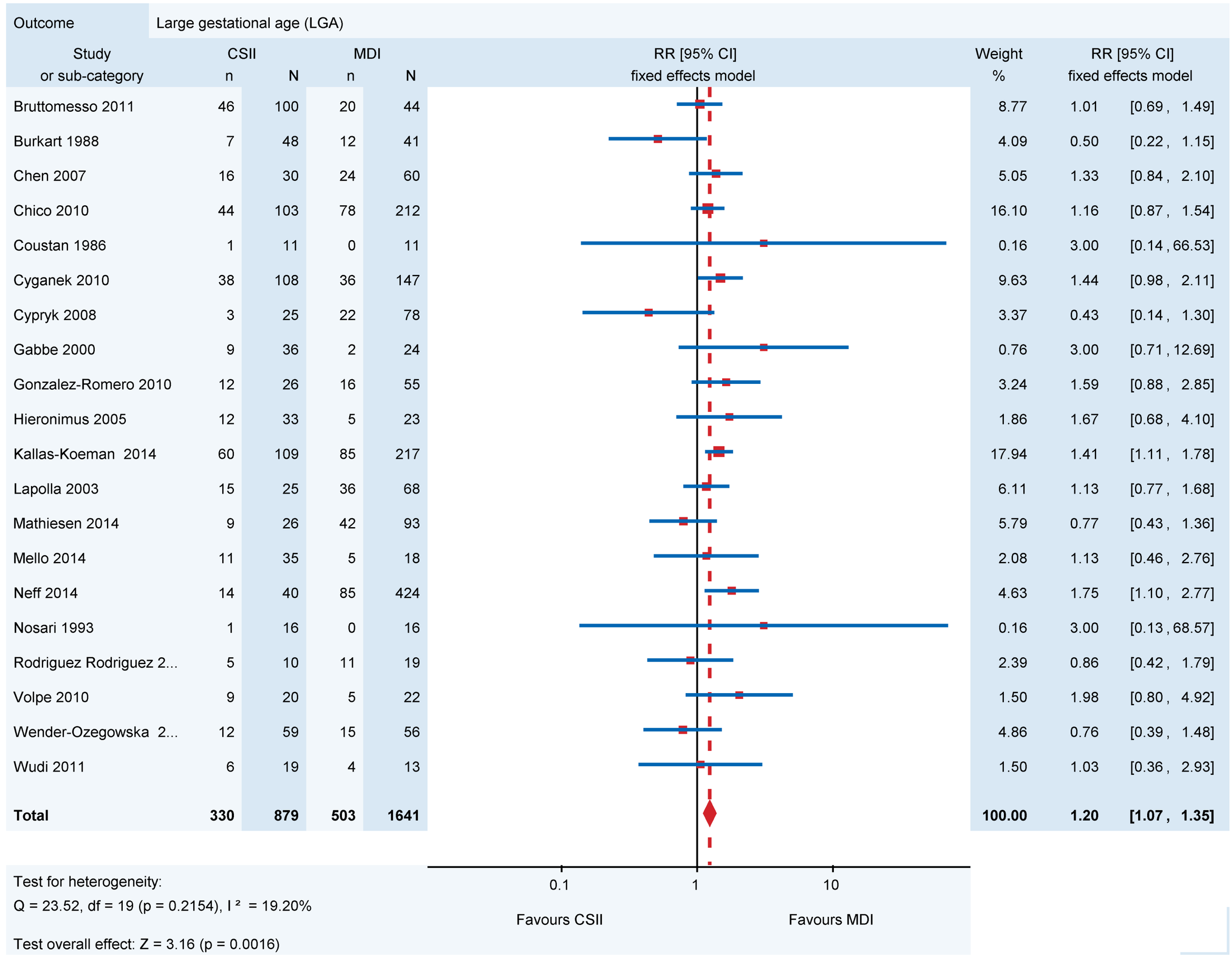


Large of gestational age and macrosomy

LGA was reported in 20 studies enrolling 2520 pregnancies and in most of them was defined as gestational body weight above the 90th percentile, however in one study data representative for over 95th percentile was presented, while some other did not present the definition of the outcome. Pooled estimates from all available studies indicate significantly -higher risk of LGA in CSII group when compared with MDI strategy (RR = 1.20 [1.07; 1.35]), with an acceptable between-study heterogeneity (p= 0.21, I^2=19%) (**Figure 5**). Sensitivity analysis including only studies reporting LGA defined as body weight above the 90th percentile confirmed the outcomes of base-case meta-analysis showing elevated risk of LGA in CSII group (RR= 1.26 1.10, 1.44]), with comparable estimates for heterogeneity.

Overall number of 17 studies reported the risk of macrosomy using heterogeneous definitions. Meta-analysis of studies reporting macrosomy defined as body weight ≥4000 g revealed significantly higher risk of this complication in CSII group (RR = 1.32 [1.05, 1.65]) with no apparent between-trial heterogeneity (I^2 = 0%).

Figure 5. Risk of large for gestational age for the comparison between CSII and MDI



Neonatal complications and caesarian sections

No significant difference between CSII and MDI was noticed for the risk of cesarean section as well for neonatal complications, including respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, shoulder dystocia and ICU admissions (**Table 1**).

Conclusions

Both strategies of insulin delivery were characterized with similar risk of all analyzed fetal complications, with exception of the risk of LGA/macrosomia, which risk was significantly higher when mother had been receiving insulin therapy using CSII.

Tabele 1. Metaanalysis results for the risk of neonatal outcomes and caesarian sections

Endpoint	N studies	n/N CSII	n/N MDI	RR[95% CI]	P for overall effect	Hetero-geneity	References
Premature birth	20	232/931 (24.92)	570/2319 (24.58)	0.99 [0.86; 1.13]	0.8418	I^2=0.00	1–4,6,7,9,11–13, 16–24,33
Caesarian section	25	650/1056 (61.55)	1386/2358 (58.78)	1.04 [0.94; 1.15]	0.4182	I^2=56.82	1–9,11–13,16, 18–24,26,30,33,34
Apgar score <7 in 1st minute of life	2	14/64 (21.88)	21/61 (34.43)	0.55 [0.31; 0.98]	0.0429	I^2=0.00	8,9
Apgar score <7 in 5th minute of life	3	2/63 (3.17)	2/51 (3.92)	0.76 [0.16; 3.59]	0.7338	I^2=0.00	5,9,20
Low birth weight	16	31/789 (3.93)	87/1498 (5.81)	0.75 [0.50; 1.15]	0.1891	I^2=0.00	1–7,9,11–13, 16,19,22,23
Shoulder dystocia	3	5/152 (3.29)	9/187 (4.81)	0.90 [0.34; 2.41]	0.8319	I^2=5.16	1,13,16
Respiratory diseases syndrome	10	36/413 (8.72)	47/573 (8.20)	0.96 [0.63; 1.48]	0.8658	I^2=0.00	1,3–5,8,9,11, 16,20,23
Hypoglycemia	19	179/763 (23.46)	255/1102 (23.14)	0.98 [0.83; 1.16]	0.8104	I^2=23.82	1,3–5,7–9,11,13,16–18,20–23,30,32,37
Hypocalcemia	4	14/137 (10.22)	31/226 (13.72)	0.53 [0.31; 0.91]	0.0218	I^2=0.00	3,8,16,23
Hyperbilirubinemia	10	108/486 (22.22)	160/726 (22.04)	0.90 [0.72; 1.13]	0.3580	I^2=5.23	1,3,4,8,9,11, 13,16,22,30
Polycythemia	3	2/79 (2.53)	12/179 (6.70)	0.43 [0.12; 1.61]	0.2119	I^2=2.03	3,11,16
Intensive therapy	7	116/379 (30.61)	349/969 (36.02)	1.00 [0.84; 1.20]	0.9642	I^2=0.00	1,13,18,22, 24,26,34

Abbreviations

CI	*Confidence Intervals*	RB	*Relative Benefit*	RAA	*Rapid-Acting Insulin Analog*
CSII	*Continuous Subcutaneous Insulin Infusion*	RHI	*Regular Human Insulin*	T1DM	*Type 1 Diabetes Mellitus*
MDI	*Multiple Daily Insulin Injections*	RR	*Relative Risk*		

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