Am J Transl Res 2024;16(10):5191-5206
www.ajtr.org /ISSN:1943-8141/AJTR0158506

Review Article

The relationship between small for gestational age infants and maternal health: a meta-analysis

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Received June 17, 2024; Accepted September 11, 2024; Epub October 15, 2024; Published October 30, 2024

Abstract: Background: Fetal growth restriction, commonly referred to as small for gestational age (SGA) in academic contexts, is associated with increased mortality rates and significant health risks. Fetal development is influenced by a complex interplay of maternal factors, fetal characteristics, and placenta fiction. This meta-analysis explored the relationship between the prevalence of SGA infants and various maternal conditions, such as overall health, lifestyle choices, and underlying medical conditions. Methods: A comprehensive literature search on maternal factor and SGA was conducted in PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wan Fang, and China Biology Medicine (CBM) (SinoMed) databases from 2000 to 2022. The Cochrane Collaboration tool was adopted to assess the quality of the selected literature. STATA 14.0 software was used to perform the statistical analysis and graphic presentation. Meta-analysis was registered with International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) (202410045). Results: In total, 15 studies with 41,446 infants identified as being SGA were included in this Meta-analysis. SGA occurrence was not associated with maternal age or multi-parameter, but was related to abnormal Body Mass Index (BMI) (RR=2.23, 95% CI [1.24, 4.00]). Smoking was strongly associated with SGA (RR=3.09, 95% CI [1.53, 6.23]), while drinking was not. SGA was negatively correlated with pregestational diabetes (RR=0.59, 95% CI [0.40, 0.88]) and pregnancy complications, including gestational diabetes (RR=0.74, 95% CI [0.56, 0.97]), hypertension (RR=2.84, 95% CI [1.88, 4.29]) and preeclampsia (RR=2.38, 95% CI [1.77, 3.20]). Conclusions: Maternal risk factors, including BMI, smoking, pregestational diabetes, gestational diabetes, gestational hypertension, and preeclampsia, are associated with SGA.

Keywords: Small for gestational age, meta-analysis, pregnant diseases, maternal factors

Introduction

Birth weight is a critical indicator of fetal development and newborn health [1-3]. Fetal growth restriction is associated with many adverse perinatal outcomes; however, its etiology and diagnosis remain subjects of debate [4, 5]. The American College of Obstetricians and Gynecologists (ACOG) defines fetal growth restriction, commonly known as small for gestational age (SGA), as a condition in which a fetus's weight is below the tenth percentile for the corresponding gestational age [6]. In 2010, about 32.4 million infants were born with SGA in low- and middle-income countries, with the prevalence of preterm SGA being 46.8% in Asia and 4.2% in Africa. Most of the infants with SGA were born in India, Pakistan, Nigeria and Bangladesh [7].

Infants with SGA often experience impaired organ development due to intrauterine growth retardation, which can manifest as neonatal respiratory distress syndrome, necrotizing enterocolitis, intracranial hemorrhage and other diseases [8-10]. Therefore, SGA is one of the leading causes of perinatal infant mortality [11-13]. Furthermore, newborns with SGA are prone to experience metabolic syndrome, cardiovascular disease, short stature, and other diseases in adulthood compared to non-SGA infants [14, 15].

https://doi.org/10.62347/EGPT7518

The causes of SGA are complex and not yet fully understood. Recent research suggests that a combination of maternal, fetal, placental, umbilical cord, and paternal factors may influence the occurrence of SGA. Maternal conditions are crucial for fetal growth and development. Factors such as age, height, body mass index (BMI), nutrient, race, income, educational level, parity, and history of spontaneous abortion or miscarriage, can significantly impact the health of both the fetus and infants. Advanced maternal age is a known risk factor for SGA. A systematic review revealed that the risk of intrauterine growth restriction was three times higher in women over the age of 35 [16, 17]. Another study found that a low BMI would also increase the occurrence of SGA [18]. Voskamp et al. reported that women who have delivered an SGA infant are more likely to have subsequent SGA deliveries, and that women who were born as SGA themselves are likely to give birth to SGA infants [19, 20]. Many studies have confirmed that the occurrence of SGA is closely related to certain maternal habits, such as smoking, alcohol consumption, and drug use. Both active smoking and exposure to secondhand smoke before or during pregnancy can increase the risk of SGA [21-23]. In addition, the incidence of SGA is associated with excessive alcohol consumption, while low to moderate alcohol intake does not appear to increase this risk [24, 25]. Additionally, certain maternal health conditions can also elevate the risk of having an SGA infant. Expectant mothers who suffer from systemic illnesses like severe heart disease, chronic kidney issues, chronic hypertension, adrenal insufficiency, and antiphospholipid syndrome are at a heightened risk of giving birth to SGA babies [26-28]. Pregnancy complications, including gestational hypertension, diabetes, hypermesis gravidarum, placentae abruption, and preeclampsia, can also raise the risk of SGA [29-31].

Therefore, we conducted this meta-analysis to further verify the maternal factors influencing the incidence of SGA. The results from this analysis will provide suggestions for pregnant women to improve pregnancy outcomes and enhance the quality of their prenatal care.

Materials and methods

Search strategy

Following the PRISMA guidelines, a comprehensive literature search was conducted in the databases of Cochrane Library, PubMed, China National Knowledge Infrastructure (CNKI), Wan Fang and China Biology Medicine (CBM, SinoMed) from January 1, 2000, to October 1, 2022. We used the following search formulas: (((((((SGA) OR (fetal growth restriction)) OR (intrauterine growth retardation)) AND (mother)) OR (maternal)) AND (factor)) OR (risk)) AND (randomized controlled trial (RCT)). This Meta-analysis was registered at INPLASY (International Platform of Registered Systematic Review and Meta-Analysis Protocols, 202410045).

Selection criteria

Studies were eligible for inclusion based on the following criteria: (1) They included both SGA and non-SGA participant groups; (2) They were reported as randomized controlled trials (RCTs); (3) They provided adequate information necessary for conducting a meta-analysis; (4) They were published works with full-text access. Studies were excluded if they: (1) lacked a control group; (2) were animal studies, case reports, or reviews; (3) did not present relevant data; (4) were not accessible in full text; (5) involved duplicated data or research groups; or (6) were unrelated to the topic of interest.

Based on the inclusion and exclusion criteria, two authors (You Lu and Di Qie) independently reviewed all abstracts and articles to determine their eligibility for inclusion in this meta-analysis. In cases of disagreement, a third author (Jinhui Wu) was consulted to make the decision. All information extracted from the included articles were verified by all authors.

Data extraction

The information extracted from the selected studies included the first author's name, year of publication, country of origin, sample size, and various maternal health factors. These factors encompassed maternal age and BMI, history of multiple pregnancies, as well as detrimental

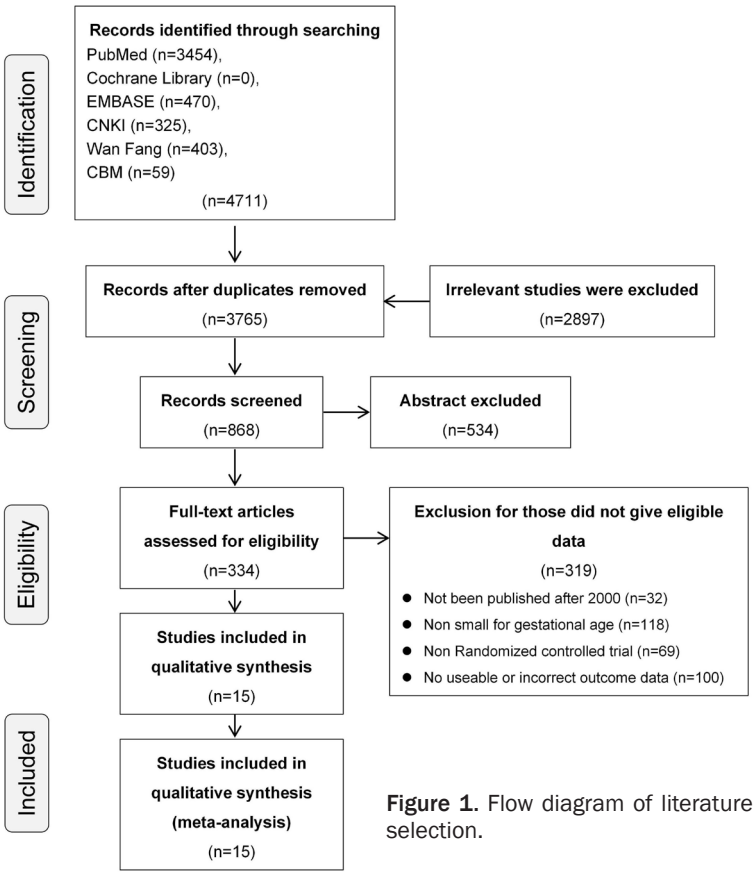

Figure 1. Flow diagram of literature selection.

habits such as smoking and alcohol consumption. Additionally, any maternal health issues, including pregnancy-related conditions and associated complications, were documented. All information was recorded in a data collection form and validated by You Lu and Di Qie. In cases of disagreement, Fan Yang was consulted to assess the conflicting data and help achieve consensus. The quality of the studies included in the analysis was evaluated utilizing the Cochrane Collaboration risk of bias tool encompassing the aspects of sequence generation, allocation concealment, blinding of participants and healthcare professionals, blinding of outcome assessors, handling of incomplete data, selective outcome reporting, and other potential sources of bias. Based on these criteria, studies were categorized into three risk categories: 'high risk', 'unclear risk', and 'low risk' [32].

Statistical analysis

All statistical analyses were conducted with STATA 14.0 (College Station, Texas, USA). The analysis focused on dichotomous data, with the association between maternal factors and SGA expressed as relative risk (RR) with 95% confidence intervals (CI). An RR was deemed significant when CI did not include 1. Heterogeneity across the studies was assessed using the I^2 statistic and *p*-values. I^2 less than or equal to 50% or p greater than 0.1 indicated no significant heterogeneity, and a fixed-effect model was employed. In the presence of significant heterogeneity (I^2 greater than 50% or *p*-value less than 0.1), a random-effects model was applied, and subgroup analyses were conducted to uncover potential sources of variance. Furthermore, in the presence of significant heterogeneity, a sensitivity analysis was conducted by sequentially excluding one study at a time to assess the robustness of the findings. To detect publication bias, Begg's test and a funnel plot analysis were performed, with publication bias considered significant if the *p*-value was below 0.05.

Results

Literature search and evaluation

Initially, 4,711 potentially relevant articles were obtained according to the search strategy. Among these, 334 studies with full-text access were carefully screened for eligibility, and 15 studies were finally included in this meta-analysis (**Figure 1**). As shown in **Table 1**, this study involved a total of 601,495 infants, of whom 41,446 were considered to be SGA.

The quality of the included literature was assessed, as shown in **Figure 2**. Two studies were rated as 'unclear risk' for sequence generation, 1 for 'high risk' and 12 for 'low risk'. For allocation concealment, nine studies were evaluated as 'low risk', while the remaining studies were assessed as 'unclear'. Only one study was assessed as 'high risk' to blinding

Table 1. Characteristics of the studies included

Study	Year	Country	Sample size (SGA/AGA)	General conditions			Bad habits		Disease	
				Age >35 (SGA/AGA)	Abnormal BMI (SGA/AGA)	Multipara (SGA/AGA)	Smoking (SGA/AGA)	Alcohol intake (SGA/AGA)	Prepregnancy (SGA/AGA)	Pregnancy complication (SGA/AGA)
Iwama [45]	2022	Japan	1126/15947	323/4298	582/7966	-	49/363	218/3072	Diabetes, 4/59; SLE or APS, 4/27; CKD, 3/48; TD, 29/398	HDP, 124/722; GD, 28/410
Giuseppe [46]	2021	Italy	10/90	-	-	-	2/10	1/18	-	HDP, 2/3; GD, 2/8
Souza [47]	2020	Brazil	2481/20173	-	341/2644	1136/10898	-	-	Hypertension, 65/454; Diabetes, 12/194	Preeclampsia, 418/1878; GD, 127/1510
Barquiel [48]	2019	Spain	287/2390	-	90/807	-	62/496	-	Hypertension, 13/48	Preeclampsia, 3/21; HDP, 27/121
Bartal [49]	2019	America	426/1889	55/373	240/1103	197/1120	79/246	-	Hypertension, 205/559	GD, 20/232
Galiano [50]	2018	Spain	518/518	-	-	-	149/80	189/229	-	Preeclampsia, 46/11
Eskes [51]	2017	Netherlands	162/465470	40/96819	37/133	81/254973	44/83	-	Hypertension, 18/33506	-
Fisher [52]	2017	America	1045/10019	164/1349	418/4482	-	149/818	-	Hypertension, 21/892	GD, 47/448
Leng [53]	2016	China	164/1408	-	-	59/553	-	-	-	-
Tul [54]	2016	Slovenija	736/6928	-	125/1046	-	-	-	Diabetes, 3/23; Hypertension, 27/110	Preeclampsia, 178/518; GD, 23/310
Milidou [55]	2014	Denmark	6007/54149	3244/32002	-	2204/28753	2325/13050	-	Diabetes, 6/162; Hypertension, 3/162; TD, 108/975	Preeclampsia, 336/1462; GD, 36/650
Zhang [56]	2009	China	57/122	-	-	15/2	-	-	TD, 10/3; Diabetes, 8/25; Hypertension, 4/1; Autoimmune disease, 2/0	-
Rodrigues [57]	2007	Portugal	342/3538	29/226	-	179/1714	55/293	-	Chronic diseases, 62/456	-
Tsukamoto [58]	2007	Japan	250/2722	30/327	54/635	143/1277	59/433	-	-	-
Chiaffarino [59]	2006	Italy	555/1966	112/382	-	-	141/255	252/834	-	HDP, 120/103

SGA: small for gestational age; AGA: average for gestational age; HDP: hypertensive disorders of pregnancy; GD: gestational diabetes; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; CKD: chronic kidney disease; TD: thyroid disease.

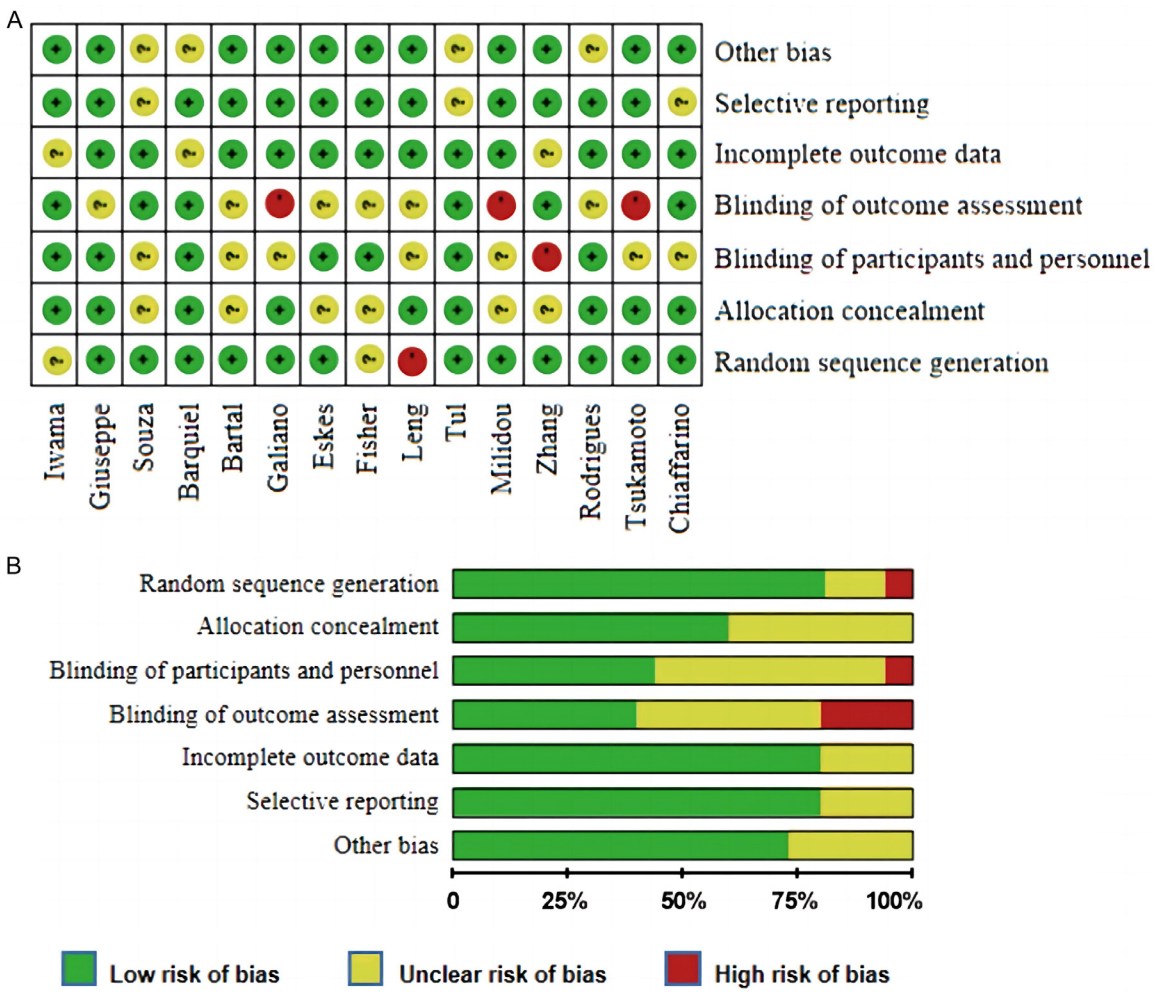

Figure 2. Quality and bias assessments. A. Risk of bias for each RCT; B. Risk of bias summary.

participants and personnel, while 3 were assessed as 'high risk' for blinding the outcome assessment. For incomplete outcome data and selective reporting, 12 articles were categorized as 'low risk'.

The relationship between general maternal conditions and SGA infants

The influence of general maternal conditions, such as age, BMI, and number of pregnancies on the incidence of SGA infants was analyzed. Regarding age, a threshold of 35 years old was set. The results indicated that maternal age had little effect on SGA occurrence (RR=1.01, 95% CI [0.90, 1.14], **Figure 3A**), and no correlation was observed between multipara and SGA (RR=0.93, 95% CI [0.80, 1.09], **Figure 3C**). However, substantial heterogeneity was observed in these analyses, with I^2=79.1% and 96.1%, respectively. Therefore, a random-effect model was adopted. Conversely, as shown in **Figure 3B**, abnormal BMI appears to positively affect the occurrence of SGA (RR=2.23, 95% CI [1.24, 4.00]); while significant heterogeneity was also noted here (I^2= 99.6%, P<0.001), warranting the use of random-effects model.

The relationship between maternal habits and SGA infants

The association between unhealthy maternal habits and SGA were subsequently analyzed. As **Figure 4** shows, a significant heterogeneity (random-effect model) was observed in both meta-analyses regarding smoking (**Figure 4A**) and alcohol intake (**Figure 4B**), with I^2=99.4%

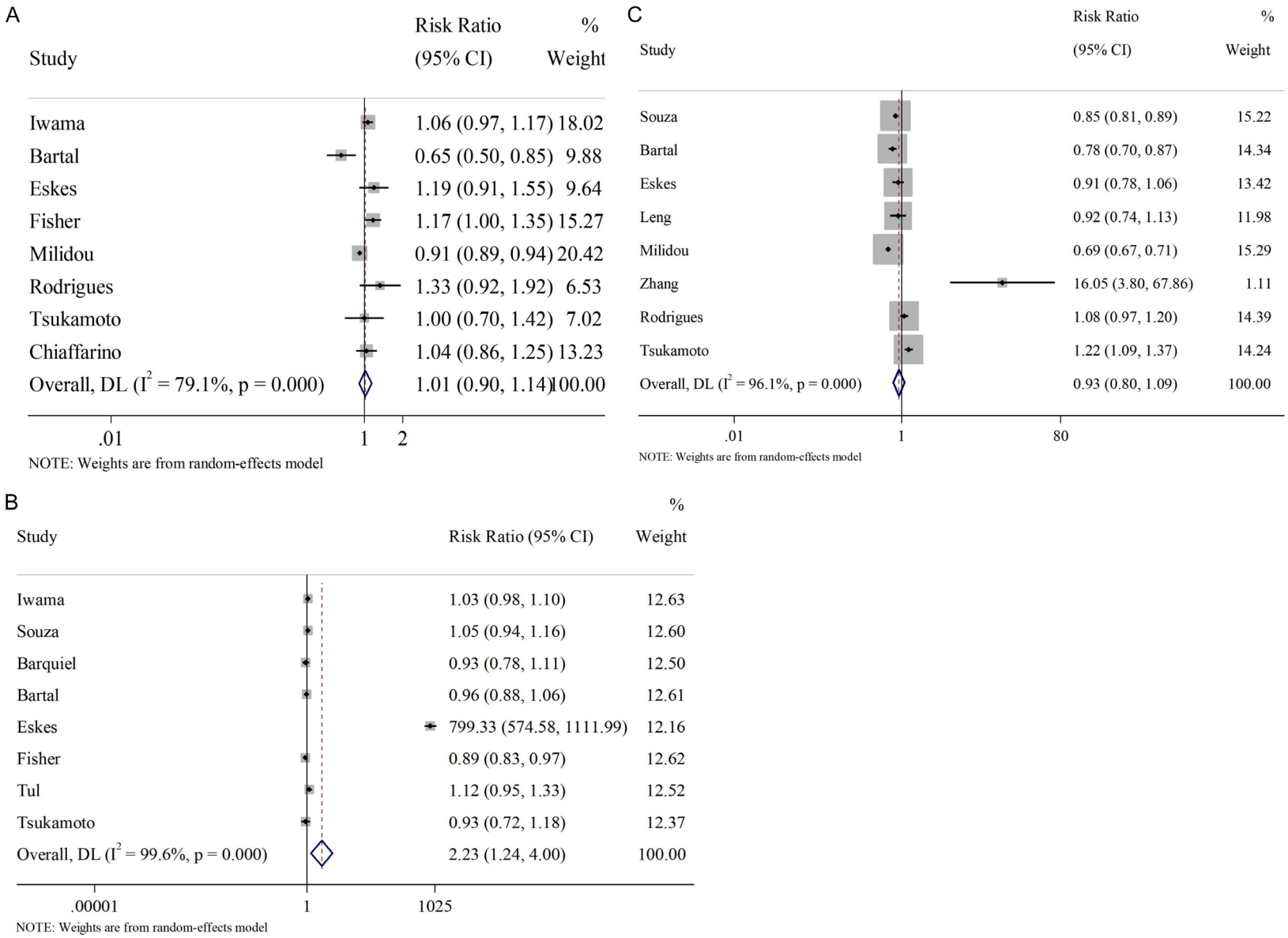

Figure 3. Relationship between general maternal conditions and SGA infants. A. Age >35; B. Abnormal BMI; C. Multipara. SGA: small for gestational age.

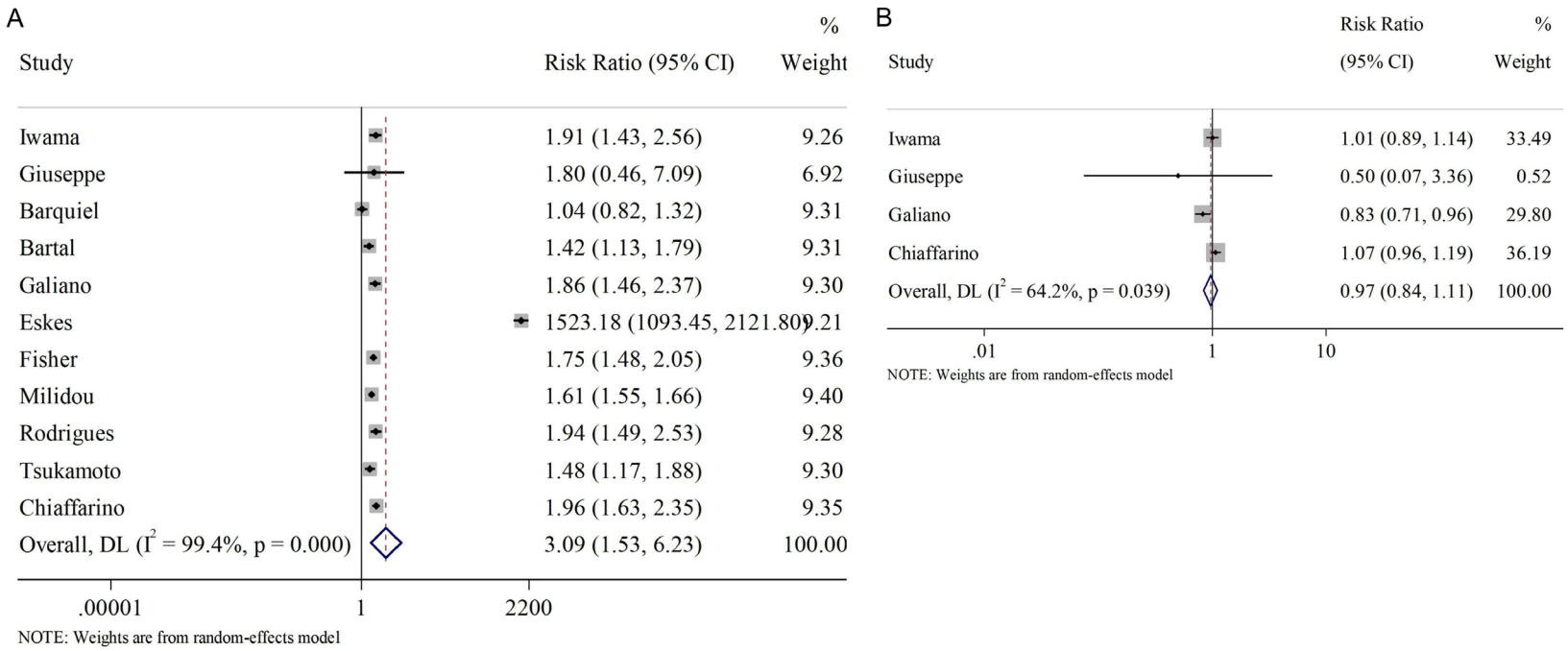

Figure 4. Relationship between maternal bad habits and SGA infants. A. Smoking; B. Alcohol intake. SGA: small for gestational age.

and 64.2%, respectively. The results indicated a positive association between smoking and SGA (RR=3.09, 95% CI [1.53, 6.23]), while no obvious correlation was found between SGA and alcohol intake (RR=0.97, 95% CI [0.84, 1.11]).

The relationship between pre-maternal diseases and SGA infants

We also evaluated whether preexisting diseases, such as diabetes, hypertension, and thyroid disease, before pregnancy influence the occurrence of SGA. Initially, we considered all three pre-pregnancy conditions together and found no overall correlation between these diseases and SGA (RR=1.18, 95% CI [0.86, 1.61], **Figure 5A**).

Subsequently, a subgroup analysis was performed to further investigate the association of each disease with SGA (**Figure 5B**). The results indicated that pre-maternal diabetes was negatively associated with SGA (RR=0.59, 95% CI [0.40, 0.88], fixed effect model). However, no significant relationship was observed between SGA and pre-maternal hypertension or thyroid disease (hypertension: RR=1.11, 95% CI [0.66, 1.87]; thyroid disease: RR=1.32, 95% CI [0.77, 2.27], random-effect models).

The relationship between pregnancy-related complications and SGA infants

We also investigated the influence of pregnancy-induced complications on the occurrence of SGA. The complications studied here included gestational diabetes, gestational hypertension, and preeclampsia. Similarly, we analyzed these pregnancy-induced complications together and found an overall correlation with the incidence of SGA (RR=1.74, 95% CI [1.34, 2.27], **Figure 6A**).

Regarding the subgroup analysis, we found that gestational diabetes negatively affected the incidence of SGA (RR=0.74, 95% CI [0.56, 0.97], random effect model); while gestational hypertension and preeclampsia were positively associated with the incidence of SGA (RR= 2.84, 95% CI [1.88, 4.29]; RR=2.38, 95% CI [1.77, 3.20], random effect models), as shown in **Figure 6B**.

Sensitivity analysis

Significant heterogeneity was observed in the meta-analysis concerning smoking. To determine the potential sources, a sensitivity analysis was performed, and the results are presented in **Table 2**. After excluding Wang et al.'s study [29], although some heterogeneity remained, the I^2 decreased from 99.4% to 63.9%, and the positive relationship between smoking and SGA persisted (RR=1.61, 95% CI [1.56, 1.67]). This suggests that the heterogeneity was primarily driven by Eske's and the results were robust.

Similarly, sensitivity analyses were also performed for the meta-analysis of pregnancy complications (**Table 3**). Notably, the I^2 of studies reporting hypertension during pregnancy decreased from 94.8% to 35.5% after excluding Heaman's study [37], while the positive association with SGA remained significant (RR=2.33, 95% CI [1.98, 2.74]). In contrast, for meta-analyses involving all pregnancy complications, gestational diabetes, and preeclampsia, the I^2 value showed little change regardless of which study was excluded.

Publication bias

As shown in **Figure 7**, Begg's test was adopted to assess possible publication bias. In general, the funnel plots appeared symmetrical in **Figure 7A**, **7C**, **7E-G**, but not in **Figure 7B** and **7D**. According to the Begg's test, no significant publication bias was found in all meta-analyses (age: P=0.902; BMI: P=0.108; multipara: P=0.536; smoking: P=0.119; alcohol intake: P=0.308; pre-maternal disease: P=0.592; pregnancy complication: P=0.108).

Discussion

Studies have shown that the perinatal mortality and prevalence of SGA are significantly higher than those of appropriate for gestational age infants (AGA). Additionally, SGA infants often exhibit lower brain development, resulting in inferior cognitive function and intellectual development in adulthood [33, 34]. Understanding SGA risk factors is crucial for healthcare providers to identify high-risk pregnancies, implement perinatal health education

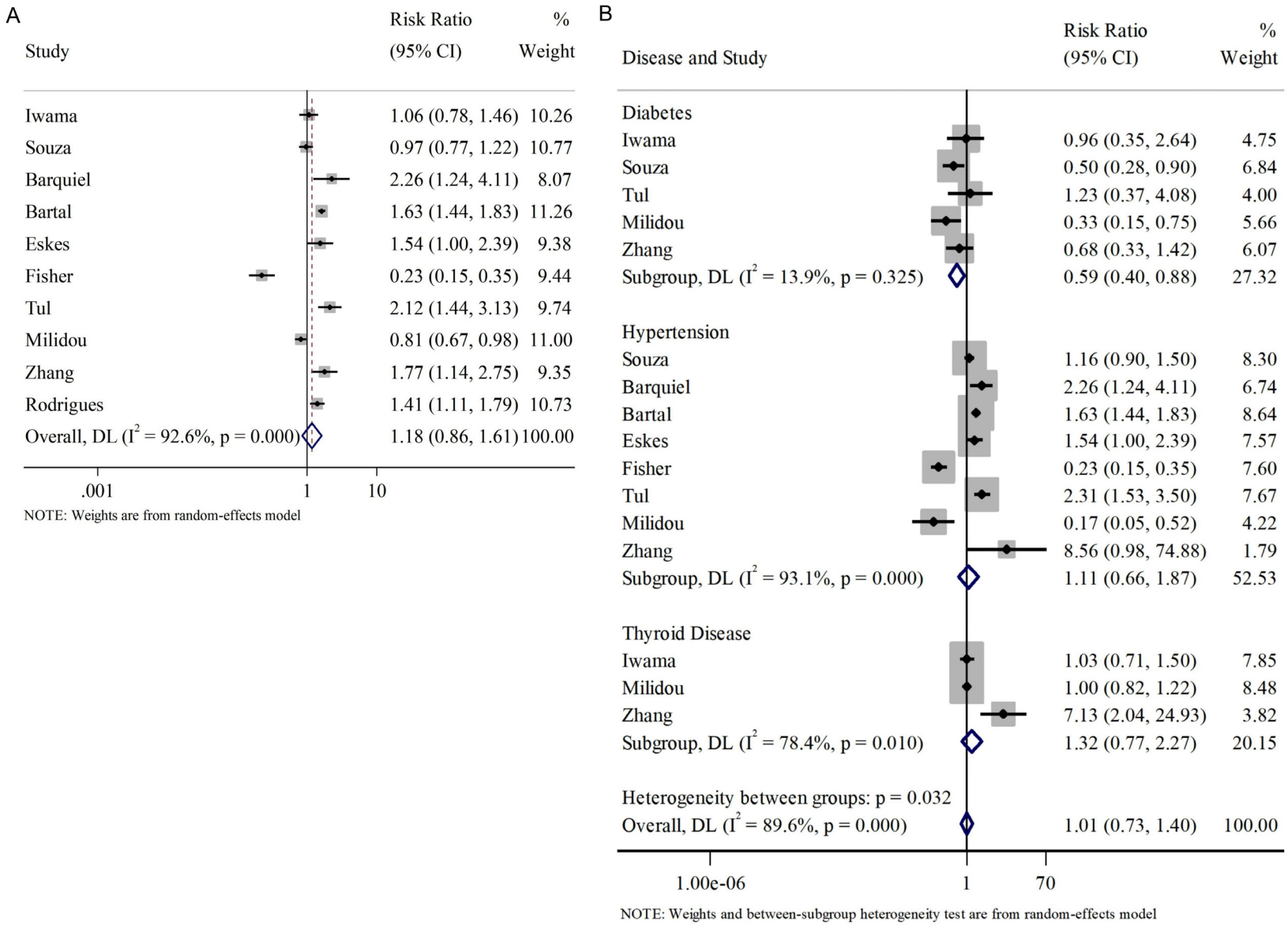

Figure 5. Relationship between pre-pregnancy diseases and SGA infants. A. Overall pre-pregnancy diseases; B. Subgroup analysis of pre-pregnancy diseases. SGA: small for gestational age.

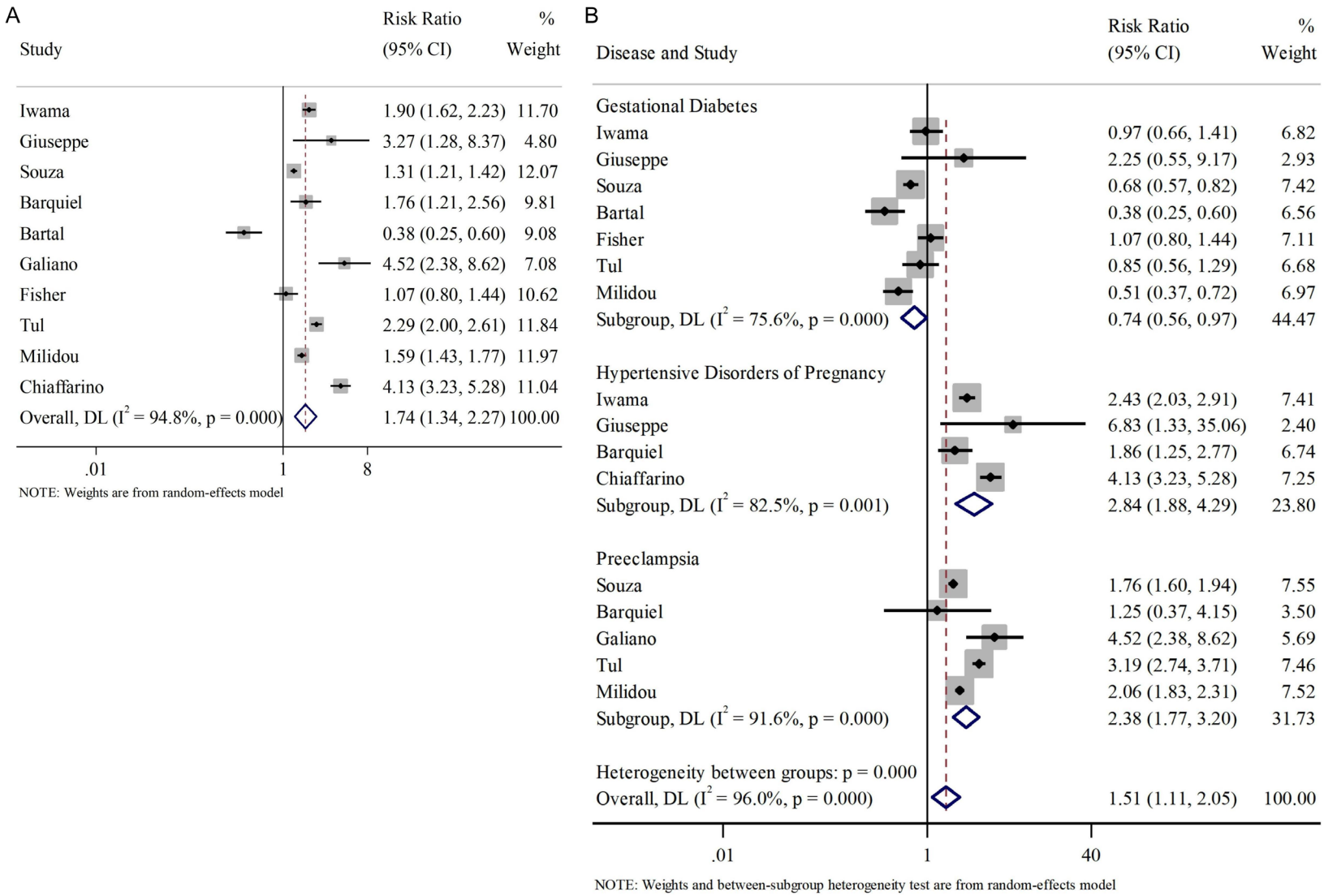

Figure 6. Relationship between pregnancy-related complications and SGA infants. A. Overall pregnancy-related complications; B. Subgroup analysis of pregnancy-related complications. SGA: small for gestational age.

Table 2. Sensitivity analysis for smoking

Excluded study	I^2	p	RR (95% CI)
Iwama [45]	99.5%	<0.001	1.64 (1.59, 1.69)
Giuseppe [46]	99.5%	<0.001	1.64 (1.59, 1.69)
Barquiel [48]	99.5%	<0.001	1.66 (1.61, 1.72)
Bartal [49]	99.5%	<0.001	1.65 (1.59, 1.70)
Galiano [50]	99.5%	<0.001	1.64 (1.58, 1.69)
Eskes [51]	63.9%	<0.001	1.61 (1.56, 1.67)
Fisher [52]	99.5%	<0.001	1.64 (1.58, 1.69)
Milidou [55]	99.4%	<0.001	1.77 (1.64, 1.91)
Rodrigues [57]	99.5%	<0.001	1.64 (1.58, 1.69)
Tsukamoto [58]	99.5%	<0.001	1.64 (1.59, 1.70)
Chiaffarino [59]	99.5%	<0.001	1.63 (1.58, 1.68)

targeting modifiable risk factors, prevent the occurrence of SGA, and reduce adverse effects. This meta-analysis primarily focuses on maternal factors.

The research findings on the influence of maternal age on SGA are inconsistent. A retrospective study analyzing the incidence of SGA in 1,393 pregnant women up to the age of 25 years concluded that there was no significant association between age and SGA [35]. Furthermore, Odibo *et al.* found that the incidence of SGA increased with age in pregnant women over 35 years [36]. This meta-analysis involved 8 studies investigating the association between age and SGA, and the result showed that maternal age over 35 years did not increase the risk of SGA. Heaman et al. found that pre-pregnancy BMI of less than 18 kg/m^2 or gestational weight gain of less than 9.1 kg were associated with an increase in SGA [37]. The normal BMI range for women is between 18.5 and 24 kg/m^2. In our study, we analyzed the correlation between abnormal BMI and SGA, demonstrating that abnormal BMI is positively related to the incidence of SGA (RR=2.23, 95% CI [1.24, 4.00]). Furthermore, we discovered that multipara is not associated with SGA occurrence.

Studies have shown that 18% of SGA cases are associated with maternal smoking [38], and our study also confirms this (RR=3.09, 95% CI [1.53, 6.23]). However, the correlation between alcohol intake and SGA in pregnant women remains controversial. While some studies believe that alcohol consumption during pregnancy is significantly associated with SGA [39, 40], others have found no such link [41]. Our meta-analysis did not find any significant association between maternal alcohol intake and SGA.

Some pregnancy-related diseases are also closely related to SGA. Studies have found that gestational hypertension and preeclampsia are important factors contributing the occurrence of SGA [42, 43]. Our study yielded similar results, showing that both gestational hypertension and preeclampsia were positively related to SGA, with RR=2.84, 95% CI [1.88, 4.29] and RR=2.38, 95% CI [1.77, 3.20], respectively. Furthermore, we found that both pre-pregnancy and gestational diabetes were negatively associated with SGA (pregestational: RR=0.59, 95% CI [0.40, 0.88]; gestational: RR=0.74, 95% CI [0.56, 0.97]). However, diabetes was shown to be related to large gestational age (LGA) [44].

Inevitably, this study has some limitations that shouldn't be ignored. First, some analyses, such as those concerning alcohol intake and thyroid disease, were based on a limited number of studies. Second, the high heterogeneity observed in several analyses may have impacted the reliability of this meta-analysis. Third, publication bias could potentially affect the authenticity of the conclusions of this paper. Despite the these limitations, this study still holds value in highlighting key areas for pregnant women to focus on for optimal fetal development and health outcomes.

Conclusions

In conclusion, this meta-analysis provides insights into maternal risk factors, such as abnormal BMI, smoking, and pregnancy complications, which may increase the risk of SGA. These findings underscore the importance for pregnant women to focus on maintaining a healthy weight, quitting smoking, and preventing pregnancy-related complications to reduce the risk of SGA.

Acknowledgements

This research was supported by the Department of Science and Technology of Sichuan Province - Metagenomics and metabolomics study of the gut microbiota in Han children with autism spectrum disorder in Sichuan, China (No. 2021YFS0113).

Table 3. Sensitivity analysis for pregnancy complications

Excluded study	All			Gestational Diabetes			Hypertensive disorders of pregnancy			Preeclampsia		
	I^2	P	RR (95% CI)	I^2	p	RR (95% CI)	I^2	p	RR (95% CI)	I^2	p	RR (95% CI)
Iwama [45]	95.3%	<0.001	1.53 (1.45, 1.62)	77.8%	<0.001	0.68 (0.60, 0.77)	83.1%	0.003	3.33 (2.71, 4.08)	-	-	-
Giuseppe [46]	95.3%	<0.001	1.56 (1.49, 1.64)	77.7%	<0.001	0.69 (0.62, 0.78)	87.5%	<0.001	2.80 (2.45, 3.21)	-	-	-
Souza [47]	93.9%	<0.001	1.76 (1.65, 1.88)	79.7%	<0.001	0.71 (0.60, 0.83)	-	-	-	88.1%	<0.001	2.39 (2.18, 2.62)
Barquiel [48]	95.4%	<0.001	1.56 (1.48, 1.64)	-	-	-	84.2%	0.002	2.99 (2.59, 3.46)	93.6%	<0.001	2.08 (1.94, 2.22)
Bartal [49]	93.9%	<0.001	1.63 (1.55, 1.71)	69.3%	0.006	0.74 (0.65, 0.84)	-	-	-	-	-	-
Galiano [50]	95.1%	<0.001	1.55 (1.47, 1.63)	-	-	-	-	-	-	92.9%	<0.001	2.04 (1.91, 2.18)
Fisher [52]	95.2%	<0.001	1.59 (1.51, 1.67)	69.7%	0.005	0.65 (0.57, 0.74)	-	-	-	-	-	-
Tul [54]	94.4%	<0.001	1.49 (1.41, 1.58)	79.5%	<0.001	0.69 (0.61, 0.78)	-	-	-	74.2%	<0.001	1.92 (1.78, 2.07)
Milidou [55]	95.4%	<0.001	1.56 (1.47, 1.65)	75.4%	<0.001	0.74 (0.65, 0.84)	-	-	-	93.7%	<0.001	2.08 (1.92, 2.26)
Chiaffarino [59]	93.0%	<0.001	1.50 (1.42, 1.58)	-	-	-	35.3%	0.213	2.33 (1.98, 2.74)	-	-	-

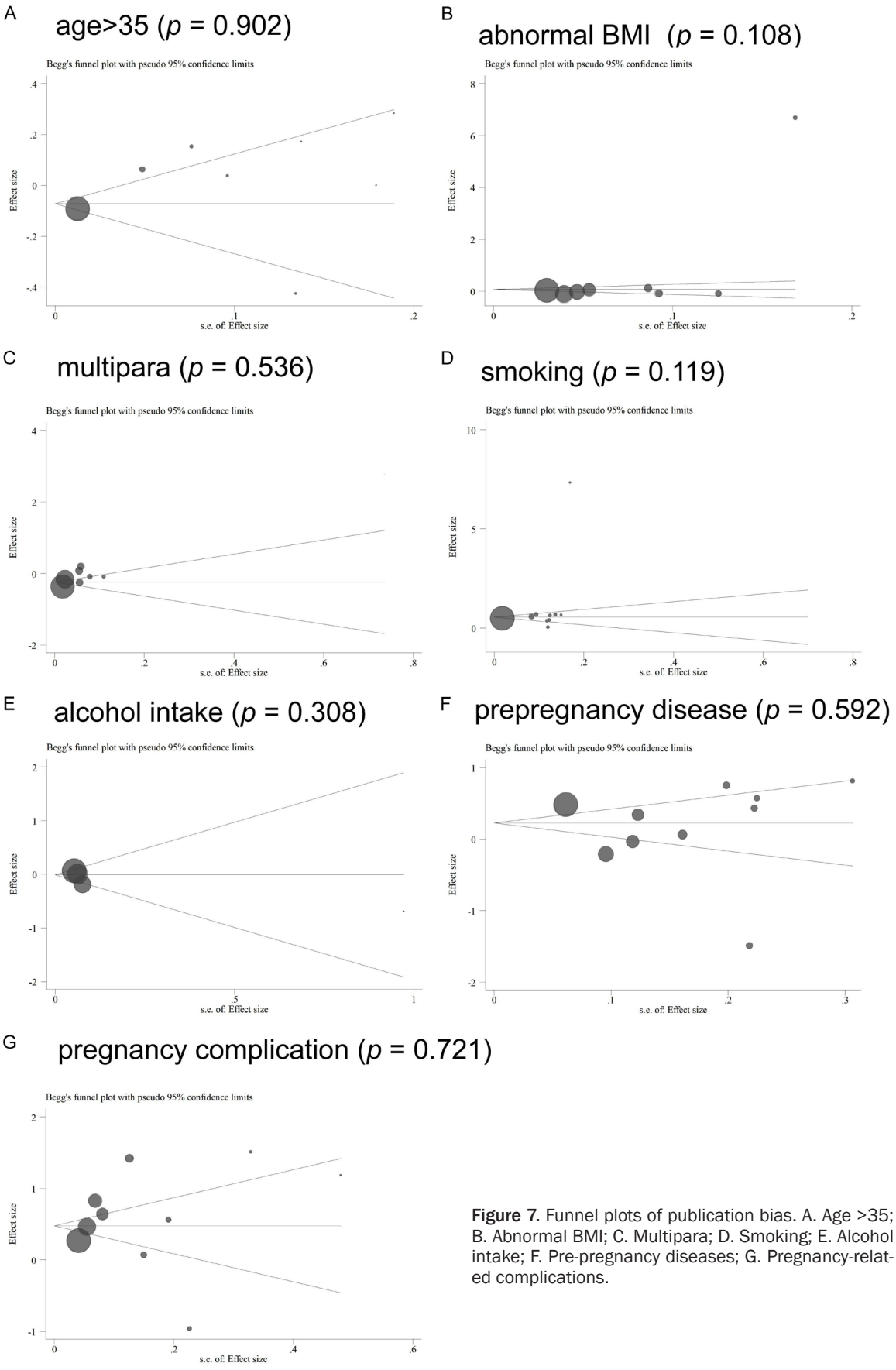

Figure 7. Funnel plots of publication bias. A. Age >35; B. Abnormal BMI; C. Multipara; D. Smoking; E. Alcohol intake; F. Pre-pregnancy diseases; G. Pregnancy-related complications.

Disclosure of conflict of interest

None.

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