




Systematic Review

Incidence of Intrahepatic Cholestasis of Pregnancy and Its Impact on Maternal and Neonatal Outcomes: A Systematic Review and Meta-Analysis

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Abstract

Background: This study employed a meta-analysis approach to investigate the incidence of intrahepatic cholestasis of pregnancy (ICP) and its impact on adverse outcomes in both pregnant and postpartum women, as well as neonates. **Methods:** We obtained studies published from the inception of the PubMed, Cochrane Library, and Web of Science databases through January 2024. A total of 21 original articles were included, reporting on ICP and its associated adverse outcomes in maternal and neonatal populations. The included studies involved 1,497,951 controls non-intrahepatic cholestasis of pregnancy (non-ICP) and 12,262 ICP patients. Sensitivity analyses and evaluations for publication bias were also conducted. **Results:** The pooled analysis estimated an ICP incidence of 3% (95% confidence interval [CI], 1%–7%), while the meta-analysis demonstrated the following risk ratios: postpartum hemorrhage showed a relative risk (RR, 0.82; 95% CI, 0.69–0.99), whereas significant increases were observed for preeclampsia (RR, 2.39; 95% CI, 2.21–2.59), Cesarean section (RR, 1.28; 95% CI, 1.15–1.42), preterm birth (RR, 2.71; 95% CI, 1.77–4.15), and maternal infection (RR, 3.22; 95% CI, 2.48–4.19). Other outcomes included labor induction (RR, 1.60; 95% CI, 0.51–4.99), gestational diabetes mellitus (GDM; RR, 1.29; 95% CI, 0.83–2.01), stillbirth (RR, 1.25; 95% CI, 0.64–2.42), and small for gestational age (SGA; RR, 1.06; 95% CI, 0.71–1.57), which were not statistically significant. Neonatal intensive care unit (NICU) admission (RR, 1.79; 95% CI, 1.35–2.37), with a significant increase in risk. **Conclusions:** This meta-analysis demonstrates a global incidence of ICP at 3% and identifies significant associations with adverse maternal and neonatal outcomes. ICP is associated with increased risks of preeclampsia, Cesarean section, preterm birth, maternal infection, and neonatal intensive care needs. Interestingly, a relative risk of postpartum hemorrhage was observed, suggesting the need for further investigation into the underlying mechanisms. Although labor induction, GDM, and stillbirth showed non-significant trends toward increased risk, their clinical relevance persists. These findings underscore the necessity for risk-stratified surveillance in ICP management, emphasizing infection control and preterm prevention, alongside regionally tailored clinical protocols. **Registration:** The study has been registered on <https://inplasy.com/inplasy-2025-3-0132/> (registration number: INPLASY202530132).

Keywords: intrahepatic cholestasis of pregnancy; maternal health; neonatal health; risk factors; meta-analysis

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver condition that occurs during pregnancy. It is mainly characterized by intrahepatic cholestasis and heightened bile acid levels. Pruritus is often a significant symptom, especially in the third trimester of pregnancy [1]. ICP is the most common pregnancy-related liver disease that poses a threat on maternal-fetal health. It is associated with maternal risks, including preterm labor and postpartum hemorrhage, potential hepatic impairment in postpartum women, and neonatal complications such as asphyxia and meconium aspiration syndrome [2]. As reported, the global incidence of ICP varies widely by region, with significantly higher incidence rates observed in certain high-risk populations and regions [3]. In Scandinavia and several Asian countries, including China and India, the incidence of ICP exceeds the global average [3]. Women with a family history of the disease, advanced maternal age, or preexisting liver conditions or

pregnancy complications are at higher risk of developing ICP [4]. These variations may be closely associated with genetic susceptibility, environmental factors, and the quality of prenatal care.

The pathophysiology of ICP involves hormonal fluctuations, bile acid dysmetabolism, and genetic susceptibility, with emerging evidence highlighting immune dysregulation as a contributor to its inflammatory nature [5–7]. ICP is associated with a range of maternal and neonatal complications, beyond the common symptoms of pruritus and liver dysfunction [8]. ICP increases the risk of preterm delivery, fetal distress, and other adverse fetal outcomes due to elevated bile acids, which can disrupt placental function, impair nutrient and oxygen transfer, and exacerbate intrauterine stress. Furthermore, ICP is linked to heightened risks of gestational diabetes mellitus (GDM), postpartum hemorrhage, and even fetal stillbirth, with cardiac arrhythmia being a primary cause of fetal death in severe cases [9]. While effective management can improve outcomes, the condition



remains a significant obstetric risk, requiring careful monitoring and clinical attention [10,11]. Therefore, this study aims to systematically evaluate the impact of ICP on maternal and neonatal outcomes, offering clearer evidence for optimizing clinical management.

Although existing literature has preliminarily explored the epidemiological features, pathological mechanisms, and the effects of ICP on pregnant and postpartum women, as well as neonates, significant heterogeneity exists in the quantitative assessment of ICP incidence and neonatal adverse outcomes. This variability arises from differences in study design, sample size, data quality, and regional factors. Current studies lack unified incidence data, and significant controversy remains regarding the factors influencing adverse outcomes, as incidence rates and baseline characteristics of patients vary across regions. This study aims to conduct a systematic evaluation and meta-analysis to integrate high-quality research data, accurately estimate the incidence of ICP, and quantify its specific impact on adverse outcomes in pregnant and postpartum women, as well as neonates. This study synthesizes robust epidemiological evidence to inform risk stratification models and optimize clinical decision-making for ICP. The findings supports the development of targeted screening protocols and preventive strategies, ultimately contributing to improved maternal-fetal health outcomes.

2. Materials and Methods

2.1 Literature Search and Screening

The study protocol was registered on INPLASY (registration number: INPLASY202530132) in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.

A thorough search was performed in the PubMed (<https://pubmed.ncbi.nlm.nih.gov>), Cochrane Library (<https://www.cochranelibrary.com>), and Web of Science (<https://www.webofscience.com>) databases. Relevant papers published from the inception of these databases through January 2024 were included. The focus was on studying the incidence of ICP and its impact on adverse outcomes in pregnant and postpartum women, as well as neonates. Search terms encompassed: (“Intrahepatic cholestasis of pregnancy”) AND (“Emergency Cesarean sections” OR “Postpartum hemorrhage” OR “Cesarean delivery” OR “Preeclampsia” OR “Hemorrhage” OR “Unplanned cesarean sections” OR “Preterm birth” OR “Premature delivery” OR “Small for gestational age” OR “Stillbirth” OR “Neonatal intensive care unit” OR “NICU admission” OR “Neonatal outcomes” OR “Perinatal complications”). Search strategies were tailored to meet the requirements of each database. All references from the included studies were manually checked to identify any potentially overlooked research. Two researchers independently conducted the screening and cross-validated the results. If disagreements arose, a third researcher was responsible for making

the final decision. The screening process involved reviewing titles, abstracts, and full texts.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria were as follows: ① Participants (P) included pregnant women diagnosed with ICP; ② Intervention (I): ICP; ③ Control (C): pregnant women without ICP; ④ Outcomes (O): adverse maternal and neonatal outcomes; and ⑤ Study Design (S): clinical trials, observational studies, or systematic evaluations. The inclusion criteria comprised studies examining the impact of ICP on obstetric and neonatal outcomes, with comparisons between the ICP and non-intrahepatic cholestasis of pregnancy (non-ICP) groups.

Exclusion criteria: ① Studies not directly related to ICP or its associated factors; ② Articles focused on other liver diseases or conditions, rather than specifically targeting ICP; ③ Studies with unclear methodology; ④ Studies with small sample sizes (e.g., case reports, case series), lacking statistical power, or generalizability; ⑤ Animal studies, *in-vitro* experiments, or studies involving non-human subjects; ⑥ Articles published in languages other than English, without a reliable English translation; and ⑦ Studies with inaccessible full texts.

2.3 Data Extraction

Relevant data were extracted from the included studies, including study type, groups, sample size, and average maternal age. Obstetric outcomes such as emergency Cesarean section (C-section) rate, preeclampsia, postpartum hemorrhage, gestational age, preterm delivery (spontaneous preterm birth), small for gestational age (SGA) infants, neonatal intensive care unit (NICU) admission rate, and stillbirth rate were also collected, with preterm delivery defined as gestational age less than 37 weeks. Additionally, risk assessment-related parameters from the studies were extracted. This comprehensive data extraction allowed us to assess the relationships between variables and their potential impact on maternal and neonatal health outcomes.

2.4 Quality Assessment

The ROBINS-I tool was used to assess the potential risk of bias in cohort studies. Two researchers independently evaluated the methodological quality of the included studies. Any discrepancies were resolved through consultation with a third researcher, who acted as an arbitrator. This rigorous process ensured a comprehensive and unbiased evaluation of the studies’ methodological strengths and limitations.

2.5 Meta-Analysis

Relevant data were extracted from the included studies, including study design, sample size, patient characteristics, and adverse outcomes. Two researchers independently extracted the data and cross-validated the

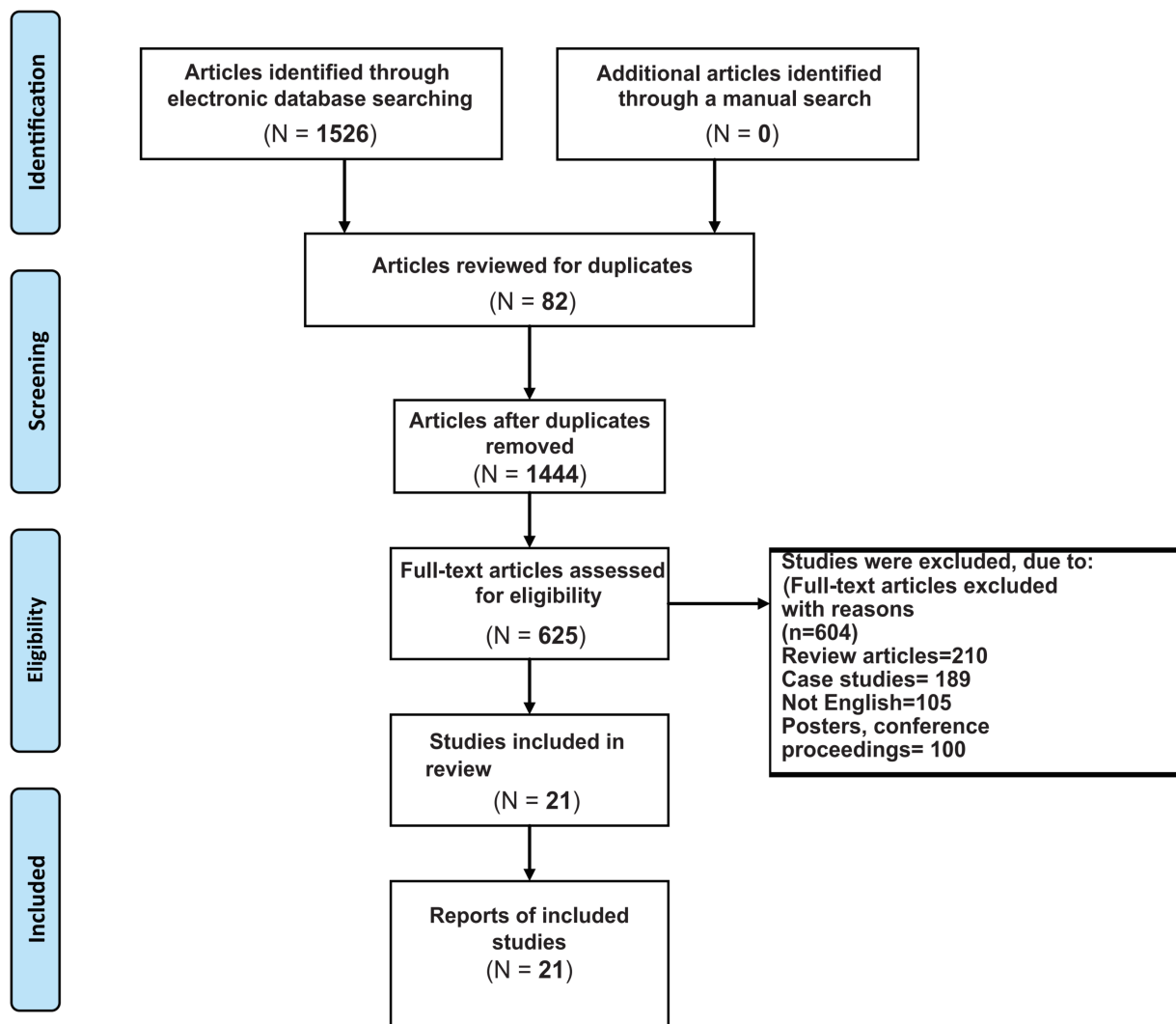


Fig. 1. Literature screening flow chart.

data. The 95% confidence interval (CI) was calculated for each parameter. The I^2 statistic was employed to assess heterogeneity between studies. An I^2 value greater than 50% suggested significant heterogeneity. All meta-analyses were performed using the RevMan 5.3 software (UK; <https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman>). For the assessment of publication bias, the trim and fill method was employed, with detection conducted using both the Miller Method and the Harbord Method. Common methods for calculating the pooled effect size include the Mantel-Haenszel method for binary outcomes and the inverse-variance method for continuous outcomes. Based on the heterogeneity results, a random effects model should be chosen if $p < 0.05$ or $I^2 > 50\%$; otherwise, a fixed-effects model should be used. This study set the significance level at $\alpha = 0.05$. A result was considered statistically significant when the p -value was < 0.05 or when the 95% CI (e.g., odds ratio (OR) or hazard ratio (HR)) did not include the null value.

2.6 Sensitivity Analysis

A sensitivity analysis was performed to assess the impact of each study on the overall effect size. This involved repeating the meta-analysis by removing one study at a time. Any changes in the overall effect size were carefully observed. If removing any study did not lead to a notable change in the effect size, the meta-analysis results were considered stable.

3. Results

Fig. 1 summarizes the results of the literature search and selection process. A total of 1526 articles were retrieved from the PubMed, Embase, and Web of Science databases. After a stepwise screening process, 21 original articles reporting on the correlation between ICP and adverse maternal and neonatal outcomes were included [9,12–31]. Table 1 (Ref. [9,12–31]) outlines the primary characteristics of these studies. The 21 studies encompassed 1,497,951 healthy controls and 12,262 ICP patients.

Table 1. Detailed information of the included studies.

First Author	Heinonen <i>et al.</i> [29]	Turunen <i>et al.</i> [17]	Al Shobaili <i>et al.</i> [22]	Wikström Shemer <i>et al.</i> [19]	Martineau <i>et al.</i> [9]	Geenes <i>et al.</i> [13]	Kawakita <i>et al.</i> [28]	Furrer <i>et al.</i> [27]	Liu <i>et al.</i> [26]	Herrera <i>et al.</i> [23]	Ozel <i>et al.</i> [12]	Wang <i>et al.</i> [14]	Arthuis <i>et al.</i> [24]	Liu <i>et al.</i> [20]	Luo <i>et al.</i> [18]	Wu <i>et al.</i> [30]	Al-Obaidly <i>et al.</i> [25]	Begum <i>et al.</i> [16]	Li <i>et al.</i> [15]	Omeroglu <i>et al.</i> [21]	Chen <i>et al.</i> [31]	
Year of Publication	1999	2010	2011	2013	2014	2014	2015	2016	2016	2018	2020	2019	2020	2020	2021	2022	2022	2023	2023	2023	2023	
Country	Finland	Finland	Saudi Arabia	Sweden	UK	UK	USA	Switzerland	China	USA	Turkey	China	France	China	China	China	Qatar	India	China	Turkey	China	
Type of Study	PC	RC	PC	PC	RC	PC	RC	PC	PC	RC	CSC	RC	PC	PC	RC	RC	RC	PC	RCC	PCC	RC	
Numbers	ICP non-ICP	91 16,818	687 1374	76 200	5477 1,208, 191	143 57,581	669 2205	26 152	345 1725	129 1793	487 298	40 40	140 560	911 94,817	114 3725	1516 38,226	263 31,230	60 60	300 300	60 60	688 38,556	
Average Maternal age (years)	ICP non-ICP	NA NA	27.50 27.20	29.18 29.86	NA NA	30.80 ± 4 30.60 ± 4	29.60 29.00	30.20 29.70	27.50 27.70	32.40 30.70	29 ± 5 29 ± 5	NA NA	29.50 ± 3 29.50 ± 3	29 29	30.80 30.60	30 30	31.20 31.13	35 35	27.63 26.73	NA NA	NA NA	29 ± 4 29 ± 4
Postpartum hemorrhage	ICP non-ICP	NA NA	NA NA	5.20% 4.50%	NA NA	NA NA	NA NA	12.70% 9.90%	NA NA	NA NA	NA NA	NA NA	20.70% 15.35%	0.90% 0.80%	0.00% 0.70%	3.60% 4.50%	5.70% 5.20%	NA NA	1.00% 0.70%	NA NA	0.15% 0.28%	
C-Section	ICP non-ICP	25.30% 15.80%	14.80% 10.60%	11.80% 8.50%	19.60% 15.60%	33.00% 29.00%	25.00% 23.00%	40.00% 38.20%	27.50% 27.70%	NA NA	32.00% 29.90%	37.50% 22.50%	NA NA	13.60% 10.90%	0.70% 0.30%	35.09% 21.93%	48.04% 38.50%	27.00% 31.30%	58.30% 35.00%	NA NA	50.00% 25.00%	51.31% 31.60%
Preeclampsia	ICP non-ICP	NA NA	NA NA	NA NA	6.70% 2.70%	NA NA	6.60% NA	7.30% 7.20%	NA NA	27.90% 12.60%	NA NA	NA NA	NA NA	NA NA	5.50% 2.40%	10.50% 0.70%	4.30% 2.60%	1.50% 1.60%	NA NA	8.00% 0.70%	NA NA	4.94% 1.56%

Table 1. Continued.

First Author		Heinonen <i>et al.</i> [29]	Turunen <i>et al.</i> [17]	Al Shobaili <i>et al.</i> [22]	Wikström She-mer <i>et al.</i> [19]	Martineau <i>et al.</i> [9]	Geenes <i>et al.</i> [13]	Kawakita <i>et al.</i> [28]	Furrer <i>et al.</i> [27]	Liu <i>et al.</i> [26]	Herrera <i>et al.</i> [23]	Ozel <i>et al.</i> [12]	Wang <i>et al.</i> [14]	Arthuis <i>et al.</i> [24]	Liu <i>et al.</i> [20]	Luo <i>et al.</i> [18]	Wu <i>et al.</i> [30]	Al-Obaidly <i>et al.</i> [25]	Begum <i>et al.</i> [16]	Li <i>et al.</i> [15]	Omeroglu <i>et al.</i> [21]	Chen <i>et al.</i> [31]
Preterm delivery	ICP	14.30%	44.00%	11.80%	0.50%	2.10%	25.00%	46.20%	NA	28.70%	9.40%	NA	NA	15.70%	0.90%	6.14%	22.40%	1.40%	21.70%	26.70%	NA	18.60%
	non-ICP	5.50%	12.00%	9.00%	0.70%	0.30%	6.50%	14.50%	NA	19.20%	6.10%	NA	NA	4.80%	1.10%	0.18%	9.26%	1.40%	10.00%	2.00%	NA	4.87%
Induction of labor	ICP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	82.10%	4.10%	NA	NA	NA	61.70%	NA	NA	NA
	non-ICP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	18.40%	6.70%	NA	NA	NA	41.70%	NA	NA	NA
Gestational diabetes mellitus	ICP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	18.40%	20.20%	NA	NA	13.30%	NA	16.60%
	non-ICP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	20.50%	18.80%	NA	NA	4.30%	NA	14.00%
Polyhydramnios oligohydramnios	ICP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.90%	NA	NA	NA	11.30%	NA	NA
	non-ICP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.20%	NA	NA	NA	3.70%	NA	NA
Maternal infection	ICP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.00%	14.00%	NA	NA	16.30%	NA	13.50%
	non-ICP	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.70%	5.10%	NA	NA	2.70%	NA	4.10%
NICU admission	ICP	NA	NA	15.70%	NA	NA	12.00%	20.40%	15.90%	50.20%	NA	27.50%	NA	2.90%	29.50%	NA	23.40%	15.30%	21.60%	NA	23.30%	NA
	non-ICP	NA	NA	4.90%	NA	NA	5.60%	27.30%	16.80%	34.90%	NA	0.00%	NA	0.40%	13.50%	NA	14.60%	11.80%	5.00%	NA	6.70%	NA
Stillbirth	ICP	0.00%	1.20%	NA	0.30%	2.10%	1.50%	0.00%	0.90%	NA	2.90%	NA	NA	0.00%	0.10%	0.00%	0.77%	0.40%	0.00%	NA	NA	0.15%
	non-ICP	0.40%	0.70%	NA	0.30%	0.30%	0.50%	0.00%	3.60%	NA	0.30%	NA	NA	0.00%	0.30%	0.00%	0.71%	0.70%	0.00%	NA	NA	0.44%
Small for gestational age	ICP	7.70%	NA	NA	1.10%	NA	NA	NA	NA	11.50%	2.19%	NA	NA	5.70%	3.50%	NA	4.25%	NA	NA	NA	NA	NA
	non-ICP	8.50%	NA	NA	2.30%	NA	NA	NA	NA	9.70%	1.45%	NA	NA	3.20%	2.00%	NA	4.71%	NA	NA	NA	NA	NA

Note: UK, United Kingdom; USA, United States of America; PC, prospective cohort study; RC, retrospective cohort study; RCC, retrospective case-control study; PCC, prospective case-control study; CSC, cross-sectional case-control; ICP, intrahepatic cholestasis of pregnancy; non-ICP, non-intrahepatic cholestasis of pregnancy; NA, not available; C-Section, cesarean section; SGA, small for gestational age; GDM, gestational diabetes mellitus; NICU, neonatal intensive care unit.

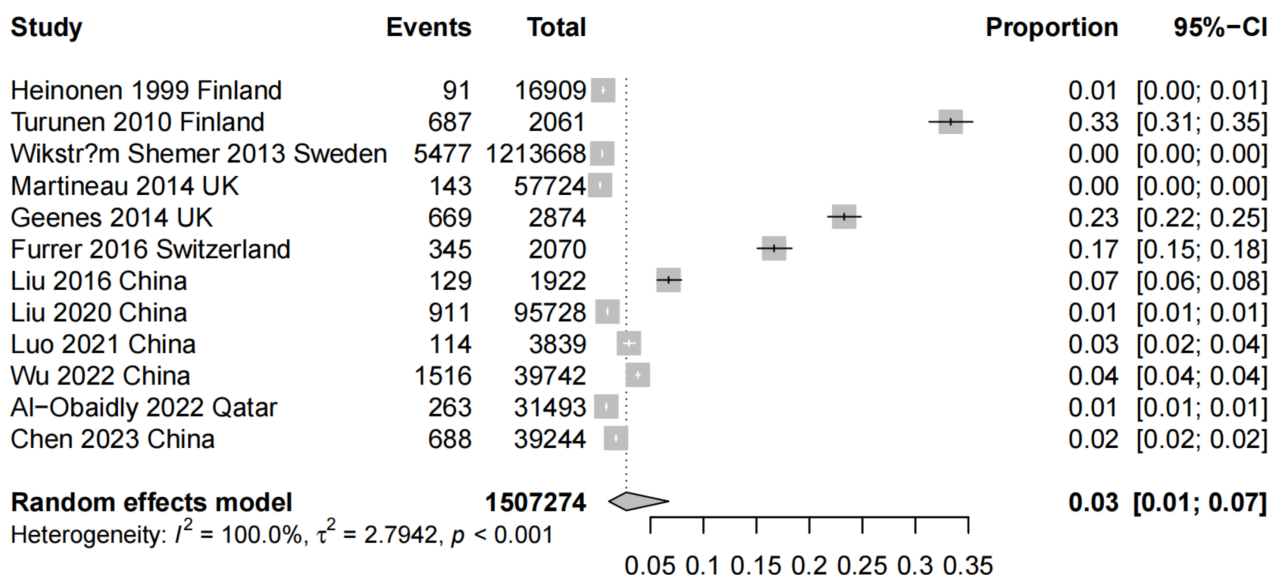


Fig. 2. Forest plot of the prevalence of ICP. CI, confidence interval.

3.1 Impact of ICP on Adverse Outcomes in Pregnant and Postpartum Women

We performed a meta-analysis on 7 different maternal outcomes based on the collected literature. After assessing heterogeneity, we used a fixed-effects model for postpartum hemorrhage and random-effects models for the other outcomes. Our results demonstrate that the incidence of ICP is 3% (95% CI: 1%–7%) (Fig. 2). ICP is significantly associated with increased risks of preeclampsia (relative risk [RR], 2.39; 95% CI, 2.21–2.59), C-section (RR, 1.28; 95% CI, 1.15–1.42), preterm delivery (RR, 2.71; 95% CI, 1.77–4.15), and maternal infection (RR, 3.22; 95% CI, 2.48–4.19), while showing a protective association with postpartum hemorrhage (RR, 0.82; 95% CI, 0.69–0.99), and no significant associations with labor induction (RR, 1.60; 95% CI, 0.51–4.99), or GDM (RR, 1.29; 95% CI, 0.83–2.01) (Fig. 3). These findings suggest a strong association between the occurrence of ICP and an increased risk of preeclampsia, C-section, preterm delivery, and maternal infection.

The sensitivity analysis results showed no significant changes, indicating that the meta-analysis results are robust and reliable (Fig. 4). The bias assessment results revealed that the funnel plots for all outcomes were generally symmetric, resembling an inverted funnel, and the p -values from bias detection tests were all greater than 0.05. This suggests that there is no strong evidence of publication bias, indicating a low likelihood of such bias and thereby enhancing the credibility and reliability of our conclusions (Fig. 5).

3.2 Impact of ICP on Neonatal Adverse Outcomes

A meta-analysis was conducted on 3 different neonatal outcomes using the collected literature. Random-effects models were applied to all indicators based on heterogene-

ity assessment. Our results demonstrate that ICP significantly increases the risk of NICU admission by 1.79-fold (RR, 1.79; 95% CI, 1.35–2.37), but does not significantly increase the risks of stillbirth (RR, 1.25; 95% CI, 0.64–2.42) or SGA (RR, 1.06; 95% CI, 0.71–1.57) (Fig. 6). These findings indicated that ICP is closely associated with an increased risk of NICU admission.

The sensitivity analysis results showed no substantial changes across groups, indicating that the meta-analysis findings are robust and reliable (Fig. 7). The bias assessment results revealed that the funnel plots for all outcomes were generally symmetric, resembling an inverted funnel, and the p -values from bias detection tests were all greater than 0.05. This suggests no strong evidence of bias, implying a low likelihood of publication bias and further enhancing the credibility and reliability of the conclusion (Fig. 8).

4. Discussion

Given the limited research on the quantitative analysis of the impact of ICP on maternal and neonatal adverse outcomes, as well as the insufficient exploration of its epidemiological features and pathological mechanisms, we conducted a systematic review and meta-analysis to comprehensively assess the effect of ICP on maternal and neonatal adverse outcomes. The following section further examines these findings, analyzing the potential impact of ICP on maternal health in the context of existing literature. It also explores directions for future research and implications for clinical management strategies.

This meta-analysis reveals significant geographical heterogeneity in the incidence of ICP ($I^2 = 100\%$), with Finnish cohorts reporting rates as high as 33%, whereas most Asian studies report rates below 5% [32,33]. This suggests that variations in diagnostic criteria and genetic pre-

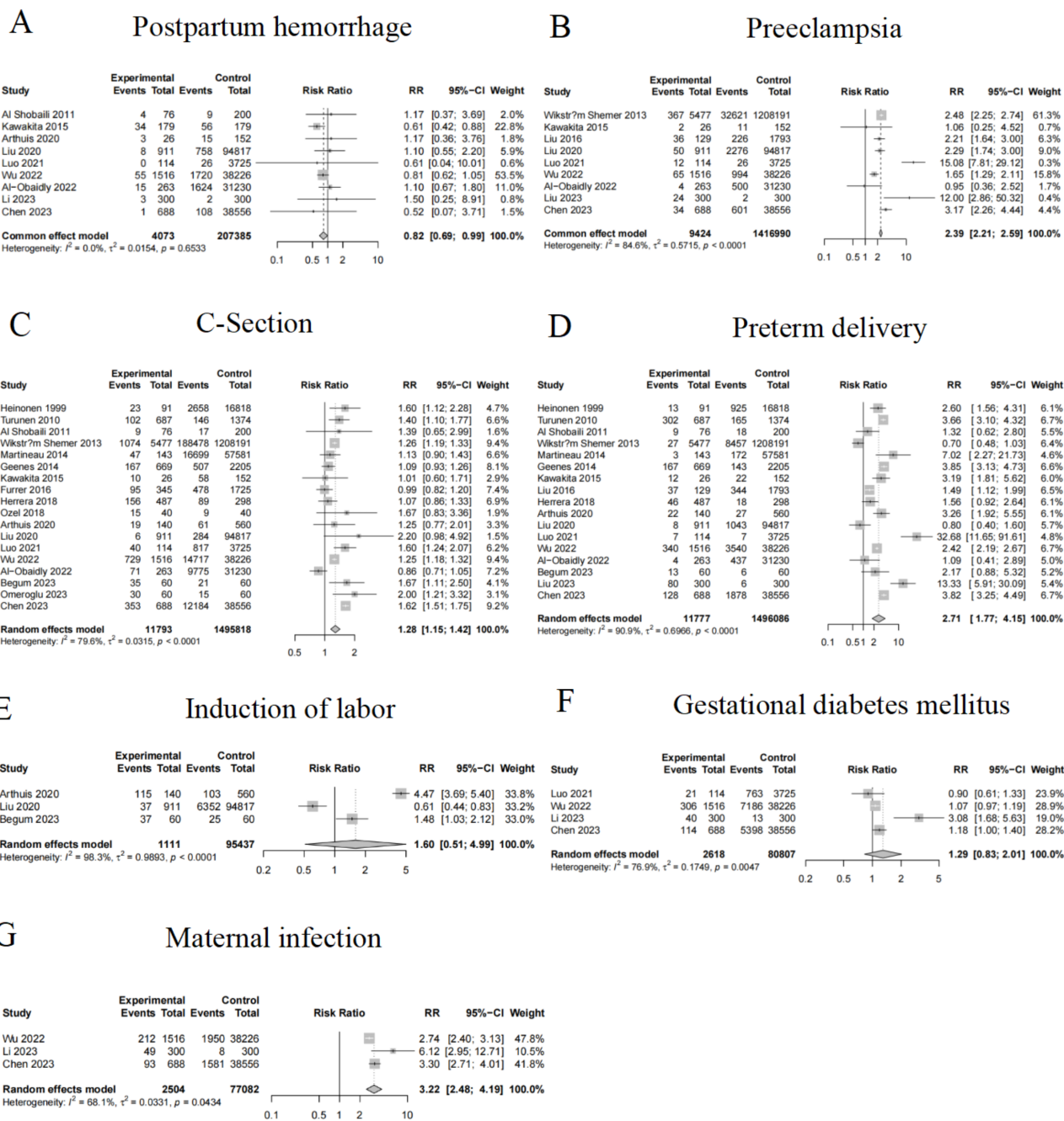


Fig. 3. Forest plot of the meta-analysis comparing the ICP group and the non-ICP group on adverse maternal outcomes. (A) displays the RR for “ICP and Postpartum hemorrhage”. (B) shows the RR for “ICP and Preeclampsia”. (C) illustrates the RR for “ICP and C-Section”. (D) presents the RR for “ICP and Preterm delivery”. (E) displays the RR for “ICP and Induction of labor”. (F) shows the RR for “ICP and Gestational diabetes mellitus”. (G) displays the RR for “ICP and Maternal infection”. Note: 95% CI represents the 95% confidence interval. Based on the heterogeneity results, a random effects model should be chosen if $p < 0.05$ or $I^2 > 50\%$; otherwise, a fixed-effects model should be used. The vertical line in the center of the plot represents the null line, where standardized mean difference (SMD) or mean difference (MD) = 0, denoting no statistical association between the study factor and the outcome. Each horizontal line represents the 95% CI of a study. The small square in the middle of the horizontal line shows the point estimate of SMD or MD. The size of the square reflects the weight of the study. If the 95% CI horizontal line of a study does not cross the null vertical line (i.e., the 95% CI does not include 1), it suggests a statistically significant association between the study factor and the outcome. C-section, Cesarean section; RR, relative risk.

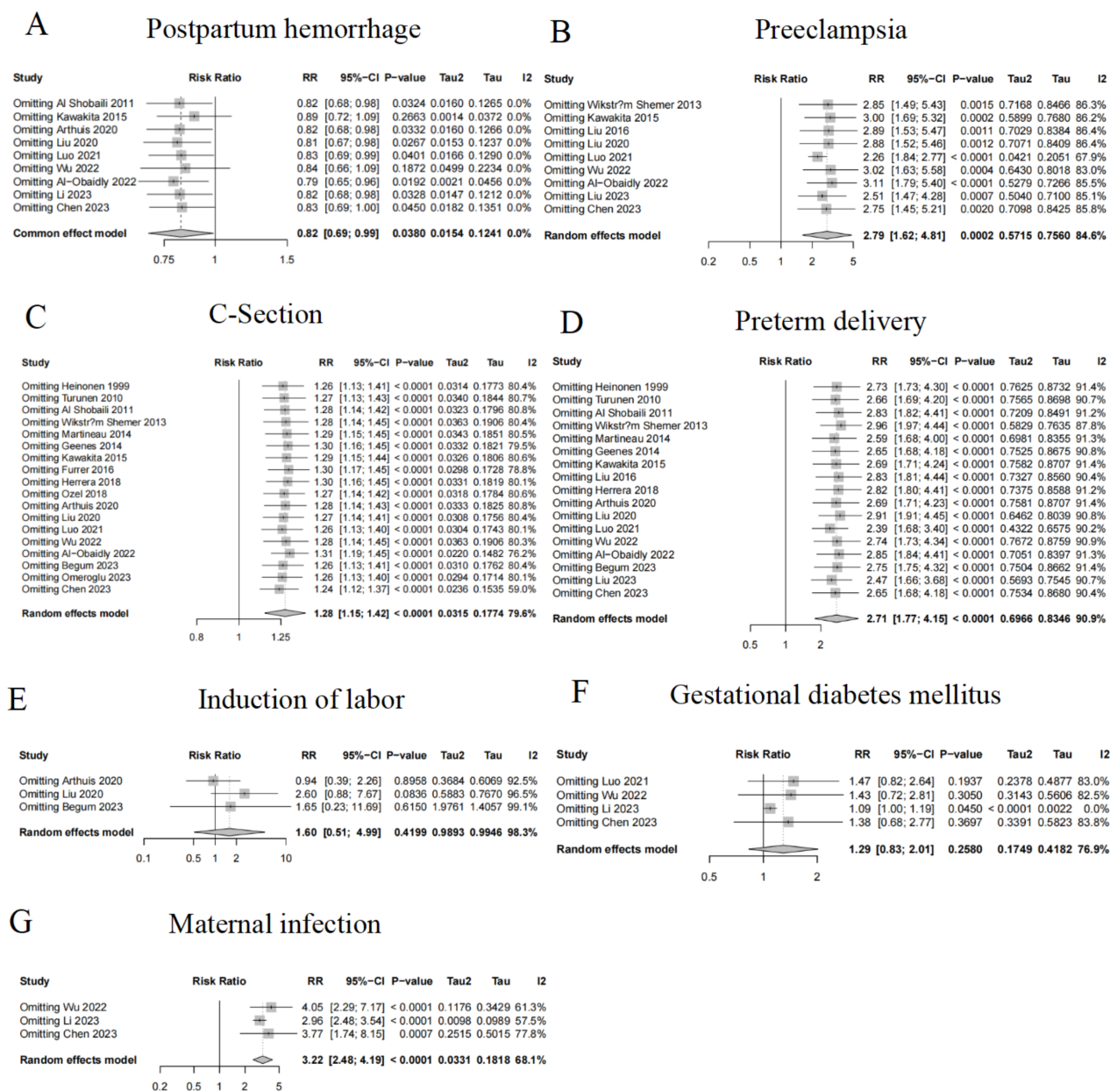


Fig. 4. Sensitivity analysis of the ICP group vs. the non-ICP group on adverse maternal outcomes. (A) Sensitivity analysis of the ICP group vs. the non-ICP group on postpartum hemorrhage outcomes. (B) Sensitivity analysis of the ICP group vs. the non-ICP group on preeclampsia outcomes. (C) Sensitivity analysis of the ICP group vs. the non-ICP group on C-section outcomes. (D) Sensitivity analysis of the ICP group vs. the non-ICP group on preterm delivery outcomes. (E) Sensitivity analysis of the ICP group vs. the non-ICP group on Induction of labor outcomes. (F) Sensitivity analysis of the ICP group vs. the non-ICP group on gestational diabetes mellitus outcomes. (G) Sensitivity analysis of the ICP group vs. the non-ICP group on Maternal infection outcomes.

dispositions may play a dominant role in influencing the incidence risk. Although the random-effects model estimates a pooled incidence of 3% (95% CI: 1%–7%), the extreme heterogeneity ($\tau^2 = 2.79$) cautions against overinterpreting the global estimate. Our study clearly shows that ICP significantly increased the risk of adverse outcomes in pregnant women. These outcomes included preeclampsia, C-section, preterm delivery, and maternal infections. The

effect of ICP on preeclampsia is consistent with previous studies [3,23,32]. Preeclampsia is a major contributor to hypertension-related diseases during pregnancy and is associated with high maternal and neonatal mortality and morbidity [33]. Studies have confirmed that ICP increases the risk of preeclampsia through various mechanisms, particularly the impact of elevated bile acid levels on the vascular endothelium [19,20,26]. Coupled with liver dysfunction,

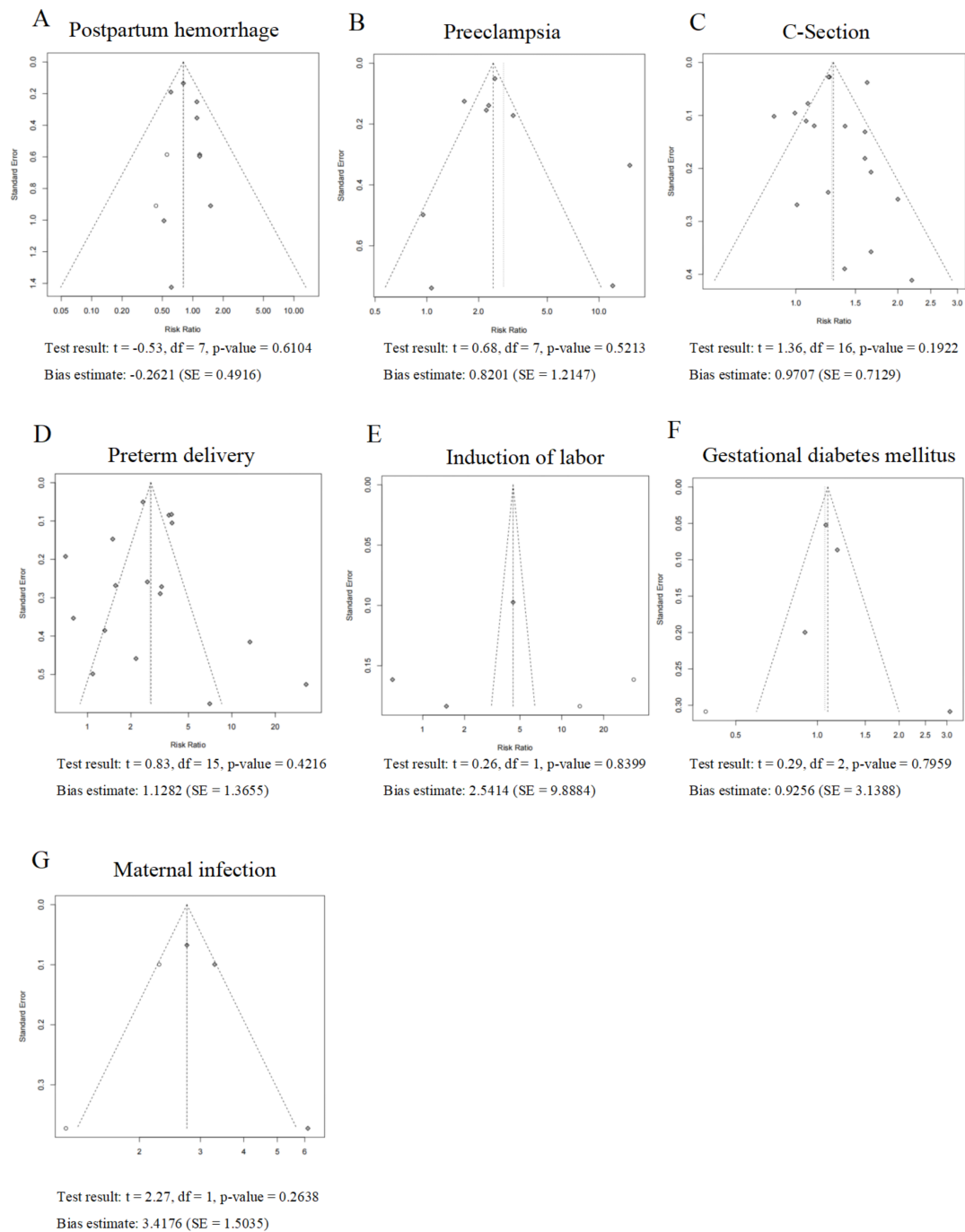
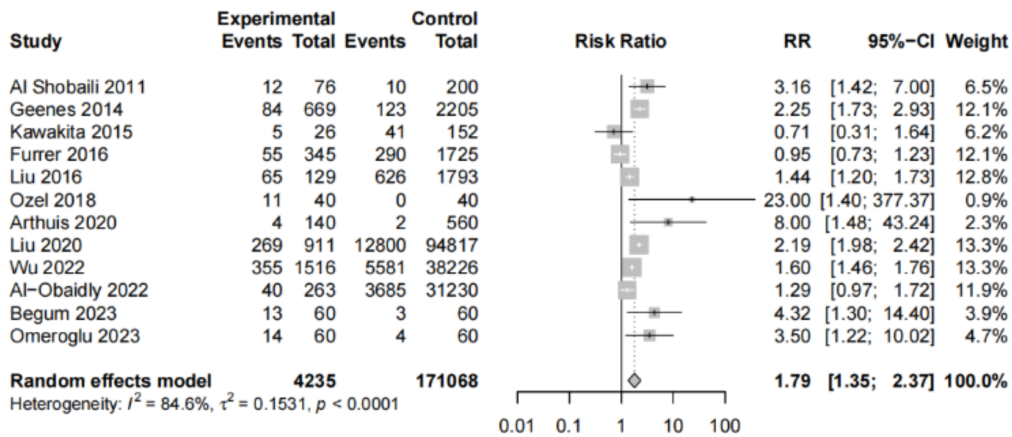


Fig. 5. Publication bias analysis of the ICP group vs. the non-ICP group on adverse maternal outcomes. (A) Funnel plot depicting publication bias for postpartum hemorrhage with the associated test results. (B) Funnel plot depicting publication bias for preeclampsia with the associated test results. (C) Funnel plot depicting publication bias for C-section with the associated test results. (D) Funnel plot depicting publication bias for preterm delivery with the associated test results. (E) Funnel plot depicting publication bias for Induction of labor with the associated test results. (F) Funnel plot depicting publication bias for gestational diabetes mellitus with the associated test results. (G) Funnel plot depicting publication bias for maternal infection with the associated test results. Each dot represents an individual study. SE, standard error; df, degrees of freedom.

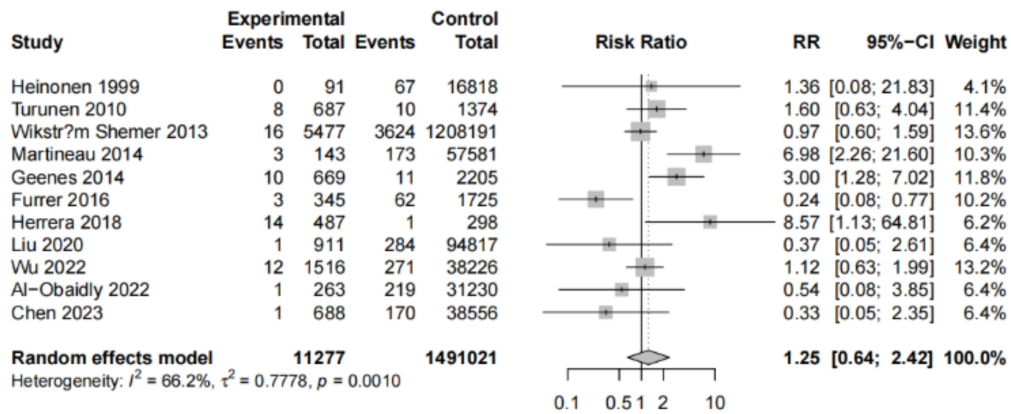
this can exacerbate the pathological processes of pregnancy hypertension [34]. The elevated serum liver enzyme levels in ICP patients further suggest the potential link between liver dysfunction and hypertension during pregnancy.

Furthermore, we observed that ICP increased the risk of C-section, with a risk ratio of 1.28 (95% CI, 1.15–1.42). This aligns with other studies, highlighting a close relationship between ICP and C-section. Possible mechanisms in-

A NICU admission



B Stillbirth



C SGA

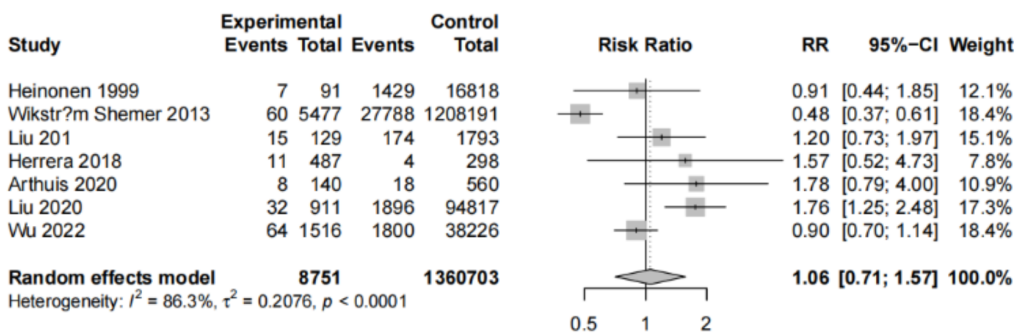
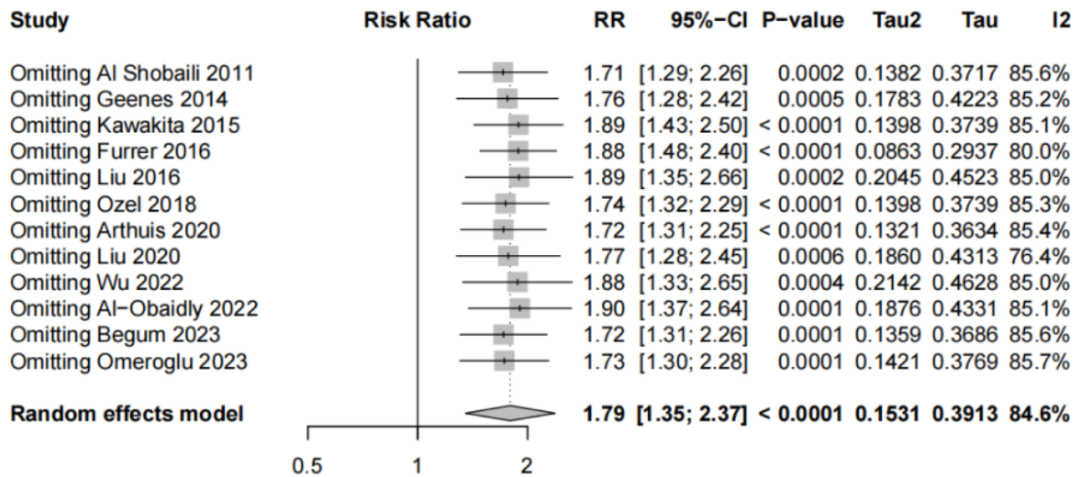


Fig. 6. Forest plot of the meta-analysis on neonatal adverse outcomes in the ICP group and the non-ICP group. (A) displays the RR for “ICP and NICU admission”. (B) shows the RR for “ICP and Stillbirth”. (C) illustrates the RR for “ICP and SGA”. NICU, neonatal intensive care unit; SGA, small for gestational age.

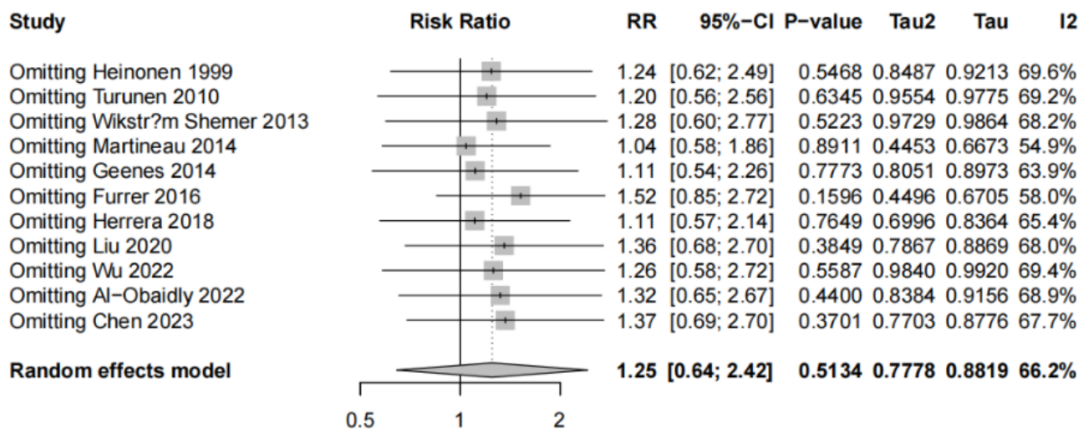
A

NICU admission



B

Stillbirth



C

SGA

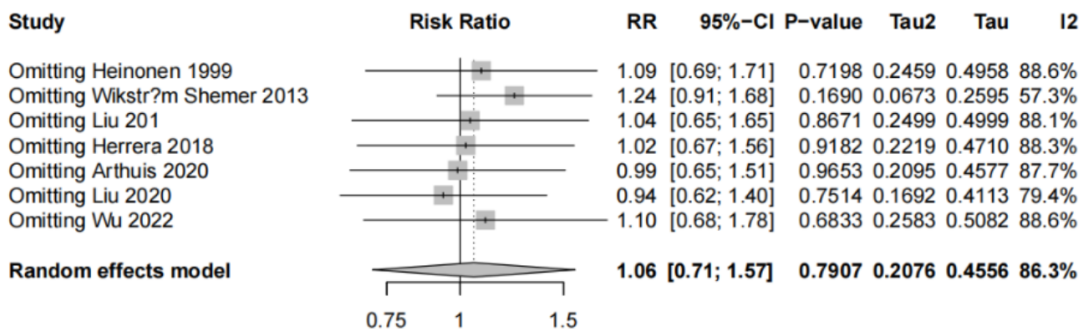


Fig. 7. Sensitivity analysis of neonatal adverse outcomes in the ICP group and the non-ICP group. (A) Sensitivity analysis of the ICP group vs. the non-ICP group on NICU admission. (B) Sensitivity analysis of the ICP group vs. the non-ICP group on Stillbirth. (C) Sensitivity analysis of the ICP group vs. the non-ICP group on SGA outcomes.

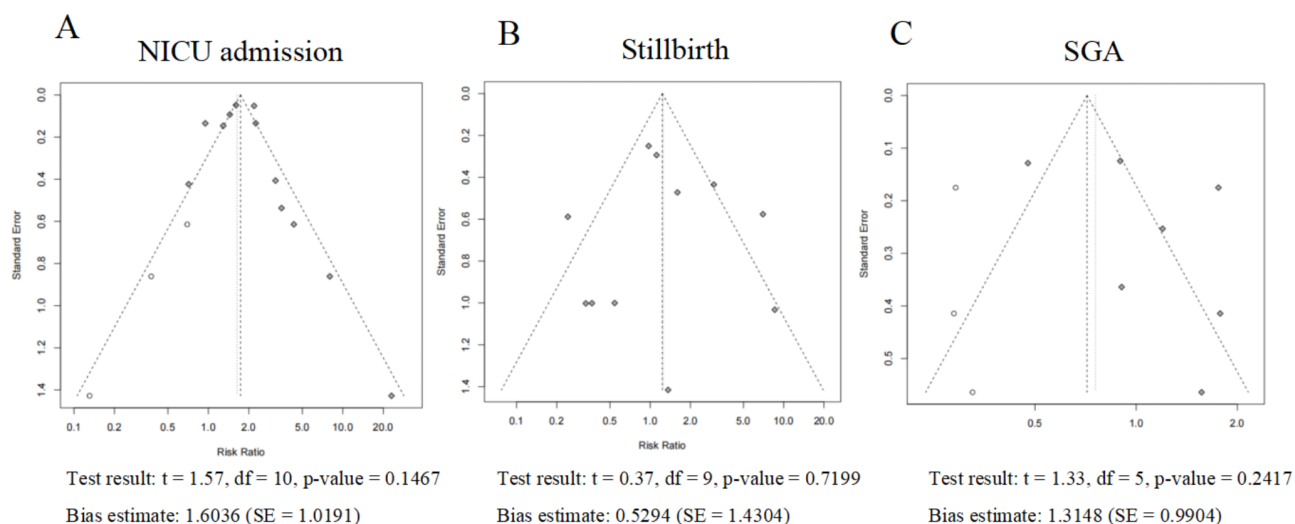


Fig. 8. Publication bias analysis of neonatal adverse outcomes in the ICP group and the non-ICP group. (A) Funnel plot depicting publication bias for NICU admission with the associated test results. (B) Funnel plot depicting publication bias for Stillbirth with the associated test results. (C) Funnel plot depicting publication bias for SGA with the associated test results. Each dot represents an individual study.

clude fetal intrauterine stress responses, particularly the occurrence of fetal distress. This often leads to an emergency C-section to protect both maternal and fetal lives [5,25,35]. ICP patients may also suffer from placental insufficiency, which affects fetal oxygen supply and growth. This contributes to the increased need for C-section [25]. Additionally, ICP patients frequently experience severe pruritus and elevated bile acid levels. These factors can affect maternal physical health and increase psychological stress. This may influence the choice of delivery method and clinical decision-making, further raising the risk of C-section [28].

As found in our study, ICP significantly increased the risk of preterm delivery. Preterm delivery is a common complication of pregnancy that directly impacts maternal and neonatal health, particularly concerning fetal growth and development. Elevated bile acid levels can affect fetal development through the placenta, potentially disrupting the intrauterine environment and promoting the onset of preterm delivery [35]. Bile acids can affect fetal oxygen and nutrient supply through the placenta and may also activate maternal immune responses, leading to complications like uterine contractions and premature rupture of fetal membranes. Preterm delivery is commonly correlated with higher neonatal mortality and birth defects. This finding highlights the need for early screening and intervention in ICP patients to prevent preterm delivery.

The risk of maternal infections in ICP patients is increased. This aligns with existing literature, indicating that elevated bile acid levels, liver dysfunction, and immune system dysregulation are likely mechanisms behind the increased risk of infection in ICP patients. These patients often exhibit abnormal immune function, making them more

susceptible to infections. During labor, factors like surgical trauma or birth canal infections further elevate the risk of infections [36]. Therefore, ICP patients need treatment for heightened bile acid levels and liver dysfunction, along with special attention to prevent pregnancy-related infections, especially during labor.

Although this study primarily focused on maternal adverse outcomes, we also analyzed the potential impact of ICP on neonatal outcomes. As evidenced by the results, ICP is closely associated with an increased risk of neonatal admission to NICU. Indeed, the risk of neonatal NICU admission in the ICP group was 1.79 (95% CI, 1.35–2.37), highlighting the significant impact of ICP on neonatal health. Elevated bile acid levels not only impair maternal liver function but also cross the placenta, affecting fetal development and health. This can lead to fetal distress, increasing the likelihood of NICU admission. The heightened risk of intrauterine stress responses in the fetus may expose the fetus to more acute complications, raising the demand for NICU care [37].

The quantitative evidence from this study provides crucial decision-making support for the clinical management of ICP. Given the global incidence of 3% (95% CI: 1%–7%), it is recommended that systematic liver function screening begin at 24 weeks of gestation in high-risk regions, such as Asia, along with dynamic monitoring of pruritus symptoms for early diagnosis. In response to the significantly increased risks of preeclampsia (RR = 2.39), maternal infection (RR = 3.22), and preterm delivery (RR = 2.71), clinicians should establish a multidimensional monitoring system. For diagnosed patients, weekly monitoring of fetal heart rate and biophysical scoring should be

gin at 32 weeks of gestation, with the planned delivery time advanced to 37–38 weeks. During labor, routine dynamic monitoring of C-reactive protein and procalcitonin should be implemented, and an infection warning scoring system should be initiated within 48 hours postpartum. Notably, although the risk of C-section is increased (RR = 1.28), the risk of postpartum hemorrhage shows a paradoxical reduction (RR = 0.82), suggesting that regional guidelines should balance the use of uterotonic agents and thrombosis prevention strategies. For example, in Asian populations, the indications for uterotonic agents may be moderately relaxed, whereas European populations should maintain current standards. Additionally, the increased demand for neonatal intensive care (RR = 1.79) calls for collaborative perioperative transition plans between obstetric and pediatric teams. Future research should focus on elucidating the dose-response relationship between bile acid levels and complications, as well as conducting multicenter intervention trials to validate the generalizability of stratified management pathways, ultimately achieving comprehensive optimization from risk warning to precise intervention.

The main strength of this study lies in its systematic design and rigorous implementation, particularly in the application of various statistical tools during the literature search and data analysis. These included the use of fixed-effects and random-effects models, as well as sensitivity analysis and funnel plots to validate the stability of the results. These methods enhanced the credibility and reliability of the conclusions. By comprehensively analyzing multiple obstetric outcomes, this study provided detailed reference data for clinicians. It helps identify high-risk individuals among ICP patients and provides theoretical support for personalized management and early intervention. Our meta-analysis integrated a large amount of data and helped strengthen the scientific understanding of the association between ICP and maternal health risks. It also supports better clinical decision-making. While this systematic review and meta-analysis provide robust evidence through rigorous methodology, several limitations warrant consideration. First, the generalizability of findings is constrained by the geographical and ethnic composition of included studies. Over 80% of primary data originated from European and North American populations, potentially underrepresenting developing regions where ICP prevalence and risk profiles may differ substantially. Second, critical clinical variables such as maternal comorbidities, particularly pregestational diabetes, socioeconomic status, and longitudinal bile acid monitoring data were inconsistently reported across studies, limiting our ability to conduct stratified analyses. Third, despite employing random-effects models and sensitivity analyses to address heterogeneity, residual confounding may persist due to unmeasured factors like genetic predisposition and regional variations in obstetric care protocols. Additionally, while funnel plots showed

no significant publication bias for maternal outcomes, the exclusion of gray literature and non-English studies might have skewed neonatal outcome estimates. Future research should prioritize prospective registries with standardized ICP diagnostic criteria and improved reporting of ethnodemographic confounders.

In summary, this study offers valuable evidence on the correlation between ICP and adverse outcomes in pregnant and postpartum women, as well as neonates. However, these results still need to be validated through broader, more methodologically rigorous future research. As our understanding of ICP deepens, future studies should not only focus on assessing the risk of obstetric complications but also explore its underlying pathophysiological mechanisms and biomarkers. This will help provide a solid theoretical foundation for the early diagnosis and personalized treatment of ICP.

5. Conclusions

This study, through systematic evaluation and meta-analysis, suggests a strong association between ICP and adverse outcomes in pregnant and postpartum women, such as preeclampsia, C-section, preterm delivery, GDM, and maternal infections. It provides valuable scientific evidence to inform clinical management. However, the heterogeneity observed in certain outcomes, the potential influence of confounding variables, and statistical limitations in the analysis of neonatal outcomes indicate that further validation is needed. Future research should focus on higher-quality, larger-scale prospective studies to further examine the mechanisms by which ICP impacts maternal and fetal health, thereby offering more precise guidance for clinical diagnosis and treatment.

Availability of Data and Materials

The data and materials used in this meta-analysis are publicly available. The individual study data were retrieved from the PubMed, Embase, and Cochrane Library databases. The search strategies and inclusion/exclusion criteria are described in the Materials and Methods section.

Author Contributions

PY and MZ conceived the study. PY, MZ, and CH developed the study protocol and data analysis plan. MZ and CH conducted the study quality assessment. PY, MZ, and CH performed the statistical analysis. PY, CH and MZ wrote the first draft of the manuscript. All authors reviewed and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/CEOG37850>.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this systematic review and meta-analysis, we used ChatGPT, an artificial-intelligence-based tool, to check spelling and grammar during the initial drafting stage of the manuscript. After composing the text, ChatGPT scanned it to identify potential spelling errors and improper grammar usage. Nevertheless, this tool was just a part of the overall writing process. We thoroughly reviewed and edited the content as required after using ChatGPT and remains fully responsible for the final content of the publication, including data accuracy, analysis validity, and result interpretation, thus ensuring the academic integrity and scientific rigor of the work.

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