Very young and advanced maternal age strongly elevates the occurrence of nonchromosomal congenital anomalies: a systematic review and meta-analysis of population-based studies

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BACKGROUND: Nonchromosomal congenital anomalies (NCAs) are the most common cause of infant mortality and morbidity. The role of maternal age is well known, although the specifics are not thoroughly elucidated in the literature.

OBJECTIVE: To evaluate the role of maternal age in the incidence of NCAs and to pinpoint age groups at higher risk to refine screening protocols.

STUDY DESIGN: A systematic review and meta-analysis were conducted following the PRISMA 2020 guidelines and *Cochrane Handbook*. Searches were performed on October 19, 2021, across MEDLINE (via PubMed), Cochrane Library (CENTRAL), and Embase. Population-based studies assessing the impact of maternal age on the incidence of NCAs in pregnant women were included, without restrictions on age range, country, or comorbidities. A random-effects model was used for pooling effect sizes, considering the heterogeneity across studies.

RESULTS: From 15,547 studies, 72 were synthesized. Maternal age >35 showed an increased NCA risk (risk ratio [RR]: 1.31, confidence interval [CI]: 1.07 -1.61), rising notably after>40 (RR: 1.44, CI: 1.25 -1.66). The latter changes to 1.25 (CI: 1.08 -1.46) if the co-occurrence of chromosomal aberrations is excluded. Specific anomalies like cleft lip/palate (>40, RR: 1.57, CI: 1.11 -2.20) and circulatory system defects (>40, RR: 1.94, CI: 1.28 -2.93) were significantly associated with advanced maternal age. Conversely, gastroschisis was linked to mothers <20 (RR: 3.08, CI: 2.74 -3.47).

CONCLUSION: The study confirms that both very young and advanced maternal ages significantly increase the risk of NCAs. There is a pressing need for age-specific prenatal screening protocols to better detect these anomalies, especially considering the current trend of delayed childbearing. Further research is required to fully understand the impact of maternal age on the prevalence of rarer NCAs.

Key words: aging, congenital abnormalities, maternal age, nonchromosomal anomalies, pregnancy, screening

Introduction

Congenital anomalies are structural or functional abnormalities that occur during intrauterine life and can be identified intrauterinely, at birth, or, less often, only during infancy.[1] Congenital anomalies are the most common cause of infant mortality and morbidity, accounting for the loss of 25.3 to 38.8 million disability-adjusted life years worldwide.[2] According to data provided by the World Health Organization, 6% of babies are born with a congenital anomaly.[3] Maternal age is included among the many known risk factors, and the significance of advanced maternal age (AMA) (≥35) particularly appears to be supported.

Over the last few decades, there has been an increasing trend in women's average delivery age.[4] An increasing portion of couples are having their first child over the maternal age of 30 to 35 years.[5] Many studies have associated the postponement of childbearing with various pregnancy and fetal complications[6–8] sand made

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The authors report no conflict of interest.

Ethical approval: No ethical approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct or interpretation of our study.

The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

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AJOG at a Glance

Why was this study conducted?

This study was conducted to investigate how maternal age affects the risk of nonchromosomal congenital anomalies by analyzing data from numerous population-based studies.

Key findings

Very young and advanced maternal ages are linked to a higher incidence of these anomalies. Specifically, risks increase significantly for those over 40 years old, with elevated risks for conditions affecting the circulatory system and cleft lip/palate, and for those under 20, with a notable rise in gastroschisis cases.

What does this add to what is known?

First in-depth meta-analysis of the age dependence of the risk of nonchromosomal congenital anomalies by anomaly category. This highlights the necessity for age-specific prenatal screening protocols to better detect congenital anomalies.

recommendations on managing these high-risk pregnancies.[9] Among congenital anomalies, chromosomal abnormalities (CAs) are clearly associated with AMA,[10–13] a long-established fact that has led to the current professional screening protocols that are widely used worldwide and constantly evolving.[14,15] However, the etiology of nonchromosomal congenital anomalies (NCAs) is far from being fully understood. While the role of maternal age in the development of NCAs is well known and is the subject of active research, the literature is inconsistent in its assessment of the risk of NCAs in different age groups. This is a major issue not only because of the trend towards delayed childbearing but also because of the emerging risks of adolescent pregnancies.

Objective

Considering the disagreement in the literature, we aimed to investigate the role of maternal age in the occurrence of NCAs in a meta-analysis. There are currently no meta-analyses or other comprehensive studies that specifically and exclusively examine the association of NCAs with maternal age. We hypothesized that both very young and AMAs increase the risk of NCAs. We aimed to identify high-risk age groups to improve screening protocols and reach a better detection rate for NCAs.

Methods

We reported our systematic review and meta-analysis based on the recommendation of the PRISMA 2020 guideline[16] (see Supplemental Table 1), and we followed the Cochrane Handbook for Systematic Reviews of Interventions.[17] The protocol of the study was prospectively registered on International Prospective Register of Systematic Reviews[18] (registration number CRD42021283593), and we adhered to it, with some deviations: title adjustment for clarity and summary purposes; subgroup analyses were conducted but not prespecified; searches included screening reference lists of eligible articles; only population-based studies with exact NCA counts were included to enable risk assessment; risk ratios (RRs) were used instead of odds ratios for ease of interpretation; publication bias assessed only visually. However, these modifications are fundamentally technical in nature and do not alter the conceptual framework of the study.

Information sources

The systematic search was conducted in 3 comprehensive medical databases: MEDLINE (via PubMed), the Cochrane Library (CENTRAL), and Embase on October 19, 2021.

Search strategy

We used for the systematic search the following search key: (“maternal age” OR “maternal ages” OR “mother age” OR “mother ages”) AND (((congenital OR birth) AND (anomaly OR anomalies OR disorder OR disorders OR malformation OR malformations OR defect OR defects)) OR congenital abnormalities. No language restrictions or filters were applied during the search. We also screened the reference list of eligible articles.

Eligibility criteria

We formulated our research question using the population, exposure, comparator, outcome framework. We included population-based studies reporting on pregnant women (P). We did not have predefined exclusion criteria (eg, age range, country, comorbidities) for our population. Eligible studies compared different maternal age groups (E and C) regarding NCAs. We examined every predefined age group reported by the eligible studies. Our primary outcome (O) was the rate of total NACs, while we considered as secondary outcomes the various structural defects regarding different organ systems (eg, congenital heart defects [CHDs]) and common birth defects separately. We did not have predefined diagnostic criteria for the NCAs. Studies not reporting on the exact number of NCAs in the different age groups and the total number of patients were not eligible. The following exclusion criteria were predefined: CAs as target outcomes; case-control or cohort studies; case series; and case reports, because our concept was to analyze relative frequency.

Study selection

After removing duplicates, the selection was performed independently by 3 review authors (B.P., F.I., and Z.B.), first by title, then by abstract, and finally based on full text according to the aforementioned criteria. Endnote v20 (Clarivate Analytics, Philadelphia, PA) reference manager software was used for the selection. We calculated Cohen’s kappa coefficient (κ) after each selection process to measure interrater reliability.[19] Disagreements were resolved by consensus; if consensus was not reached, a final decision was made with involvement from a fourth independent review author (S.V.). The study selection process is shown using PRISMA 2020 flowchart (Figure 1).

Data extraction

Three authors (B.P., F.I., and Z.B.) independently collected data from the eligible articles. In the case of disagreement, the decision was based on consensus. If consensus was not reached, a final decision was made by involving a fourth author (S.V.).

The following data were extracted with a standardized collection method to an Excel sheet (Office 365, Microsoft, Redmond, WA): first author, the year of publication, study population, study period, study site (country), study design, demographic data of the patients, total number of patients in the age groups, number of NCAs in the age groups, and information for assessing the risk of bias in the studies.

We extracted the total number of live births and events involving birth defects from each study. To investigate which maternal age increases the probability of particular birth defects, we used the age categories from the included studies or defined new ones by merging 2 or more age groups. The age group of 20- to 30-year-old mothers was used as a reference group. In defining the age groups, the ideal 10-year period was based on other studies, including our own work.[20] We aimed to look at AMA (35 or older), as commonly defined; very young mothers (under 20); and mothers over 40. In addition, between 30 and 40 years of age, we created additional groupings with a 5-year split to investigate at which stage the risk increase occurs for each anomaly. We only included studies for each outcome in the analysis if the reference and at least 1 more age category could be formed. For maximum accuracy, we grouped the endpoints according to the International Classification of Diseases-10 (ICD-10) categories.

Assessment of risk of bias

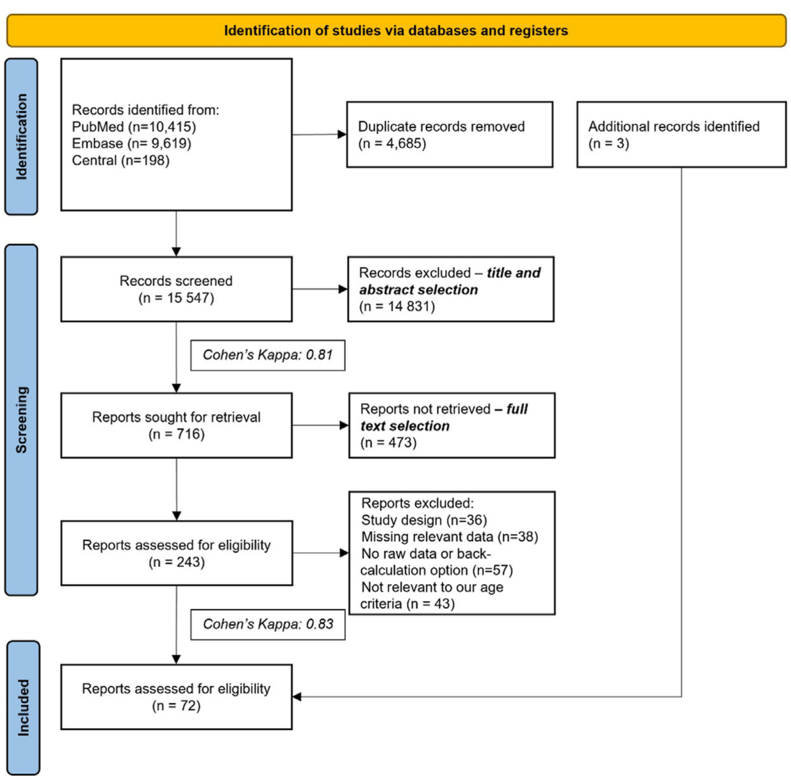
Two authors (B.P., Á.M.) performed the risk of bias assessment independently with the help of the Quality in Prognostic Studies tool.[21] Disagreements were resolved by a third review author (S.V.) (Supplementary Table 3). The specific methodological details are described in Supplemental Appendix 1. The web-based version of the Risk-of-Bias VISualization tool was used to visualization of the results (Supplementary Table 4).[22]

Data synthesis

We carried out a mathematical synthesis if there were at least 3 homogenous articles regarding the age groups and NACs.

All statistical analyses were made with R[23] using the meta (Schwarzer 2022, v5.5.0; University of Freiburg, Freiburg, Germany) and dmetar (Cuijpers

FIGURE 1
PRISMA 2020 flowchart representing the study selection process



[Amsterdam, Netherlands], Furukawa [Tokyo, Japan], and Ebert [Zurich, Switzerland] 2022, v0.0.9000) packages.[24]

We anticipated considerable between-study heterogeneity in the study population; therefore, a random-effects model was used to pool effect sizes. RR with 95% confidence interval (CI) was calculated as a random effects estimate with the metabin function of the meta (Schwarzer 2022, v5.5.0) R package. The Mantel-Haenszel method[25–27] was used to pool RRs. Since the exact Mantel-Haenszel method was used, we did not apply continuity correction to handle 0 cell counts.[28]

For outcomes with at least 5 studies, a Hartung-Knapp adjustment was used.[29,30]

We applied the Paule-Mandel method[31] to estimate the between-study variance (tau^2).

Additionally, between-study heterogeneity was investigated by Cochrane's Q test. Significant heterogeneity was considered at $P < .1$. Higgins & Thompson's I^2 statistics and 95% CI (30) were reported to illustrate the total variation across studies due to between-study heterogeneity.

Following the recommendations of IntHout et al,[32] where applicable, we also reported the prediction intervals (ie, the expected range of effects of future studies) of the pooled estimates.

A Cochrane Q test was used between subgroups to assess the age group differences. The null hypothesis was rejected at a 5% significance level. We used forest plots to summarize the results graphically. All statistical analyses were made with R (R Core Team 2022, v4.2.0) using the meta (Schwarzer 2022, v5.5.0) and dmetar (Cuijpers, Furukawa, Ebert 2022, v0.0.9000) packages.

Results

Study selection

Altogether 15,547 studies were identified by our search, from which 72 full-text articles were included in our synthesis following the selection process described above (Figure 1).

Study characteristics

The baseline characteristics of the enrolled studies are detailed in Supplemental Table 1.

Our meta-analysis includes population-based studies from around the world. A precise geographic location is indicated in the baseline table. From the American continent, 37 articles were included; from Europe, 17; from Asia, 14; from Australia, 3; and from Africa 1. In terms of the study's examination period, the included articles encompass an overall timeframe between 1940 and 2018. All studies are population-based, with 36 studies carried out at the national level, 34 at the subnational level, and 2 at the multinational level, mostly based on the corresponding registries.

Risk of bias assessment

The results of the risk of bias assessment are presented in Supplemental Table 2.

Publication bias and heterogeneity: Most of our analyses showed high heterogeneity. This is attributable to the diversity of geographical regions, population sizes, date, and duration of the study periods represented by the included studies.

Based on the visual inspection of the funnel plots we did not find significant publication bias. The inspection of funnel plots was used to assess publication bias when a minimum of 10 articles were available for 1 outcome (Supplemental Figures 18–37).

Synthesis of results

The role of maternal age in the occurrence of NCAs

Table summarizes our results, while in the Supplementary Materials, we detail each of our forest plots. By default forest plots and summary statistics were prepared including all eligible studies regadless concommittant CAs.

Regarding our primary outcome, when we analyzed the total NCAs, we found that age >35 (RR 1.31, CI: 1.07–1.61) and especially age >40 (RR 1.44, CI: 1.25–1.66) increase the risk of NCAs (Figure 2). On this topic, we conducted 2 subgroup analyses to investigate this question more deeply. When we examined the age risk of total NCAs without the co-occurrence and influence effects of CAs, we found significant results for the >40 age category (RR 1.25, CI: 1.08–1.46). Furthermore, in the analysis where the influence of the chromosome abnormality was present, the risk of NCAs was found to increase in relation to maternal age >35 (RR 1.26, CI: 1.12–1.42) and >40 (RR 1.63, CI: 1.26–2.09), with risk increasing each year.

Congenital malformations of the nervous system (Q00–Q07)

Analyzing 5 to 10 articles from different age groups, we found no effect between maternal age and congenital nervous system malformations.

Congenital malformations of the circulatory system (Q20–Q28)

We found a risk-increasing effect of AMA (>40, RR 1.94, CI: 1.28–2.93). Among the diseases of the circulatory system, we highlighted the group of CHDs, where we also found the risk-increasing effect of AMA (>35, RR 1.50, CI: 1.11–2.04 and >40, RR 1.75, CI: 1.32–2.32), while the preventive effect of young maternal age was observed (<20, RR 0.87, CI: 0.78–0.97; Figure 3).

Cleft lip and cleft palate (Q35–Q37)

AMA (>40, RR 1.57, CI: 1.11–2.20) increased the risk of cleft lip and cleft palate. Regarding cleft palate separately, we found an even higher risk with AMA, which appears as early as the 35th maternal age (age >35, RR 1.78, CI: 1.16–2.73, and age >40, RR 1.77, CI: 1.48–2.11).

Congenital malformations of the digestive system (Q38–Q45)

We found a risk-increasing effect of AMA (age >40, RR 2.16, CI: 1.34–3.49).

Congenital malformations of the urinary system (Q60–Q64)

We could not show an association between maternal age and congenital malformations of the urinary system after analyzing 3 eligible population-based articles with homogeneous age categories.

Congenital malformations and deformations of the musculoskeletal system (Q65–Q79)

We did not find an association with maternal age. However, this can also be explained by the low number of articles, the heterogeneity, and the diverse nature of the group.

Other malformations

On the other hand, we found a clear association between maternal age and

TABLE

Summary of our results based on International Classification of Diseases-10 groups

Congenital anomaly	ICD-10 category	Age<20	N	Age 30—35	N	Age 35—40	N	Age>35	N	Age>40	N
All NCAs (with or without CAs)	Q00—Q89	1.08 (0.89; 1.32)	14	1.23 (0.85; 1.78)	13	1.47 (0.87; 2.49)	9	1.31 (1.06; 1.61)	13	1.44 (1.25; 1.66)	11
All NCAs (without CAs)	Q00—Q89	1.21 (0.59; 2.49)	5	1.54 (0.55; 4.32)	6	1.73 (0.45; 6.70)	5	1.37 (0.76; 2.45)	6	1.25 (1.08; 1.46)	6
All NCAs (with CAs)	Q00—Q89	1.15 (0.87; 1.52)	10	1.02 (0.99; 1.06)	7	1.20 (0.99; 1.44)	4	1.26 (1.12; 1.42)	7	1.63 (1.26; 2.09)	6
Nervous system	Q00—Q07	1.16 (0.74; 1.81)	10	1.64 (0.70; 3.81)	8	2.56 (0.64; 10.32)	5	1.53 (0.80; 2.94)	8	1.56 (0.67; 3.62)	7
Encephalocele	Q01	1.76 (0.44; 7.12)	3	1.51 (0.33; 6.83)	3	No data		1.43 (0.57; 3.60)	3	No data	
Congenital hydrocephalus	Q03	1.19 (1.02; 1.38)	2	No data		No data		No data		No data	
Spina bifida	Q05	1.30 (0.93; 1.82)	9	1.15 (0.65; 2.06)	8	1.79 (0.61; 5.31)	5	1.39 (0.75; 2.59)	8	1.96 (0.72; 5.31)	5
Anencephaly	Q00.0	1.40 (0.98; 1.99)	9	1.15 (0.72; 1.84)	8	1.20 (0.53; 2.72)	6	1.02 (0.60; 1.72)	8	1.30 (0.71; 2.38)	6
Circulatory system	Q20—Q28	0.87 (0.68; 1.11)	3	1.09 (1.00; 1.20)	3	1.18 (0.94; 1.49)	3	1.33 (0.97; 1.82)	3	1.94 (1.28; 2.93)	4
Congenital heart defects	Q20—Q26	0.87 (0.78; 0.97)	10	1.45 (0.83; 2.52)	10	1.91 (0.65; 5.62)	6	1.50 (1.11; 2.04)	10	1.75 (1.32; 2.32)	6
Cleft lip and palate	Q35—Q37	0.93 (0.76; 1.14)	6	1.58 (0.77; 3.22)	6	1.85 (0.59; 5.75)	4	1.47 (0.95; 2.28)	6	1.57 (1.11; 2.20)	4
Cleft palate	Q35	0.99 (0.56; 1.73)	6	1.42 (0.66; 3.06)	8	2.08 (0.54; 7.99)	5	1.78 (1.16; 2.73)	8	1.77 (1.48; 2.11)	5
Digestive system	Q38—Q45	0.98 (0.71; 1.37)	2	No data		No data		No data		2.16 (1.34; 3.49)	2
Urinary system	Q60—Q64	No data		0.97 (0.75; 1.26)	3	No data		0.86 (0.57; 1.29)	3	No data	
Hypospadiasis	Q54	0.99 (0.91; 1.07)	5	1.06 (0.96; 1.17)	4	No data		1.11 (0.88; 1.39)	4	No data	
Musculoskeletal system	Q65—Q79	0.88 (0.72; 1.08)	2	No data		0.93 (0.71; 1.22)	2	0.94 (0.65; 1.37)	2	0.90 (0.55; 1.46)	3
Congenital diaphragmatic hernia	Q79.0	0.96 (0.88; 1.06)	5	1.74 (0.52; 5.80)	4	No data		1.52 (0.79; 2.91)	5	No data	
Omphalocele	Q79.2	1.44 (1.08; 1.92)	14	1.13 (0.85; 1.50)	14	1.35 (0.98; 1.87)	13	1.47 (1.20; 1.79)	14	2.57 (1.77; 3.73)	13
Gastroschisis	Q79.3	3.08 (2.74; 3.47)	22	0.32 (0.23; 0.44)	17	0.27 (0.16; 0.47)	12	0.22 (0.15; 0.32)	17	0.41 (0.23; 0.74)	11

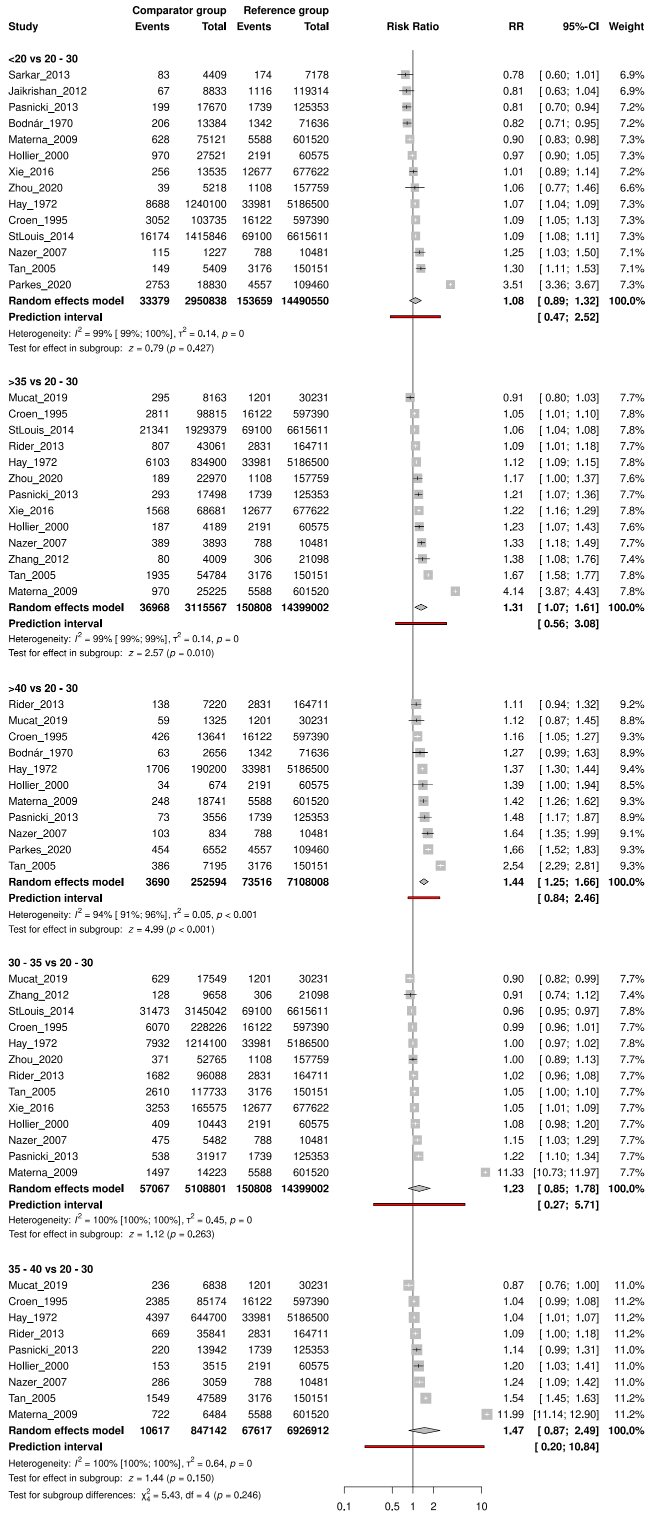
N—numbers represent the number of studies included in the analysis.

The reference group for each comparison was pregnant women between the age of 20—30.

CA, chromosomal abnormality; *ICD-10*, International Classification of Diseases-10; *NCA*, nonchromosomal congenital anomaly.

FIGURE 2

Forest plot representing the RR with 95% CI of all nonchromosomal anomalies (ICD-10: Q00—Q89) in different age groups compared to the 20—30 age group

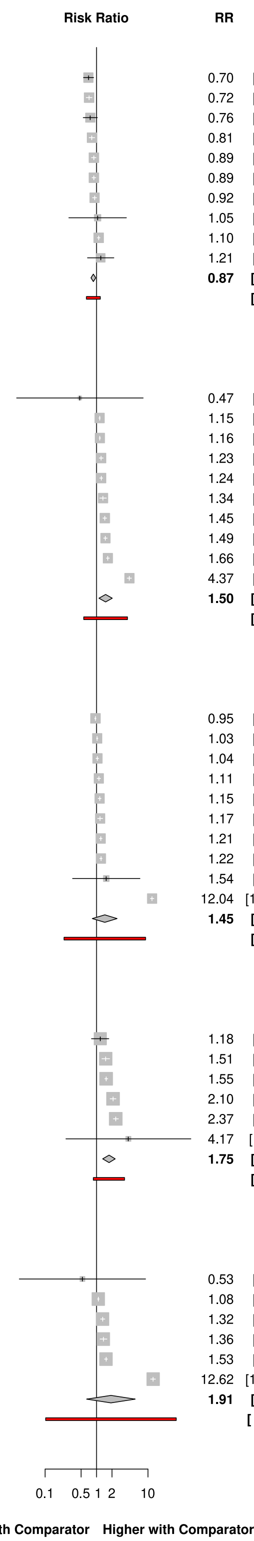


CI, confidence interval; *RR*, risk ratio.

FIGURE 3

Forest plot representing the RR with 95% CI of congenital heart defects (ICD-10: Q20—Q26) in different age groups compared to the 20—30 age group

Study	Comparator group Events	Comparator group Total	Reference group Events	Reference group Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Donghua_2018	75	12077	4291	482922	0.70	[0.56; 0.88]	10.6%
Hansen_2021	226	31831	2649	267349	0.72	[0.63; 0.82]	10.8%
Pradat_1992	41	20952	904	349375	0.76	[0.55; 1.03]	10.3%
Materna_2009	280	75121	2764	601520	0.81	[0.72; 0.92]	10.9%
Purkey_2019	456	213632	2887	1198936	0.89	[0.80; 0.98]	10.9%
Hay_1972	677	1240100	3193	5186500	0.89	[0.82; 0.96]	10.9%
Miller_2011	613	175645	2697	708470	0.92	[0.84; 1.00]	10.9%
Gupta_1967	3	488	10	1707	1.05	[0.29; 3.80]	5.0%
Liu_2013	1178	107091	10319	1036502	1.10	[1.04; 1.17]	11.0%
Jaikrishan_2012	12	8833	134	119314	1.21	[0.67; 2.18]	8.8%
Random effects model	**3561**	**1885770**	**29848**	**9952595**	**0.87**	**[0.78; 0.97]**	**100.0%**
Prediction interval						**[0.64; 1.18]**	
Heterogeneity: I^2 = 85% [75%; 91%], τ^2 = 0.02, p < 0.001							
Test for effect in subgroup: t_9 = -2.84 (p = 0.019)							
>35 vs 20 - 30							
Gupta_1967	0	171	10	1707	0.47	[0.03; 8.06]	1.6%
Persson_2019	5652	366073	9011	671819	1.15	[1.11; 1.19]	11.0%
Liu_2013	4892	422788	10319	1036502	1.16	[1.12; 1.20]	11.0%
Donghua_2018	579	52828	4291	482922	1.23	[1.13; 1.34]	10.9%
Purkey_2019	1372	461119	2887	1198936	1.24	[1.16; 1.32]	11.0%
Pradat_1992	215	62103	904	349375	1.34	[1.15; 1.55]	10.8%
Miller_2011	739	134120	2697	708470	1.45	[1.33; 1.57]	10.9%
Hay_1972	768	834900	3193	5186500	1.49	[1.38; 1.62]	10.9%
Hansen_2021	1491	90587	2649	267349	1.66	[1.56; 1.77]	11.0%
Materna_2009	506	25225	2764	601520	4.37	[3.97; 4.80]	10.9%
Random effects model	**16214**	**2449914**	**38725**	**10505100**	**1.50**	**[1.11; 2.04]**	**100.0%**
Prediction interval						**[0.57; 3.99]**	
Heterogeneity: I^2 = 99% [99%; 99%], τ^2 = 0.16, p < 0.001							
Test for effect in subgroup: t_9 = 3.04 (p = 0.014)							
30 - 35 vs 20 - 30							
Liu_2013	6810	716842	10319	1036502	0.95	[0.93; 0.98]	10.7%
Persson_2019	9257	670616	9011	671819	1.03	[1.00; 1.06]	10.7%
Purkey_2019	1608	641948	2887	1198936	1.04	[0.98; 1.11]	10.7%
Hay_1972	829	1214100	3193	5186500	1.11	[1.03; 1.20]	10.7%
Miller_2011	1240	283105	2697	708470	1.15	[1.08; 1.23]	10.7%
Pradat_1992	428	140992	904	349375	1.17	[1.05; 1.32]	10.6%
Donghua_2018	1344	125233	4291	482922	1.21	[1.14; 1.28]	10.7%
Hansen_2021	2041	168678	2649	267349	1.22	[1.15; 1.29]	10.7%
Gupta_1967	2	221	10	1707	1.54	[0.34; 7.00]	4.0%
Materna_2009	787	14223	2764	601520	12.04	[11.14; 13.01]	10.7%
Random effects model	**24346**	**3975958**	**38725**	**10505100**	**1.45**	**[0.83; 2.52]**	**100.0%**
Prediction interval						**[0.23; 8.99]**	
Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.57, p = 0							
Test for effect in subgroup: t_9 = 1.51 (p = 0.165)							
>40 vs 20 - 30							
Pradat_1992	26	8510	904	349375	1.18	[0.80; 1.74]	18.0%
Materna_2009	130	18741	2764	601520	1.51	[1.27; 1.80]	19.6%
Liu_2013	1091	70844	10319	1036502	1.55	[1.45; 1.65]	19.9%
Hay_1972	246	190200	3193	5186500	2.10	[1.85; 2.39]	19.7%
Hansen_2021	323	13745	2649	267349	2.37	[2.12; 2.66]	19.8%
Gupta_1967	0	19	10	1707	4.17	[0.25; 68.69]	3.0%
Random effects model	**1816**	**302059**	**19839**	**7442953**	**1.75**	**[1.32; 2.32]**	**100.0%**
Prediction interval						**[0.87; 3.52]**	
Heterogeneity: I^2 = 91% [84%; 95%], τ^2 = 0.05, p < 0.001							
Test for effect in subgroup: t_5 = 5.12 (p = 0.004)							
35 - 40 vs 20 - 30							
Gupta_1967	0	152	10	1707	0.53	[0.03; 9.05]	2.9%
Liu_2013	3801	351944	10319	1036502	1.08	[1.05; 1.13]	19.6%
Hay_1972	522	644700	3193	5186500	1.32	[1.20; 1.44]	19.4%
Pradat_1992	189	53593	904	349375	1.36	[1.17; 1.59]	19.2%
Hansen_2021	1168	76842	2649	267349	1.53	[1.43; 1.64]	19.5%
Materna_2009	376	6484	2764	601520	12.62	[11.36; 14.02]	19.4%
Random effects model	**6056**	**1133715**	**19839**	**7442953**	**1.91**	**[0.65; 5.62]**	**100.0%**
Prediction interval						**[0.10; 35.68]**	
Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.94, p = 0							
Test for effect in subgroup: t_5 = 1.54 (p = 0.185)							
Test for subgroup differences: χ^2_4 = 47.25, df = 4 (p < 0.001)							



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

some individual malformations. The risk of omphalocele was higher in both very young (age<20, RR 1.44, CI: 1.08−1.92) and AMA (age>40, RR 2.57, CI: 1.77−3.73) women. Based on 22 eligible articles (age<20, RR 3.08, CI 2.74−3.47), gastroschisis shows a strong association with very young maternal age. The analyses of the ICD-10 main groups and certain individual anomalies can be found in the supplementary material (Supplementary Figures 1−17).

Regarding the congenital malformations of the eye, ear, face, and neck (Q10−Q18), congenital malformations of the respiratory system (Q30−Q34), and congenital malformations of genital organs (Q50−Q56), we did not find enough studies with homogenous age groups and NACs to carry out a mathematical synthesis.

Additionally, we also resorted our study-level outcomes by year of publication to showcase any apparent trend in case of outcomes where sufficient number of articles were available to have any chance to reliably assess any effect (Supplemental Figures 38−47) and we could not see any convincing trend. We also analyzed the subset of studies published from 2005 onward (Supplemental Figures 48−57): no clear and convincing trend could be identified, only weak trends in a few cases (summarized in Supplemental Table 6).

Comment

The present study aimed to investigate the influence of maternal age on the risk of NCAs. Overall, our results suggest that maternal age plays a significant role in NCAs, with notable variations observed across different age groups. This finding is particularly important given that the focus of the analysis was specifically on the NCAs, while CAs were excluded from the analysis. The coexistence of CAs occurred in several established studies, but examining maternal age associations of CAs was not the subject of our present study.

Principal findings and comparison with existing literature

One key finding of our study is the association between AMA (≥35 years and ≥40 years) and an increased risk of NCAs. This finding is consistent with previous research,[33−35] highlighting the importance of considering AMA as a risk factor in prenatal care and genetic counseling. The meta-analysis written on the subject in 2022 also considered AMA as a risk.[36] However, the significance of our present study is given by the fact that we specifically and exclusively examined NCAs and grouped them according to the International Classification of Diseases. We separately analyzed the main groups and some individual deviations. In addition, during our study, we examined the risk of several age groups compared to the reference age group. The increased risk observed in older mothers may be attributed to various factors, including increased rate of in vitro fertilization,[37−40] increased prevalence of comorbidities especially pregestational diabetes mellitus,[41−43] and a higher likelihood of exposure to environmental factors[44,45] over an extended period. Contrary to our findings, some research has questioned the risk-increasing effect of AMA.[46,47] This may be explained by the fact that the increase in maternal age in Europe is especially associated with women of higher social status, which may have led to a decrease in the risk of NCA in this age group compared to previous trends.[47,48] Some studies show that AMA is associated with a reduced risk of NCAs, with researchers hypothesizing that the "all-or-nothing" phenomenon plays a stronger role in embryonic development as the egg ages and that anatomically normal fetuses are more likely to survive.[49]

Our findings support and strengthen previous research that has suggested a significant association between maternal age and the risk of different NCAs.[20,50,51] By pooling data from multiple studies, our meta-analysis demonstrates a consistent pattern of increased risk among older and younger mothers. This finding adds to the body of evidence and underscores the importance of considering maternal age as a critical factor in assessing the risk of these anomalies.

Interestingly, we also observed an elevated risk of NCAs among younger maternal age groups (<20 years), but this association is not statistically significant. This finding is consistent with previous studies and suggests that a very young maternal age may also be a significant risk factor for these anomalies.[47] Possible explanations for this increased risk among younger mothers include inadequate prenatal care, a higher prevalence of socioeconomic disadvantages, and increased susceptibility to nutritional deficiencies during pregnancy.[52]

It is known that in addition to CAs, the incidence of NCAs also increases with age, which is why it is worthwhile to examine the relationship even without their copresence. We found that the increased risk persisted in subgroup analyses excluding coincident chromosomal anomalies (see Supplemental Table 5) The RR for NCAs between mothers aged 20 to 30 and those aged >40, without coincidence of chromosomal anomalies, was 1.25 (95% CI: 1.08−1.46), indicating a 25% higher risk of nonchromosomal anomalies in older mothers when chromosomal anomalies were not present. This finding aligns with our recent population-based study,[20] which demonstrated an increased risk of nonchromosomal anomalies in older mothers even after excluding CAs from the analysis. According to the current guidelines, there is no specific recommendation for screening for NCAs based on maternal age. However, it has been previously demonstrated that maternal age is a significant risk factor for chromosomal anomalies. Consequently, there has been a growing emphasis on age-based screening, which has led to a notable improvement in the detection rate. While CAs are well-established in the etiology of developmental disorders, NCAs can also arise from gene abnormalities. However, no routine screening protocol is currently available for these; thus, their presence could not be excluded in this study. Moreover, their incidence is less associated with maternal age.[53,54]

A further aim of the present meta-analysis was to investigate the effect of maternal age on the prevalence of NCA using data classified by ICD-10 categories. By analyzing data from 5 different age groups (<20; 30−35; >35; 35−40; >40) and comparing them to a control age group of 20 to 30 years, we sought to provide a comprehensive understanding of the relationship between maternal age and specific types of NCAs. CHDs and neural tube defects (NTDs) should be addressed separately, as fetal echocardiography and neurosonography serve as complementary screening methods for these conditions.

In the circulatory system category, the risk of nonchromosomal anomalies was significantly higher in mothers aged >40. Specifically, CHDs within this category showed a similarly increased risk, with a 75% risk-increasing effect for mothers aged >40 compared to those aged 20 to 30. When comparing mothers aged >35 to those aged 20 to 30 a 50% increased risk was indicated in the older age group. These are significant findings from a clinical point of view, because there is currently no maternal age-related indication for fetal echocardiography.[55,56]

No association with maternal age was found for NTDs. The literature does not provide consistent findings regarding the effect of age. Most studies also highlight the role of both very young and AMA.[57,58] While other researchers suggest that a higher risk of NTD is associated with increased maternal age,[59] the diverse outcomes observed in studies may be attributed to the inconsistent definition of NTDs, as grouping was not uniformly applied across different research studies.

The included studies have span a long time period (1940−2018) during which substantial changes in lifestyle, prevention strategies,[60] and diagnostics may have happened; hence, the incidence of certain NCAs may have also changed over time. However, this shift does not appear to have impacted the dependence of RRs on maternal age.

Since no specific additional screening options are available for other NCA groups, ultrasound examinations adjusted for age in these particular age groups should prioritize the assessment of these organ systems. Special attention should be dedicated to the more frequent disparities observed in the low and high maternal age categories. Exploring the underlying causes of the risk-increasing effects within each age group can aid the identification of appropriate preventive options. Our findings indicate that the inclusion of age in screening protocols can enhance the likelihood of early detection of NCAs. While this study alone does not provide conclusive evidence regarding the isolated impact of age, it is important to consider the potential influence of lifestyle factors commonly associated with different age categories. Nevertheless, age alone can still be considered a distinct and significant risk factor.

Strengths and limitation

Regarding the strengths of our analysis, we followed our protocol, which was registered in advance. A rigorous methodology was applied. We included population-based articles, which gave us a comprehensive view of all NCAs. We included articles from around the world with a large number of cases, enabling the generalizability of the result.

However, there are several limitations. All included studies had a retrospective design that limited our ability to establish causality and precluded the assessment of certain confounding variables. The quality and heterogeneity of the included studies may have introduced some biases and limitations in interpreting our results. As with any meta-analysis, publication bias may be a concern, as studies with nonsignificant results are less likely to be published. Additionally, the sample sizes, the long study period with changing screening methods, and data reporting across the included studies may have introduced some degree of heterogeneity.

Conclusions and implication

The importance of immediate implementation of the results has been previously proven.[61,62] Based on our study, we suggest advanced ultrasound screening and additional screening methods (fetal echocardiography) in high-risk age groups, and considering this knowledge in family planning due to the clear advantages of the rapid integration of the results into clinical practice. Our results suggest that introducing fetal echocardiography may be a priority for AMA.

Further prospective data collection is needed to assess the problem in question more accurately and to understand the role of maternal age in the case of rare NCAs.

In conclusion, our meta-analysis of population-based articles provides compelling evidence of the influence of maternal age (especially AMA) on the risk of NCAs. These findings have important clinical implications, emphasizing the need for age-specific prenatal care and genetic counseling to mitigate the risk of these anomalies. ■

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Appendix

Supplementary Appendix 1. Risk of bias assessment methodology

Overall ratings for each domain were assigned as carrying 'low' (green), 'moderate' (yellow), or 'high' (red) risk of bias, based on the items included in each domain.

Study design: (1) low risk of bias was attributed if the proportion of baseline sample was available, also if the reason for lost to follow-up was detailed; (2) moderate risk of bias was attributed if a part of the above listed criteria were missing; (3) high risk of bias was attributed if data was missing for the above mentioned criteria.

Study participation measurement: (1) low risk of bias was attributed if authors adequately described the source population, including methods to identify patients and eligibility criteria; (2) moderate risk of bias was attributed if a part of the above listed descriptions were missing; (3) high risk of bias was attributed if baseline characteristics, eligibility criteria, time and place of recruitment were not described.

Prognostic factor measurement: (1) low risk of bias was attributed if clear and detailed age categories were used covering all age groups; (2) moderate risk of bias was attributed if clear categories were defined but some age groups were missing; (3) high risk of bias was attributed if only 1 group was examined.

Outcome measurement: (1) low risk of bias was attributed if there was clear definition of outcome, if the study used International Classification of Diseases-10 (ICD-10) category; (2) moderate risk of bias was attributed if a mentioned criteria were missing but can be matched to ICD-10 category; (3) high risk of bias was attributed if the anomaly could not be precisely identified or it was inadequate.

Study confounding measurement: (1) low risk of bias was attributed if important potential confounders were described and accounted for in the analysis; (2) moderate risk of bias was attributed if some of the important confounders were not measured; (3) high risk of bias was attributed if studies did not provide data on confounding factors.

Statistical analysis measurement: (1) low risk of bias was attributed if there is clear, raw data (no or negligible contradiction); (2) moderate risk of bias was attributed if requires some calculation or reading from a graph (minor contradiction); (3) high risk of bias was attributed if only approximate data can be obtained (serious contradiction).

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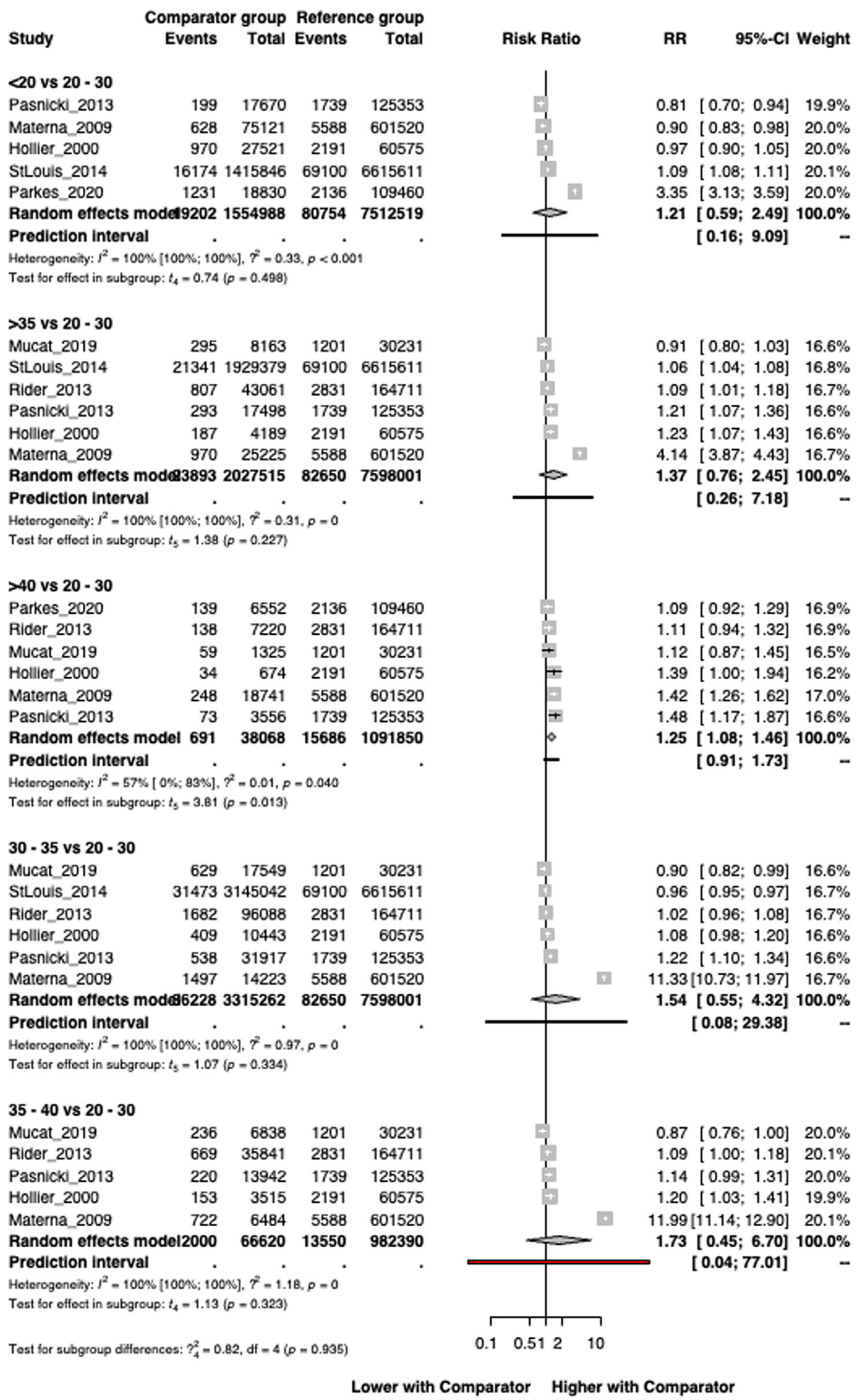
SUPPLEMENTAL FIGURE 1

Forest plot representing the RR with 95% CI of *all nonchromosomal anomalies (only studies excluding concomitant chromosomal anomalies)* (ICD-10 Q00–Q89) in different age groups compared to the 20 to 30 age group



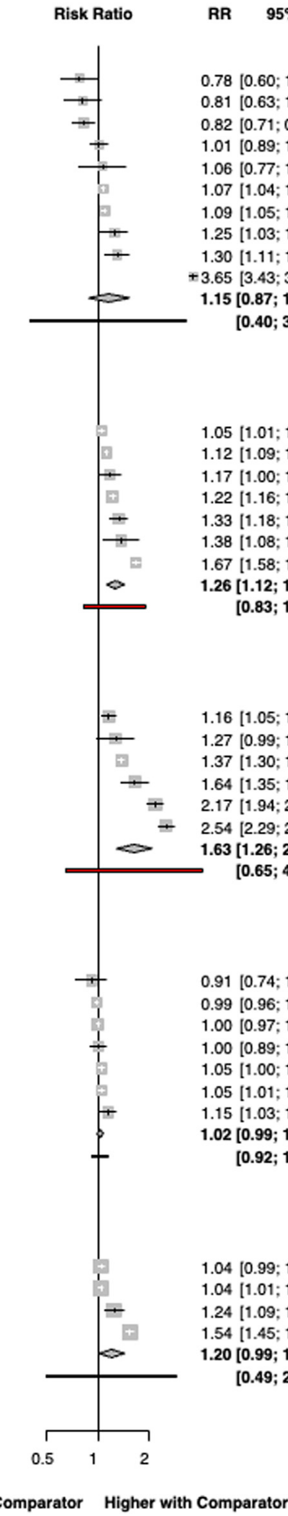
CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 2

Forest plot representing the RR with 95% CI of *all nonchromosomal anomalies (only studies including concomitant chromosomal anomalies)* (ICD-10: Q00−Q89 with Q90−Q99) in different age groups compared to the 20 to 30 age group

Study	Comparator group Events	Comparator group Total	Reference group Events	Reference group Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Sarkar_2013	83	4409	174	7178	0.78	[0.60; 1.01]	9.2%
Jaikrishan_2012	67	8833	1116	119314	0.81	[0.63; 1.04]	9.3%
Bodnár_1970	206	13384	1342	71636	0.82	[0.71; 0.95]	10.2%
Xie_2016	256	13535	12677	677622	1.01	[0.89; 1.14]	10.4%
Zhou_2020	39	5218	1108	157759	1.06	[0.77; 1.46]	8.5%
Hay_1972	8688	1240100	33981	5186500	1.07	[1.04; 1.09]	10.8%
Croen_1995	3052	103735	16122	597390	1.09	[1.05; 1.13]	10.8%
Nazer_2007	115	1227	788	10481	1.25	[1.03; 1.50]	9.9%
Tan_2005	149	5409	3176	150151	1.30	[1.11; 1.53]	10.1%
Parkes_2020	1522	18830	2421	109460	3.65	[3.43; 3.89]	10.7%
Random effects model	**14177**	**1414680**	**72905**	**7087491**	**1.15**	**[0.87; 1.52]**	**100.0%**
Prediction interval	.	.	.	.		**[0.40; 3.35]**	--
Heterogeneity: $I^2 = 99\%$ [99%; 99%], $\tau^2 = 0.19$, $p < 0.001$							
Test for effect in subgroup: $z = 1.00$ ($p = 0.320$)							
>35 vs 20 - 30							
Croen_1995	2811	98815	16122	597390	1.05	[1.01; 1.10]	14.8%
Hay_1972	6103	834900	33981	5186500	1.12	[1.09; 1.15]	14.8%
Zhou_2020	189	22970	1108	157759	1.17	[1.00; 1.37]	13.9%
Xie_2016	1568	68681	12677	677622	1.22	[1.16; 1.29]	14.7%
Nazer_2007	389	3893	788	10481	1.33	[1.18; 1.49]	14.3%
Zhang_2012	80	4009	306	21098	1.38	[1.08; 1.76]	12.8%
Tan_2005	1935	54784	3176	150151	1.67	[1.58; 1.77]	14.7%
Random effects model	**13075**	**1088052**	**68158**	**6801001**	**1.26**	**[1.12; 1.42]**	**100.0%**
Prediction interval	.	.	.	.		**[0.83; 1.90]**	--
Heterogeneity: $I^2 = 97\%$ [96%; 98%], $\tau^2 = 0.02$, $p < 0.001$							
Test for effect in subgroup: $z = 3.79$ ($p < 0.001$)							
>40 vs 20 - 30							
Croen_1995	426	13641	16122	597390	1.16	[1.05; 1.27]	17.2%
Bodnár_1970	63	2656	1342	71636	1.27	[0.99; 1.63]	15.1%
Hay_1972	1706	190200	33981	5186500	1.37	[1.30; 1.44]	17.5%
Nazer_2007	103	834	788	10481	1.64	[1.35; 1.99]	16.0%
Parkes_2020	315	6552	2421	109460	2.17	[1.94; 2.44]	17.0%
Tan_2005	386	7195	3176	150151	2.54	[2.29; 2.81]	17.1%
Random effects model	**2999**	**221078**	**57830**	**6125618**	**1.63**	**[1.26; 2.09]**	**100.0%**
Prediction interval	.	.	.	.		**[0.65; 4.09]**	--
Heterogeneity: $I^2 = 97\%$ [96%; 98%], $\tau^2 = 0.09$, $p < 0.001$							
Test for effect in subgroup: $z = 3.78$ ($p < 0.001$)							
30 - 35 vs 20 - 30							
Zhang_2012	128	9658	306	21098	0.91	[0.74; 1.12]	13.2%
Croen_1995	6070	228226	16122	597390	0.99	[0.96; 1.01]	14.6%
Hay_1972	7932	1214100	33981	5186500	1.00	[0.97; 1.02]	14.6%
Zhou_2020	371	52765	1108	157759	1.00	[0.89; 1.13]	14.1%
Tan_2005	2610	117733	3176	150151	1.05	[1.00; 1.10]	14.6%
Xie_2016	3253	165575	12677	677622	1.05	[1.01; 1.09]	14.6%
Nazer_2007	475	5482	788	10481	1.15	[1.03; 1.29]	14.2%
Random effects model	**20839**	**1793539**	**68158**	**6801001**	**1.02**	**[0.99; 1.06]**	**100.0%**
Prediction interval	.	.	.	.		**[0.92; 1.14]**	--
Heterogeneity: $I^2 = 63\%$ [17%; 84%], $\tau^2 = < 0.01$, $p = 0.012$							
Test for effect in subgroup: $z = 1.18$ ($p = 0.236$)							
35 - 40 vs 20 - 30							
Croen_1995	2385	85174	16122	597390	1.04	[0.99; 1.08]	25.3%
Hay_1972	4397	644700	33981	5186500	1.04	[1.01; 1.07]	25.3%
Nazer_2007	286	3059	788	10481	1.24	[1.09; 1.42]	24.3%
Tan_2005	1549	47589	3176	150151	1.54	[1.45; 1.63]	25.1%
Random effects model	**8617**	**780522**	**54067**	**5944522**	**1.20**	**[0.99; 1.44]**	**100.0%**
Prediction interval	.	.	.	.		**[0.49; 2.92]**	--
Heterogeneity: $I^2 = 98\%$ [96%; 99%], $\tau^2 = 0.03$, $p < 0.001$							
Test for effect in subgroup: $z = 1.91$ ($p = 0.057$)							

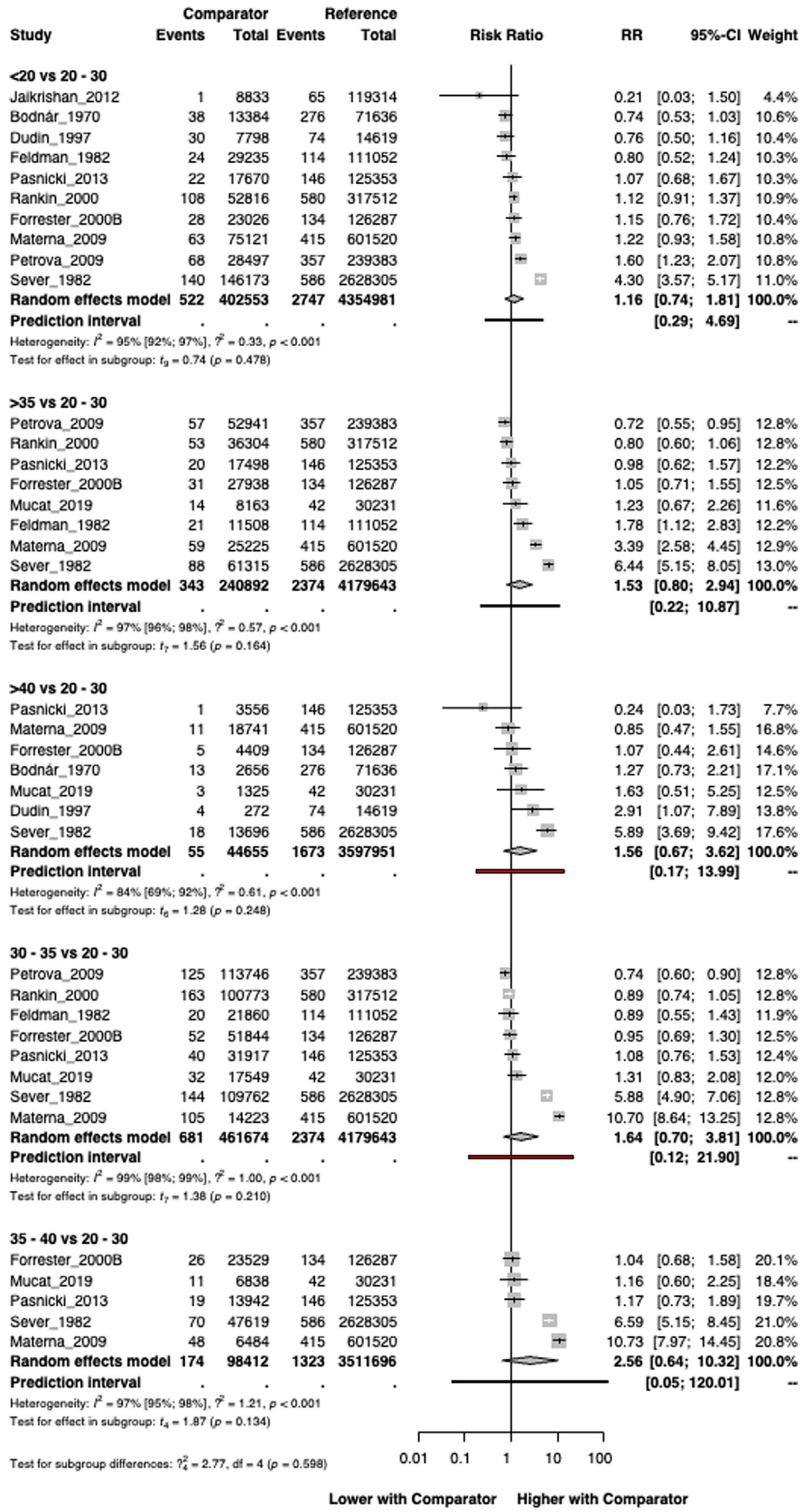
Test for subgroup differences: $\chi^2_4 = 24.41$, df = 4 ($p < 0.001$)



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 3

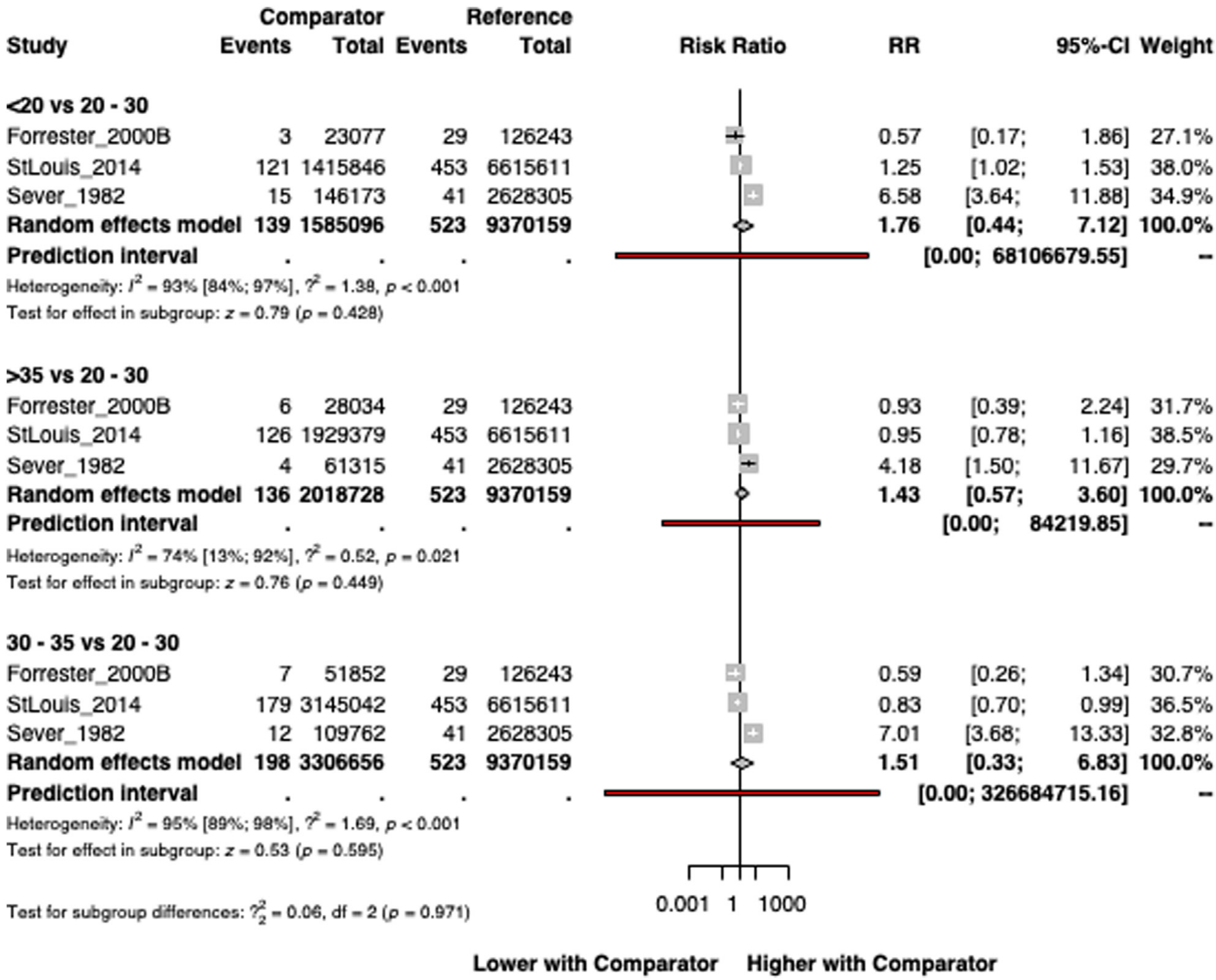
Forest plot representing the RR with 95% CI of *congenital anomalies of the nervous system* (ICD-10: Q00−Q07) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 4

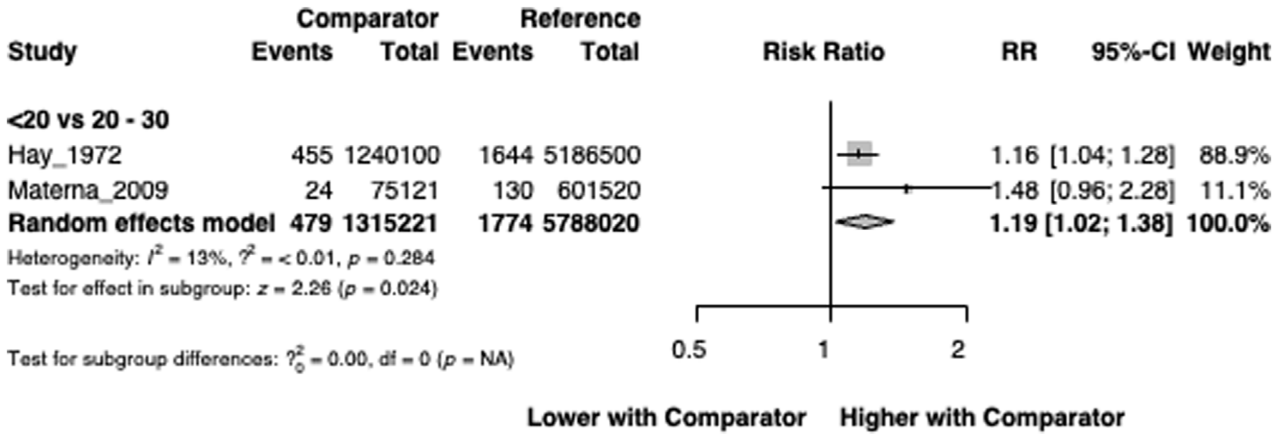
Forest plot representing the RR with 95% CI of *encephalocele* (ICD-10: Q01) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 5

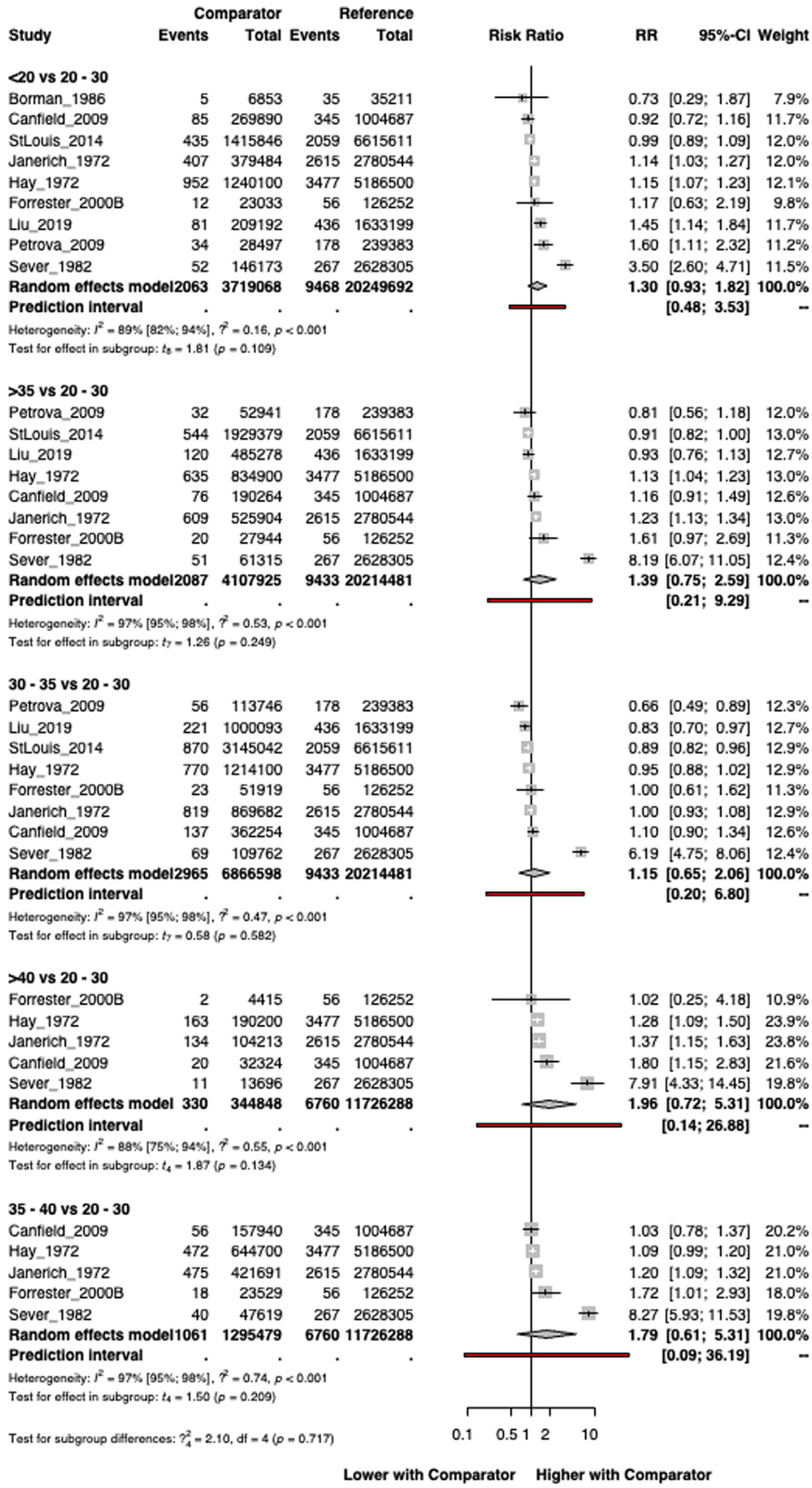
Forest plot representing the RR with 95% CI of *congenital hydrocephalus* (ICD-10: Q03) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 6

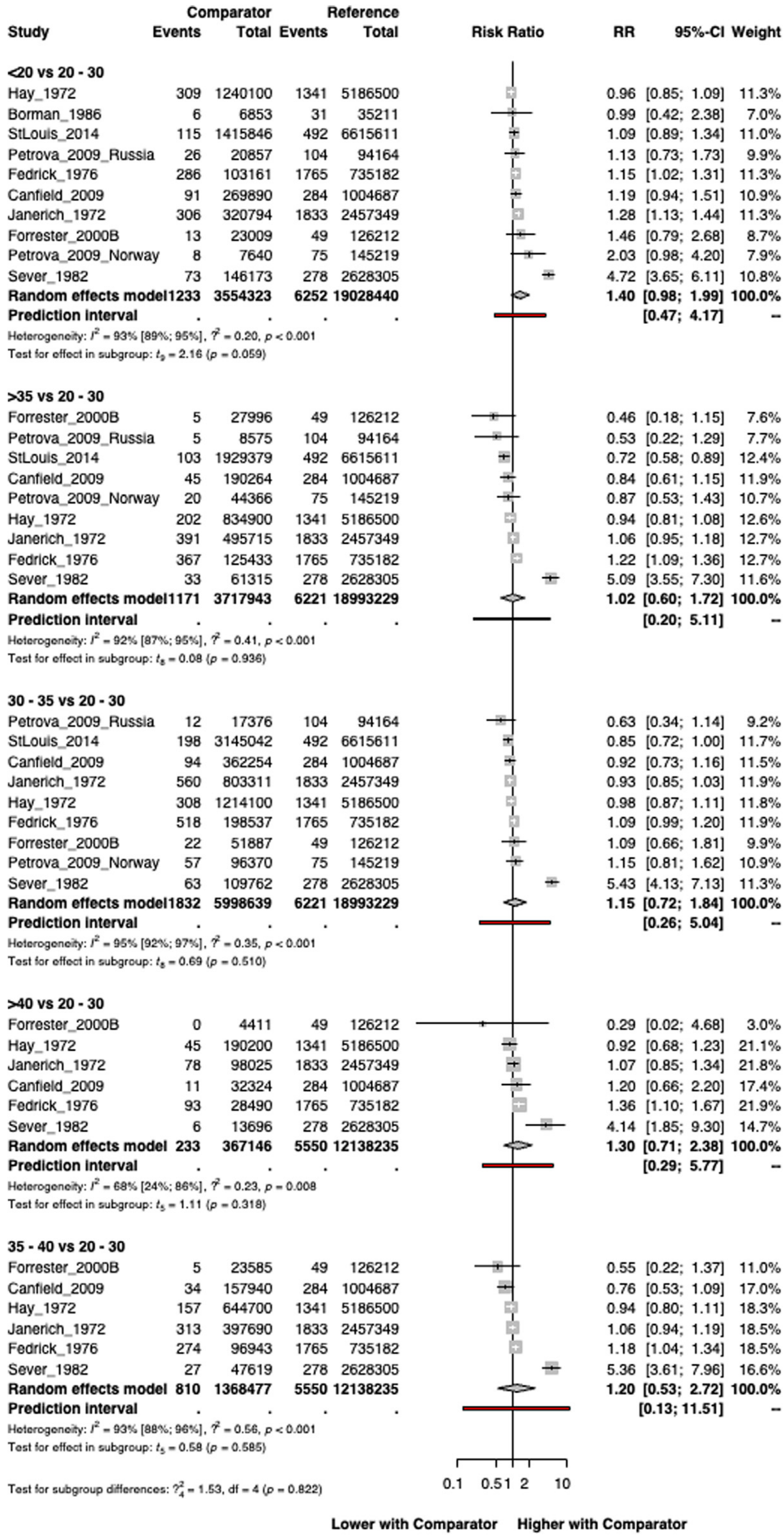
Forest plot representing the RR with 95% CI of *spina bifida* (ICD-10: Q05) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 7

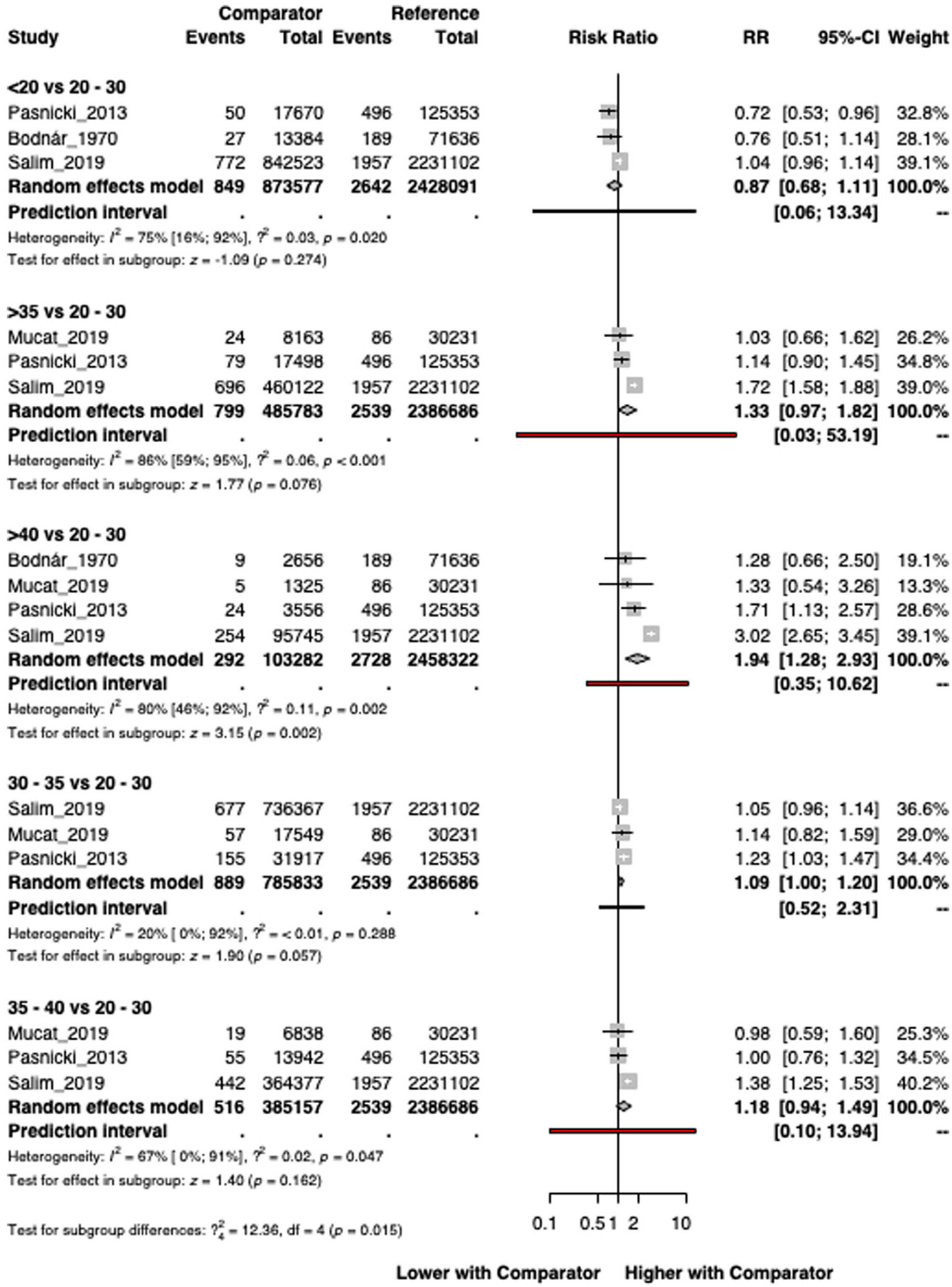
Forest plot representing the RR with 95% CI of *anencephaly* (ICD-10: Q00.0) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 8

Forest plot representing the RR with 95% CI of *congenital anomalies of the circulatory system* (ICD-10: Q20−Q28) in different age groups compared to the 20 to 30 age group



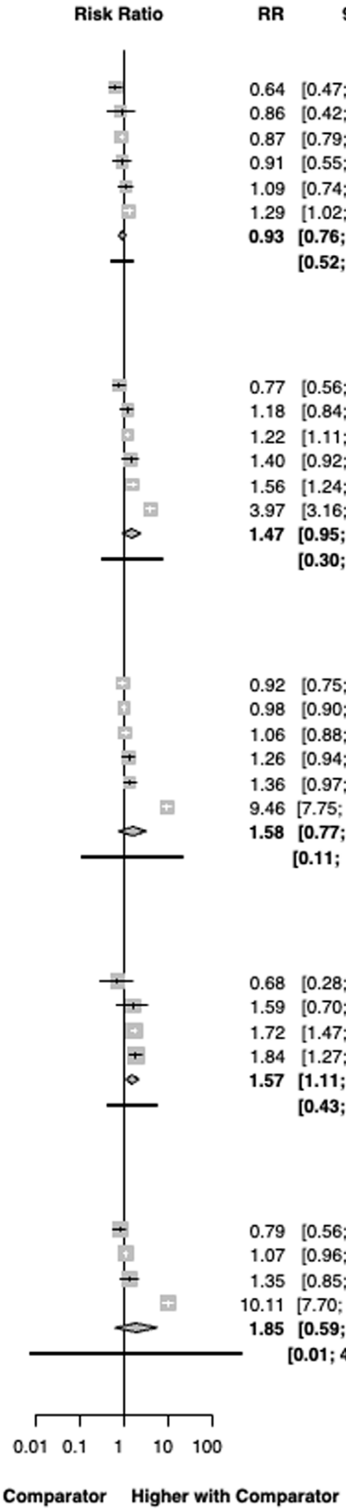
CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 9

Forest plot representing the RR with 95% CI of *cleft lip and cleft palate* (ICD-10: Q35—Q37) in different age groups compared to the 20 to 30 age group

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Materna_2009	42	75121	523	601520	0.64	[0.47; 0.88]	17.3%
Jaikrishan_2012	8	8833	126	119314	0.86	[0.42; 1.75]	14.1%
Hay_1972	556	1240100	2680	5186500	0.87	[0.79; 0.95]	18.2%
Pasnicki_2013	17	17670	133	125353	0.91	[0.55; 1.50]	15.9%
Jaruratanasirikul_2016	32	22265	126	95535	1.09	[0.74; 1.61]	16.8%
DeRoo_2003	84	31617	357	173893	1.29	[1.02; 1.64]	17.7%
Random effects model	**739**	**1395606**	**3945**	**6302115**	**0.93**	**[0.76; 1.14]**	**100.0%**
Prediction interval	.	.	.	.		**[0.52; 1.68]**	--
Heterogeneity: $I^2 = 67\%$ [20%; 86%], $\tau^2 = 0.03$, $p = 0.011$							
Test for effect in subgroup: $z = -0.69$ ($p = 0.490$)							
>35 vs 20 - 30							
DeRoo_2003	43	27067	357	173893	0.77	[0.56; 1.06]	16.5%
Jaruratanasirikul_2016	45	28891	126	95535	1.18	[0.84; 1.66]	16.4%
Hay_1972	526	834900	2680	5186500	1.22	[1.11; 1.34]	17.4%
Pasnicki_2013	26	17498	133	125353	1.40	[0.92; 2.13]	15.8%
Luo_2019	100	55368	273	235136	1.56	[1.24; 1.96]	16.9%
Materna_2009	87	25225	523	601520	3.97	[3.16; 4.98]	17.0%
Random effects model	**827**	**988949**	**4092**	**6417937**	**1.47**	**[0.95; 2.28]**	**100.0%**
Prediction interval	.	.	.	.		**[0.30; 7.24]**	--
Heterogeneity: $I^2 = 95\%$ [92%; 97%], $\tau^2 = 0.28$, $p < 0.001$							
Test for effect in subgroup: $z = 1.71$ ($p = 0.087$)							
30 - 35 vs 20 - 30							
DeRoo_2003	123	65218	357	173893	0.92	[0.75; 1.13]	16.8%
Hay_1972	617	1214100	2680	5186500	0.98	[0.90; 1.07]	17.1%
Luo_2019	175	142086	273	235136	1.06	[0.88; 1.28]	16.8%
Jaruratanasirikul_2016	66	39702	126	95535	1.26	[0.94; 1.70]	16.3%
Pasnicki_2013	46	31917	133	125353	1.36	[0.97; 1.90]	16.1%
Materna_2009	117	14223	523	601520	9.46	[7.75; 11.55]	16.8%
Random effects model	**1144**	**1507246**	**4092**	**6417937**	**1.58**	**[0.77; 3.22]**	**100.0%**
Prediction interval	.	.	.	.		**[0.11; 22.44]**	--
Heterogeneity: $I^2 = 99\%$ [98%; 99%], $\tau^2 = 0.78$, $p < 0.001$							
Test for effect in subgroup: $z = 1.26$ ($p = 0.209$)							
>40 vs 20 - 30							
DeRoo_2003	5	3559	357	173893	0.68	[0.28; 1.65]	20.7%
Pasnicki_2013	6	3556	133	125353	1.59	[0.70; 3.60]	21.7%
Hay_1972	169	190200	2680	5186500	1.72	[1.47; 2.01]	29.7%
Materna_2009	30	18741	523	601520	1.84	[1.27; 2.66]	27.9%
Random effects model	**210**	**216056**	**3693**	**6087266**	**1.57**	**[1.11; 2.20]**	**100.0%**
Prediction interval	.	.	.	.		**[0.43; 5.75]**	--
Heterogeneity: $I^2 = 30\%$ [0%; 75%], $\tau^2 = 0.06$, $p = 0.230$							
Test for effect in subgroup: $z = 2.58$ ($p = 0.010$)							
35 - 40 vs 20 - 30							
DeRoo_2003	38	23508	357	173893	0.79	[0.56; 1.10]	24.9%
Hay_1972	357	644700	2680	5186500	1.07	[0.96; 1.20]	26.3%
Pasnicki_2013	20	13942	133	125353	1.35	[0.85; 2.16]	23.5%
Materna_2009	57	6484	523	601520	10.11	[7.70; 13.27]	25.4%
Random effects model	**472**	**688634**	**3693**	**6087266**	**1.85**	**[0.59; 5.75]**	**100.0%**
Prediction interval	.	.	.	.		**[0.01; 465.66]**	--
Heterogeneity: $I^2 = 99\%$ [98%; 99%], $\tau^2 = 1.32$, $p < 0.001$							
Test for effect in subgroup: $z = 1.06$ ($p = 0.290$)							

Test for subgroup differences: $\chi^2_4 = 9.94$, df = 4 ($p = 0.041$)



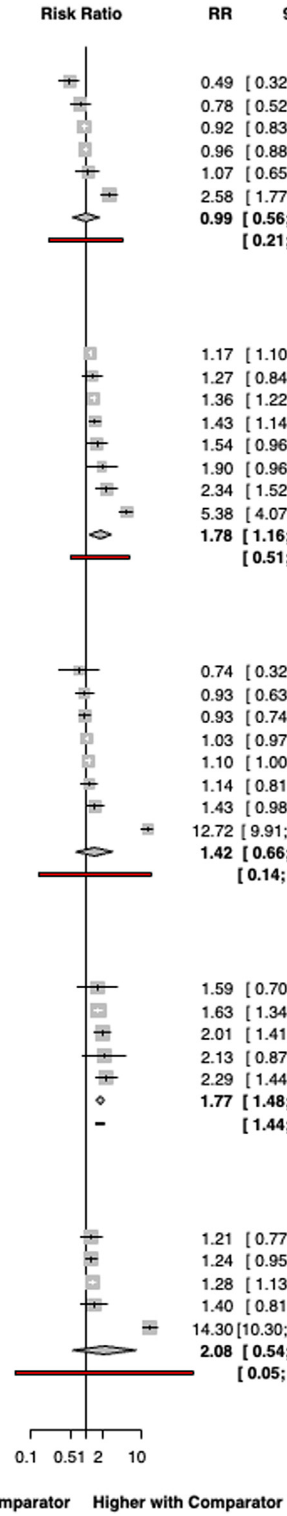
CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 10

Forest plot representing the RR with 95% CI of *cleft palate* (ICD-10: Q35) in different age groups compared to the 20 to 30 age group

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Shields_1981	23	205752	334	1463671	0.49	[0.32; 0.75]	16.2%
Materna_2009	26	75121	266	601520	0.78	[0.52; 1.17]	16.3%
Hay_1972	411	1240100	1861	5186500	0.92	[0.83; 1.03]	17.6%
StLouis_2014	742	1415846	3626	6615611	0.96	[0.88; 1.03]	17.7%
Forrester_2004C	19	28492	95	152575	1.07	[0.65; 1.75]	15.7%
Baird_1994	33	34274	145	387862	2.58	[1.77; 3.76]	16.5%
Random effects model	**1254**	**2999585**	**6327**	**14407739**	**0.99**	**[0.56; 1.73]**	**100.0%**
Prediction interval	.	.	.	.		**[0.21; 4.56]**	--
Heterogeneity: $I^2 = 87\%$ [73%; 93%], $\tau^2 = 0.25$, $p < 0.001$							
Test for effect in subgroup: $t_5 = -0.05$ ($p = 0.963$)							
>35 vs 20 - 30							
StLouis_2014	1240	1929379	3626	6615611	1.17	[1.10; 1.25]	13.4%
Forrester_2004C	29	36537	95	152575	1.27	[0.84; 1.93]	12.3%
Hay_1972	406	834900	1861	5186500	1.36	[1.22; 1.51]	13.4%
Shields_1981	98	300245	334	1463671	1.43	[1.14; 1.79]	13.1%
Baird_1994	19	32993	145	387862	1.54	[0.96; 2.48]	12.0%
Beckman_1976	15	8335	18	19008	1.90	[0.96; 3.77]	10.7%
Luo_2019	32	55368	58	235136	2.34	[1.52; 3.61]	12.2%
Materna_2009	60	25225	266	601520	5.38	[4.07; 7.12]	12.9%
Random effects model	**1899**	**3222982**	**6403**	**14661883**	**1.78**	**[1.16; 2.73]**	**100.0%**
Prediction interval	.	.	.	.		**[0.51; 6.19]**	--
Heterogeneity: $I^2 = 94\%$ [91%; 96%], $\tau^2 = 0.23$, $p < 0.001$							
Test for effect in subgroup: $t_7 = 3.19$ ($p = 0.015$)							
30 - 35 vs 20 - 30							
Beckman_1976	8	11388	18	19008	0.74	[0.32; 1.71]	9.8%
Baird_1994	30	86632	145	387862	0.93	[0.63; 1.37]	12.4%
Shields_1981	93	436986	334	1463671	0.93	[0.74; 1.17]	13.0%
StLouis_2014	1770	3145042	3626	6615611	1.03	[0.97; 1.09]	13.4%
Hay_1972	481	1214100	1861	5186500	1.10	[1.00; 1.22]	13.3%
Forrester_2004C	49	68803	95	152575	1.14	[0.81; 1.61]	12.6%
Luo_2019	50	142086	58	235136	1.43	[0.98; 2.08]	12.5%
Materna_2009	80	14223	266	601520	12.72	[9.91; 16.32]	13.0%
Random effects model	**2561**	**5119260**	**6403**	**14661883**	**1.42**	**[0.66; 3.06]**	**100.0%**
Prediction interval	.	.	.	.		**[0.14; 14.64]**	--
Heterogeneity: $I^2 = 98\%$ [97%; 99%], $\tau^2 = 0.80$, $p < 0.001$							
Test for effect in subgroup: $t_7 = 1.09$ ($p = 0.312$)							
>40 vs 20 - 30							
Forrester_2004C	6	6065	95	152575	1.59	[0.70; 3.62]	17.2%
Hay_1972	111	190200	1861	5186500	1.63	[1.34; 1.97]	23.1%
Shields_1981	34	74260	334	1463671	2.01	[1.41; 2.86]	22.1%
Baird_1994	5	6288	145	387862	2.13	[0.87; 5.19]	16.5%
Materna_2009	19	18741	266	601520	2.29	[1.44; 3.65]	21.1%
Random effects model	**175**	**295554**	**2701**	**7792128**	**1.77**	**[1.48; 2.11]**	**100.0%**
Prediction interval	.	.	.	.		**[1.44; 2.17]**	--
Heterogeneity: $I^2 = 0\%$ [0%; 79%], $\tau^2 = 0$, $p = 0.618$							
Test for effect in subgroup: $t_4 = 8.97$ ($p < 0.001$)							
35 - 40 vs 20 - 30							
Forrester_2004C	23	30472	95	152575	1.21	[0.77; 1.91]	19.3%
Shields_1981	64	225985	334	1463671	1.24	[0.95; 1.62]	20.7%
Hay_1972	295	644700	1861	5186500	1.28	[1.13; 1.44]	21.3%
Baird_1994	14	26705	145	387862	1.40	[0.81; 2.43]	18.5%
Materna_2009	41	6484	266	601520	14.30	[10.30; 19.85]	20.3%
Random effects model	**437**	**934346**	**2701**	**7792128**	**2.08**	**[0.54; 7.99]**	**100.0%**
Prediction interval	.	.	.	.		**[0.05; 86.61]**	--
Heterogeneity: $I^2 = 98\%$ [97%; 99%], $\tau^2 = 1.14$, $p < 0.001$							
Test for effect in subgroup: $t_4 = 1.51$ ($p = 0.205$)							

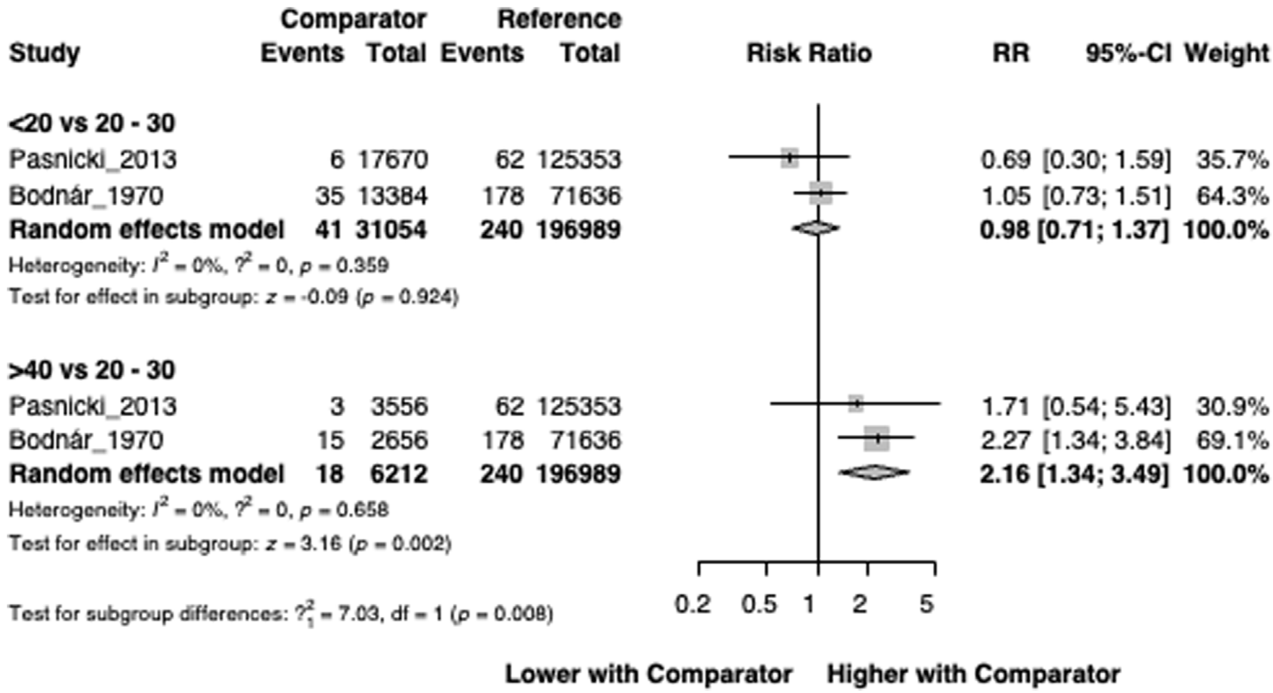
Test for subgroup differences: $\chi^2_4 = 7.08$, df = 4 ($p = 0.132$)



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 11

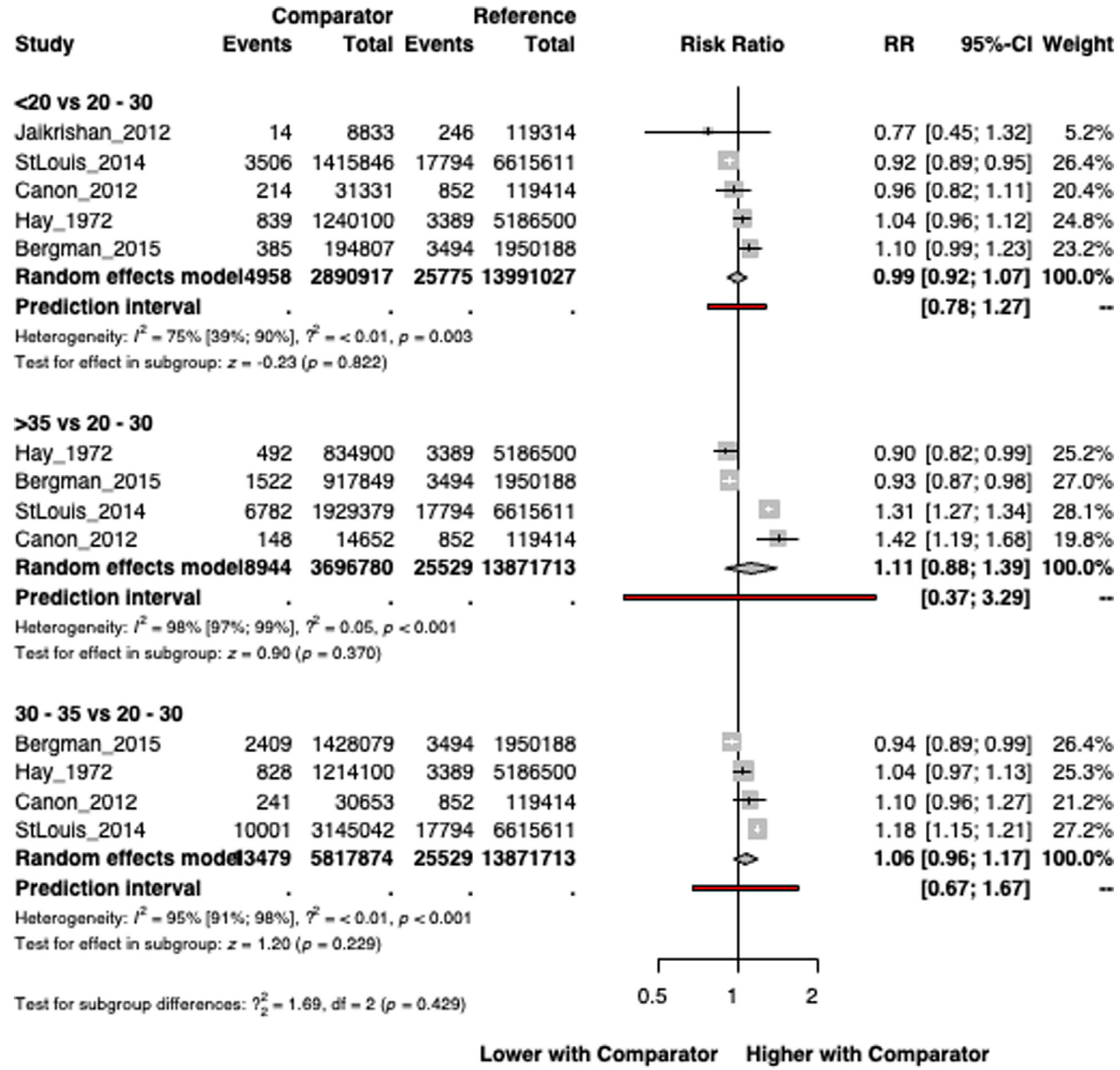
Forest plot representing the RR with 95% CI of *congenital anomalies of the digestive system* (ICD-10: Q38–Q45) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 12

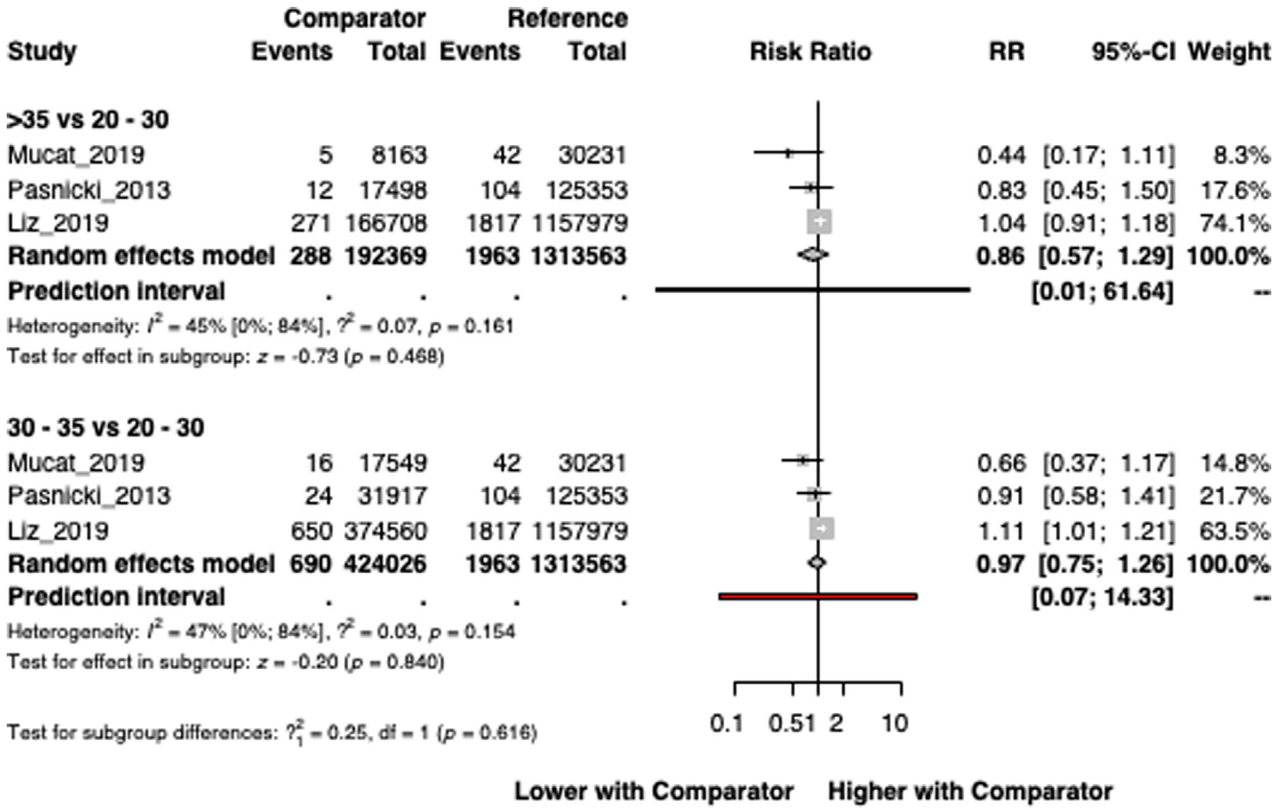
Forest plot representing the RR with 95% CI of *hypospadiasis* (ICD-10: Q54) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 13

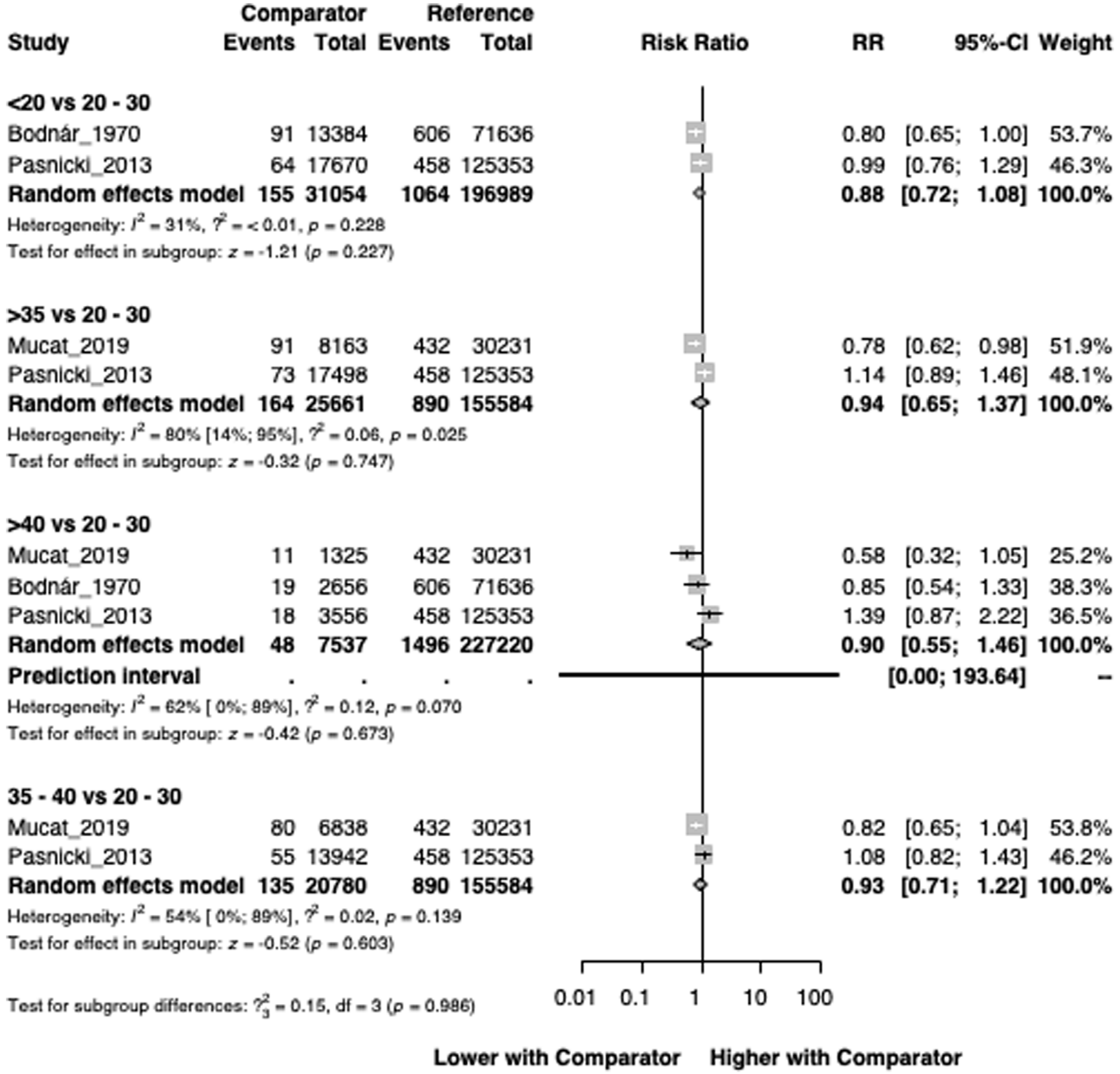
Forest plot representing the RR with 95% CI of *congenital anomalies of the urinary system* (ICD-10: Q60−Q64) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 14

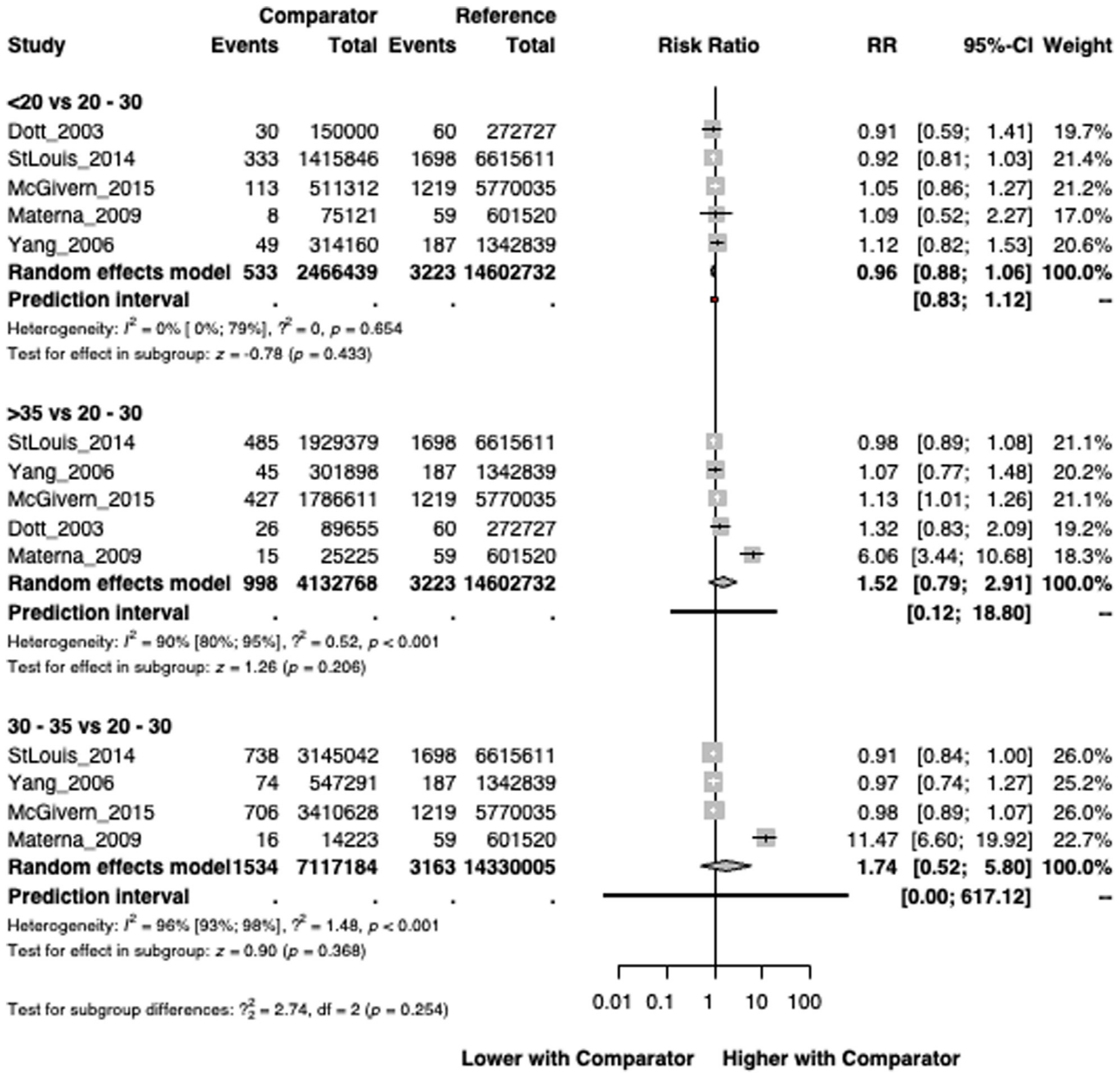
Forest plot representing the RR with 95% CI of *congenital anomalies of the musculoskeletal system* (ICD-10: Q65—Q79) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 15

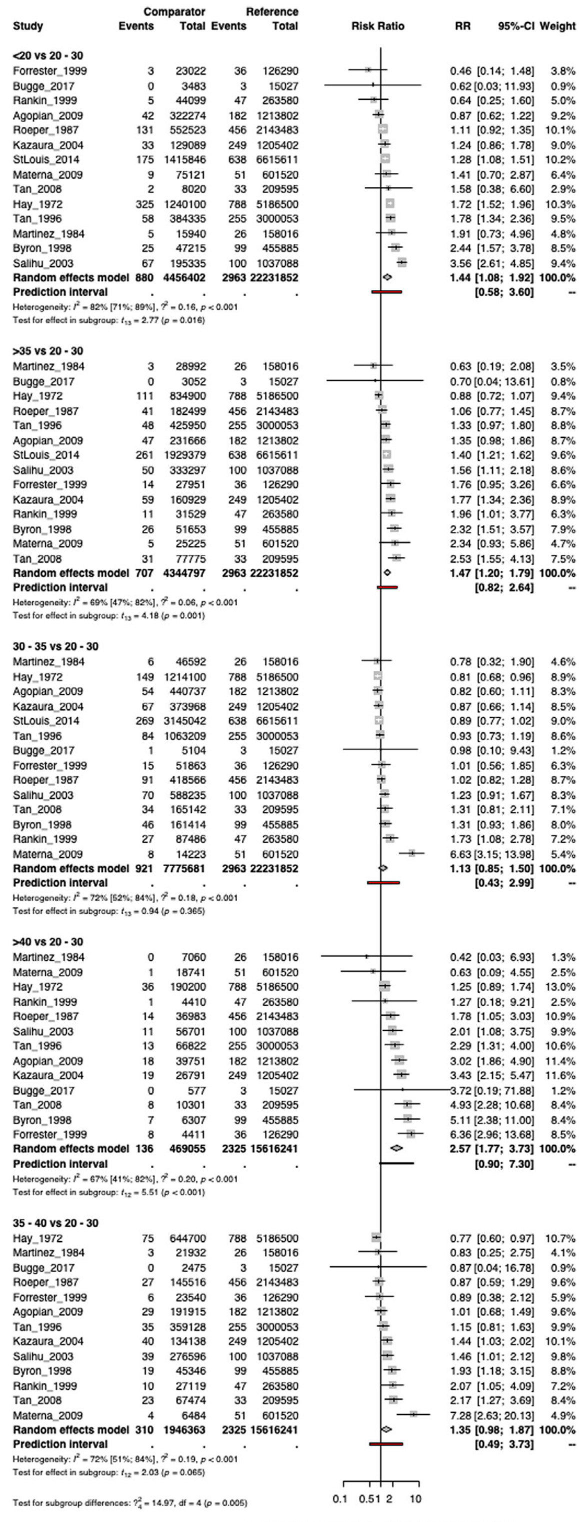
Forest plot representing the RR with 95% CI of *congenital diaphragma hernia* (ICD-10 Q79.0) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 16

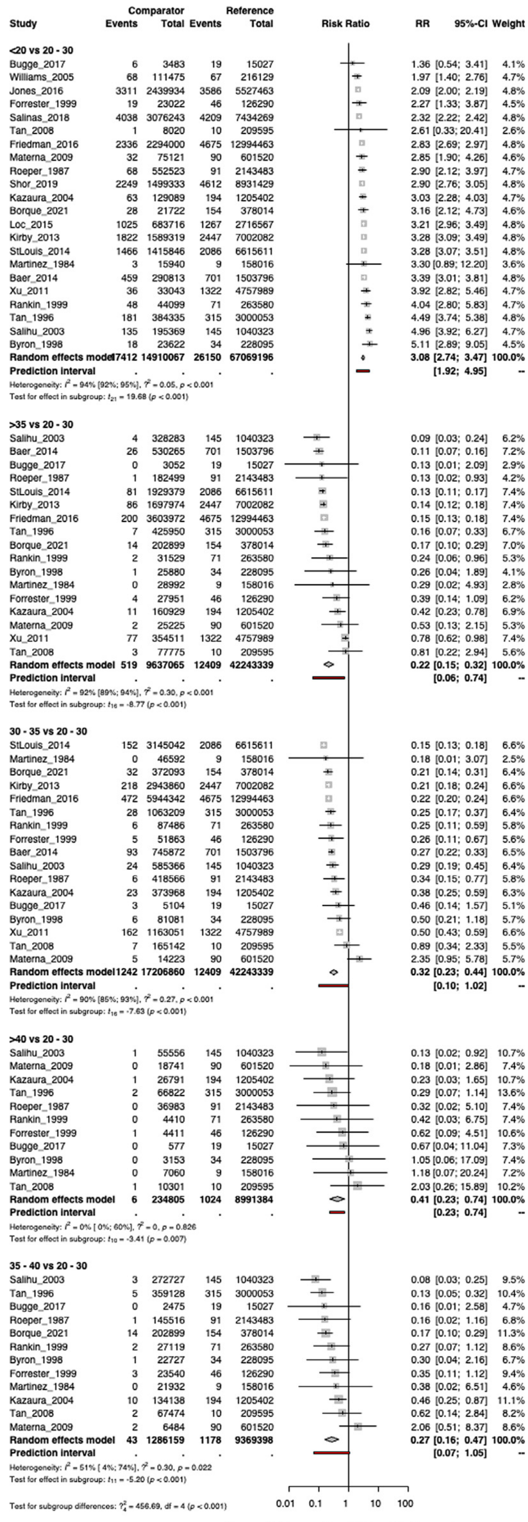
Forest plot representing the RR with 95% CI of *omphalocele* (ICD-10: Q79.2) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 17

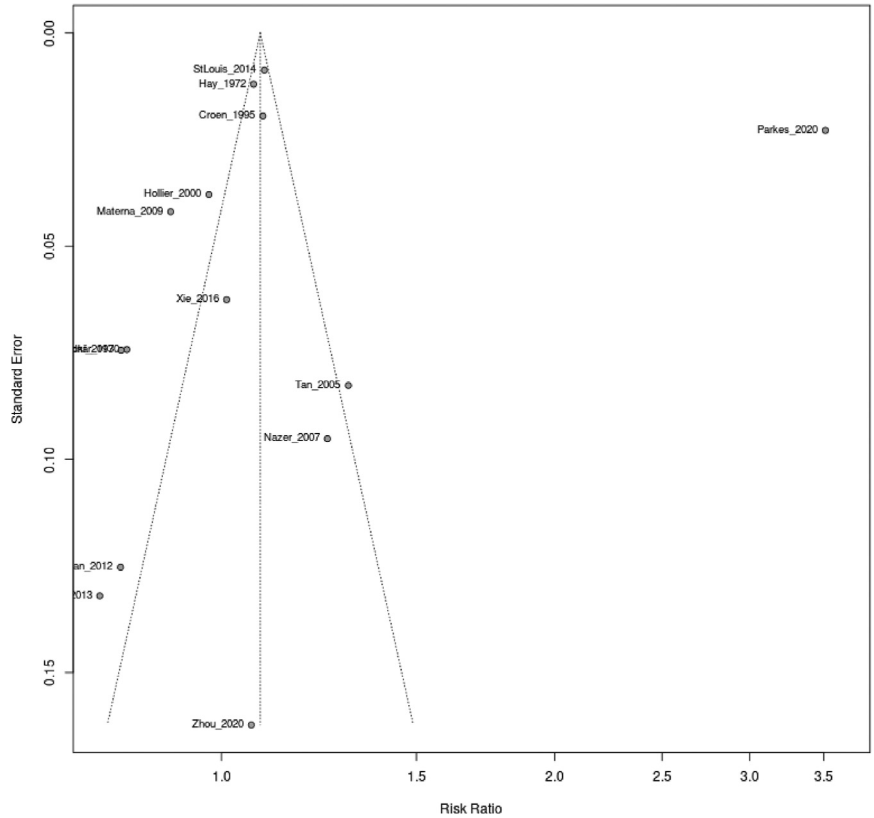
Forest plot representing the RR with 95% CI of *gastroschisis* (ICD-10: Q79.3) in different age groups compared to the 20 to 30 age group



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 18

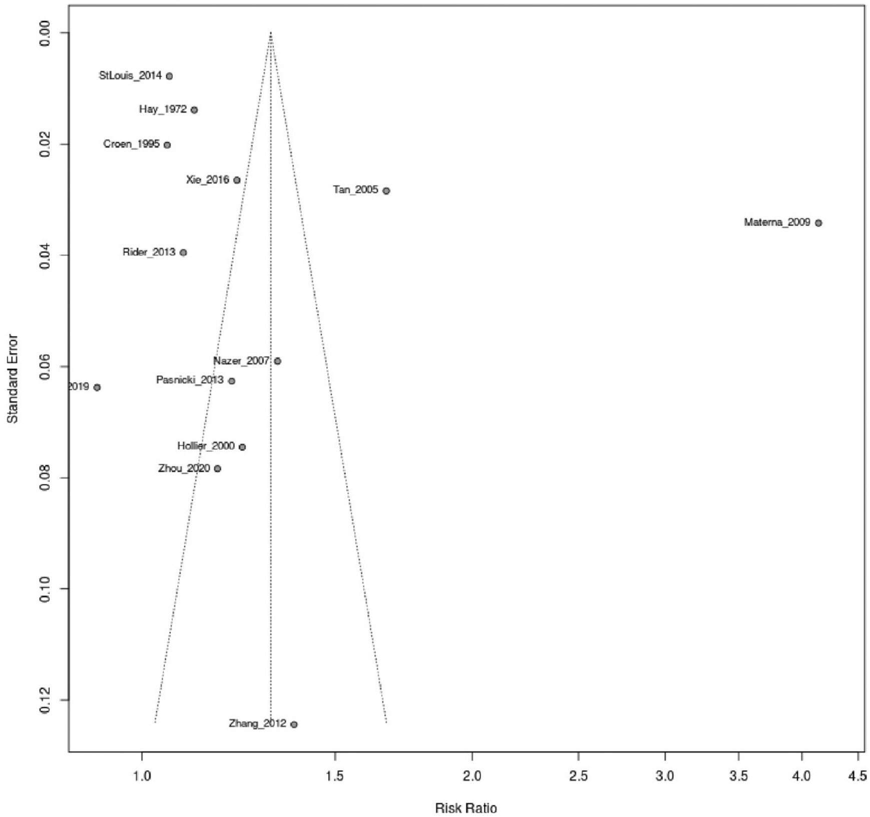
Funnel plot for the association between maternal age and *all nonchromosomal anomalies* (ICD-10: Q00−Q89) (<20 vs 20−30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 19

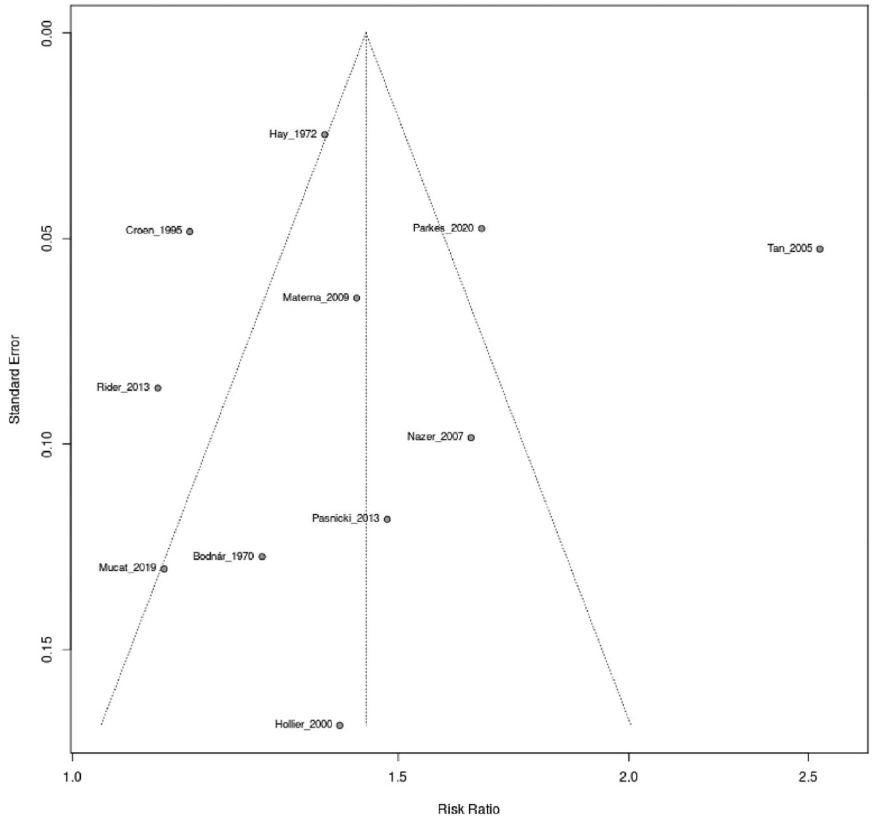
Funnel plot for the association between maternal age and *all nonchromosomal anomalies* (ICD-10: Q00–Q89) (>35 vs 20–30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 20

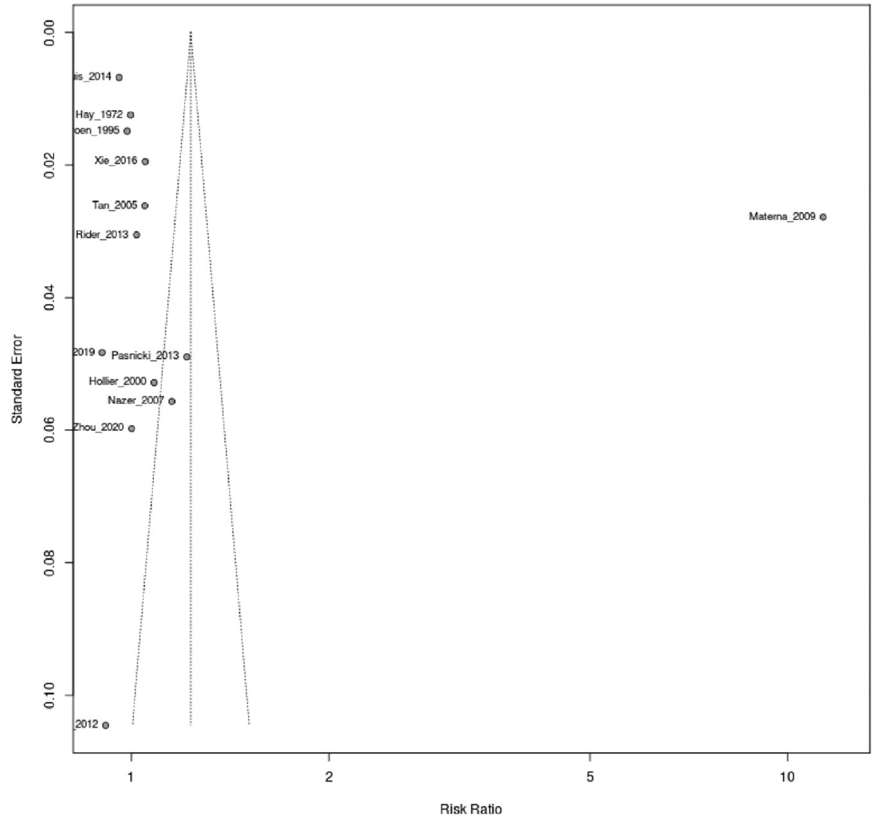
Funnel plot for the association between maternal age and *all nonchromosomal anomalies* (ICD-10: Q00–Q89) (>40 vs 20–30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 21

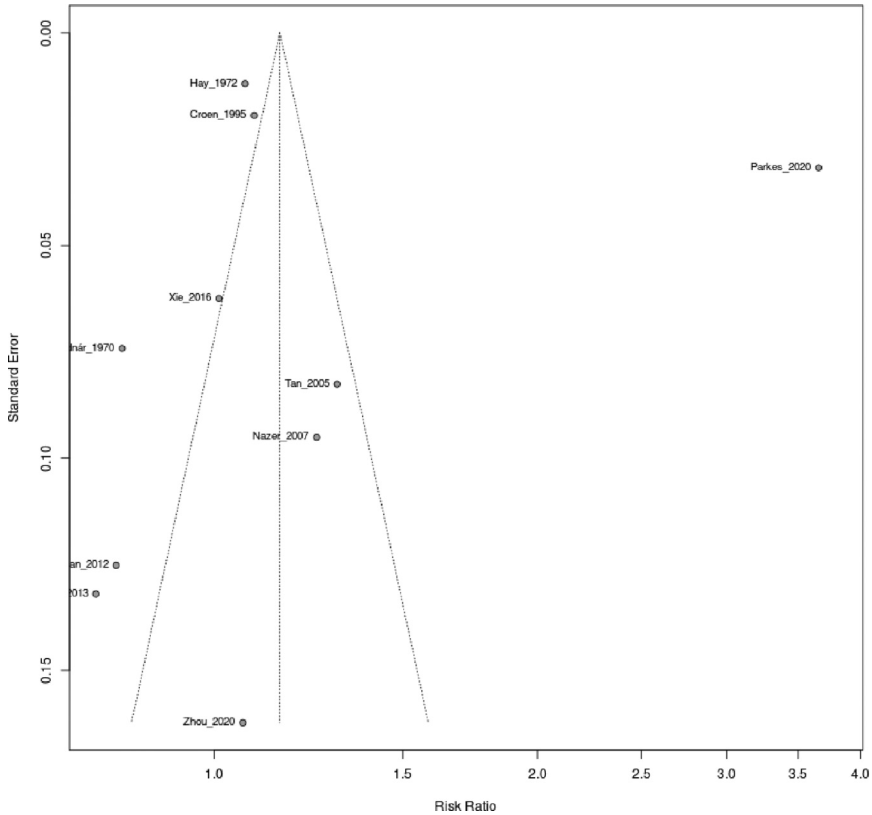
Funnel plot for the association between maternal age and *all nonchromosomal anomalies* (ICD-10: Q00—Q89) (30—35 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 22

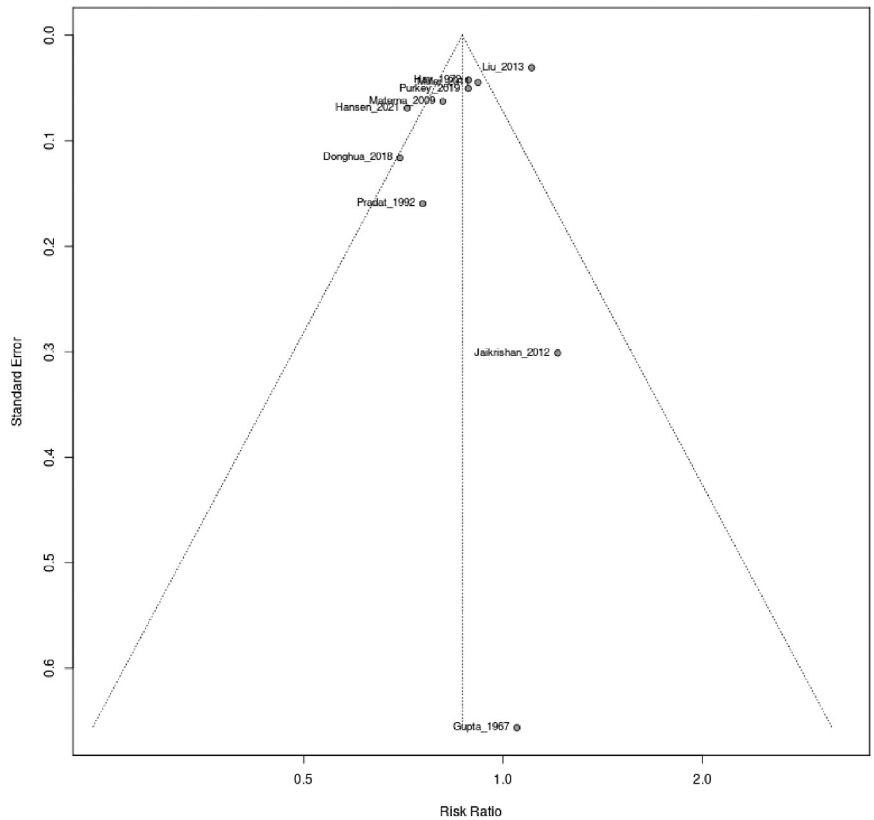
Funnel plot for the association between maternal age and *all nonchromosomal anomalies (only studies including concomitant chromosomal anomalies)* (ICD-10: Q00—Q99 with Q90—Q99) (<20 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 23

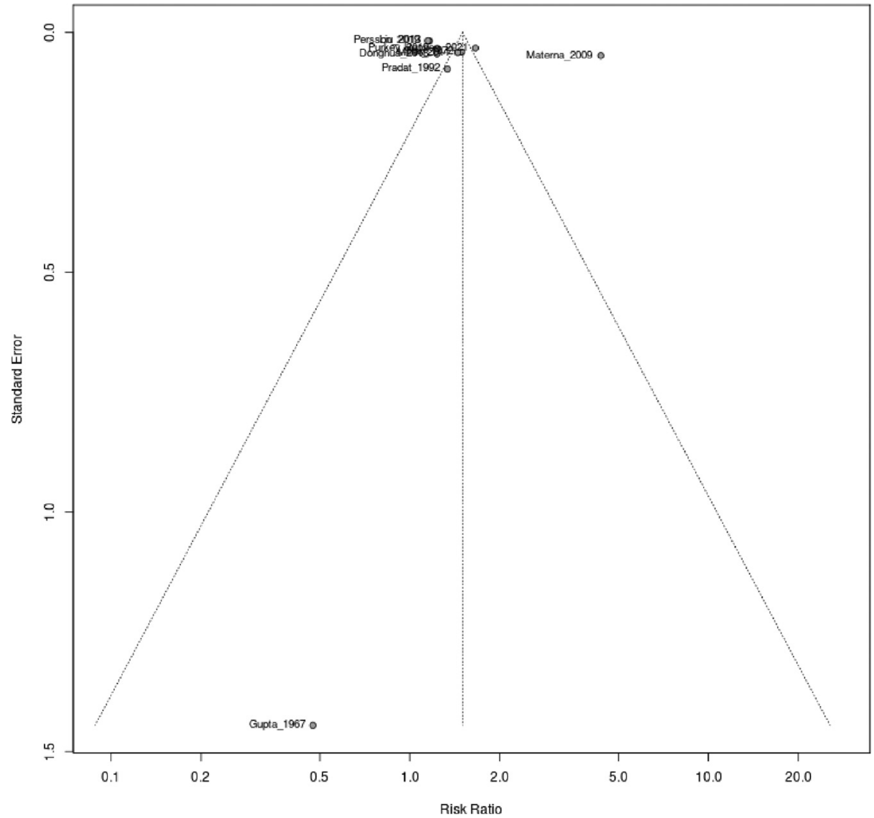
Funnel plot for the association between maternal age and *congenital heart defects* (ICD-10: Q20—Q26) (<20 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 24

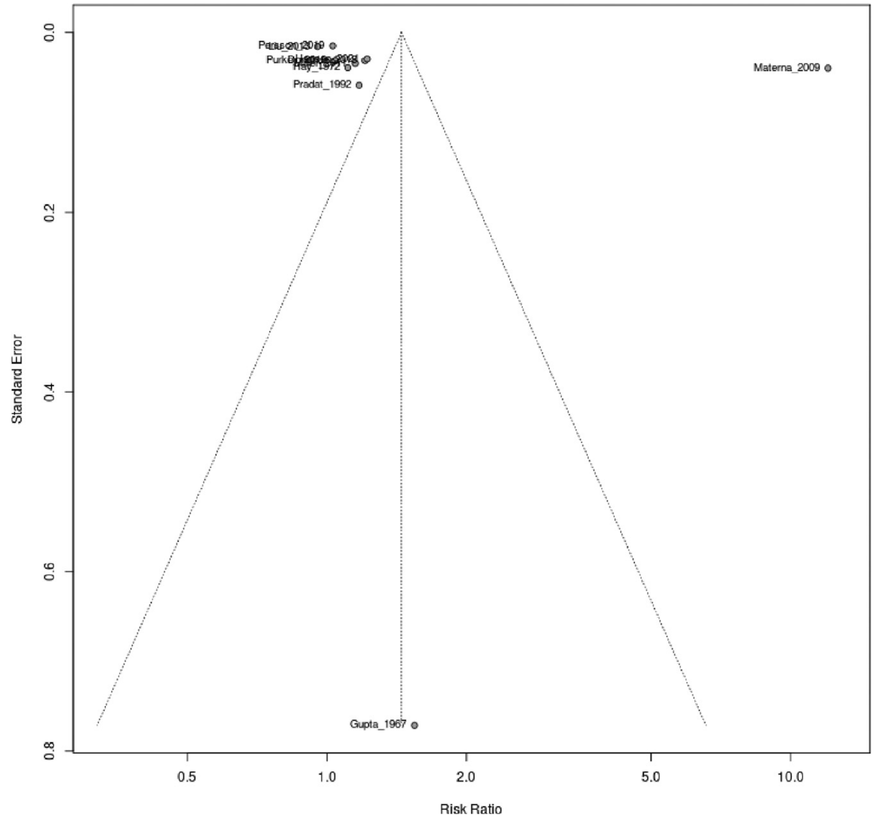
Funnel plot for the association between maternal age and *congenital heart defects* (ICD-10: Q20–Q26) (>35 vs 20–30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 25

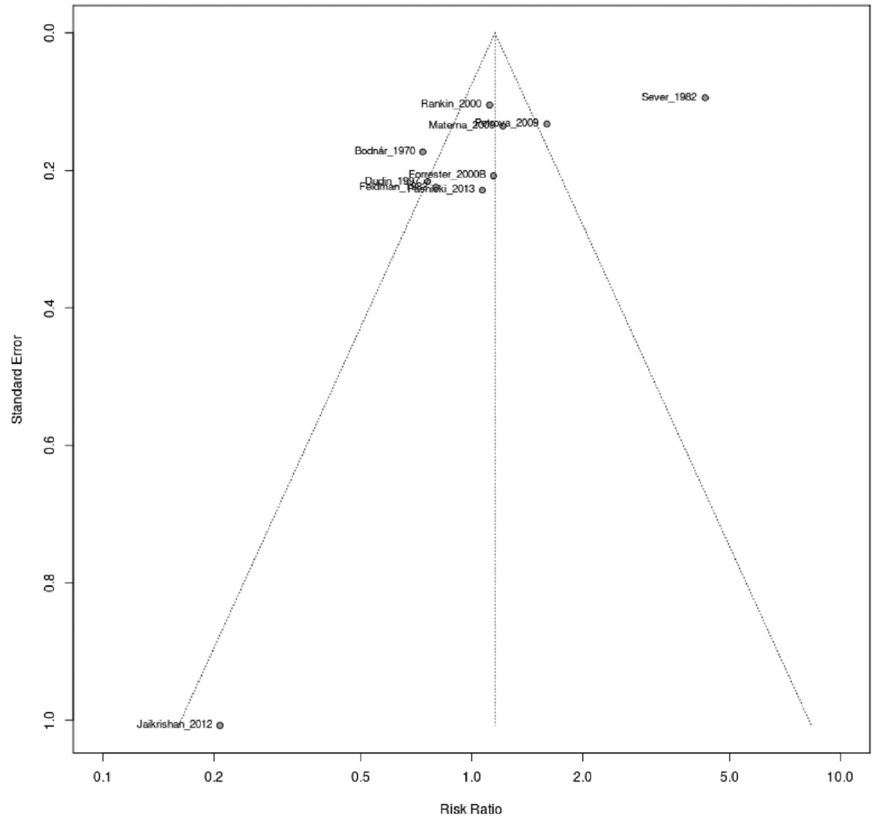
Funnel plot for the association between maternal age and *congenital heart defects* (ICD-10: Q20—Q26) (30—35 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

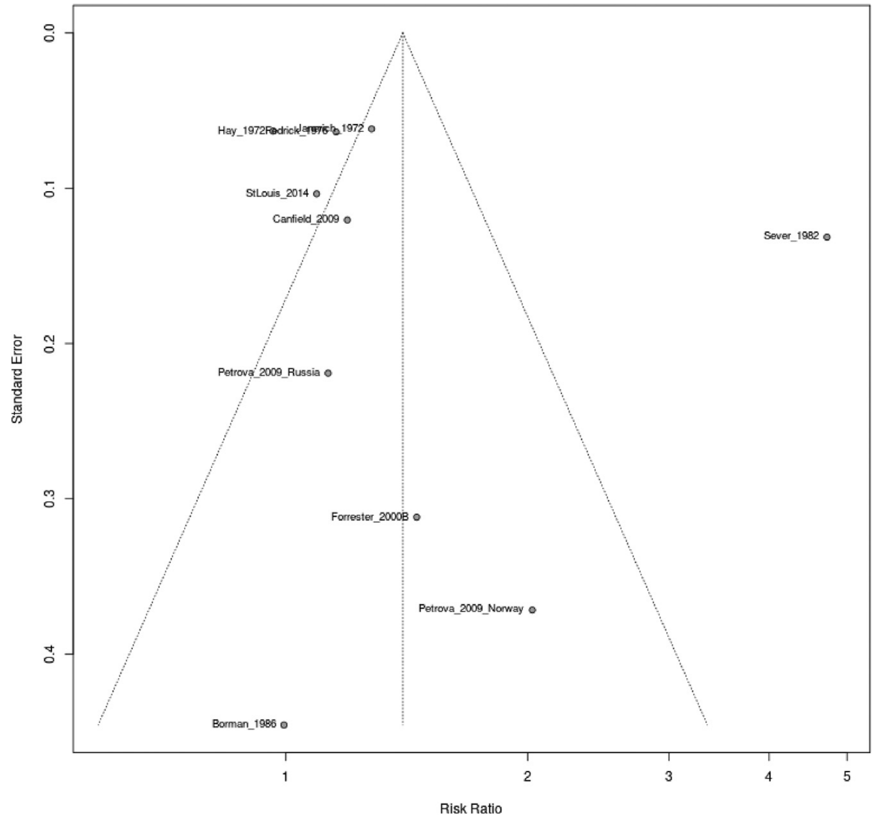
SUPPLEMENTAL FIGURE 26

Funnel plot for the association between maternal age and *congenital anomalies of the nervous system* (ICD-10: Q00–Q07) (<20 vs 20–30 age groups)



ICD-10, International Classification of Diseases-10.

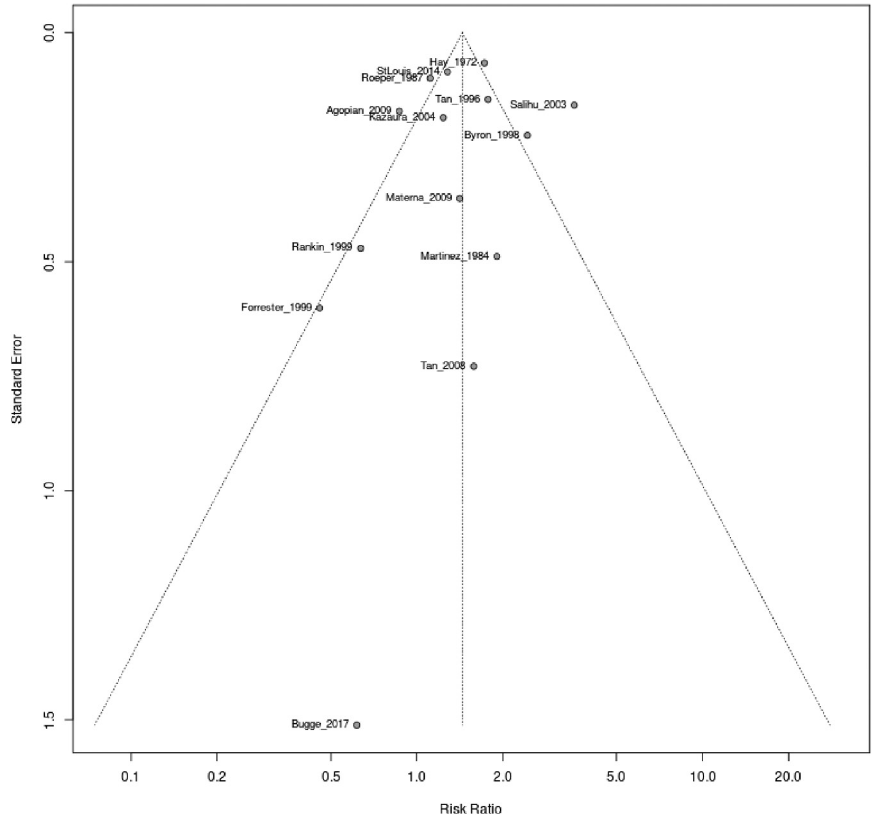
SUPPLEMENTAL FIGURE 27
Funnel plot for the association between maternal age and *anencephaly* (ICD-10: Q00.0) (<20 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 28

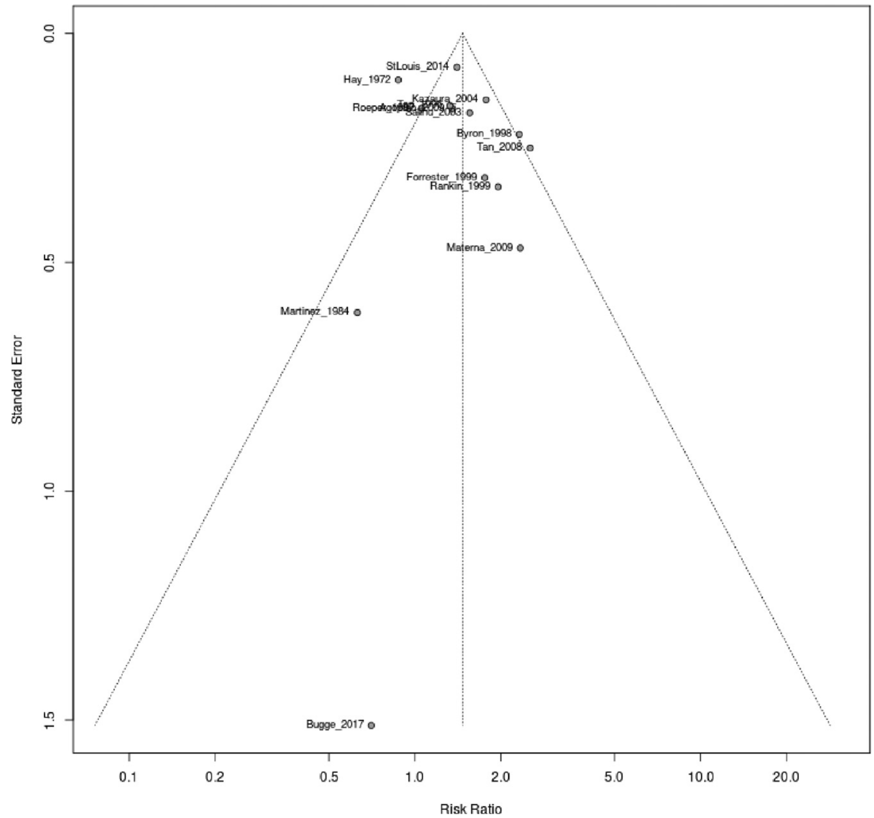
Funnel plot for the association between maternal age and *omphalocele* (ICD-10: Q79.2) (<20 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 29

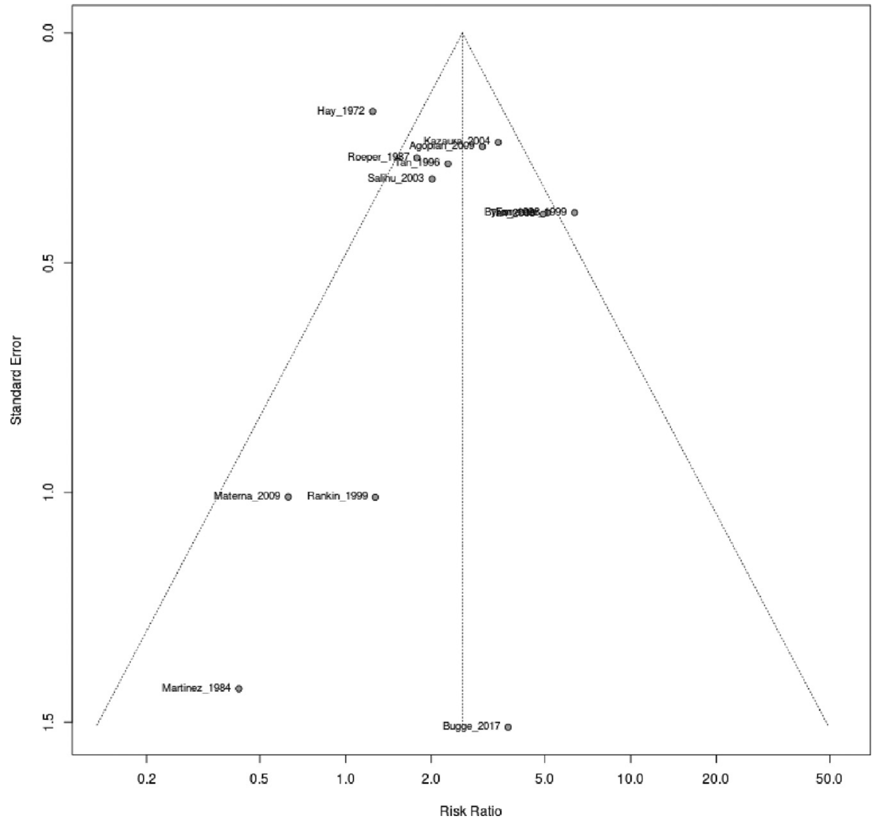
Funnel plot for the association between maternal age and *omphalocele* (ICD-10: Q79.2) (>35 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 30

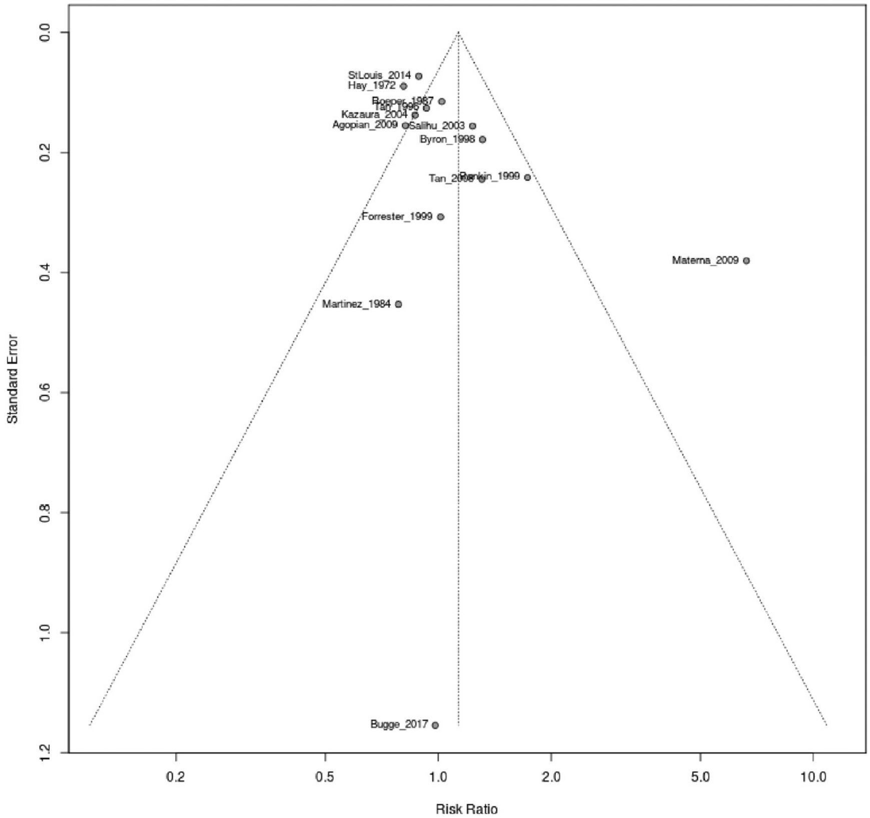
Funnel plot for the association between maternal age and *omphalocele* (ICD-10: Q79.2) (>40 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 31

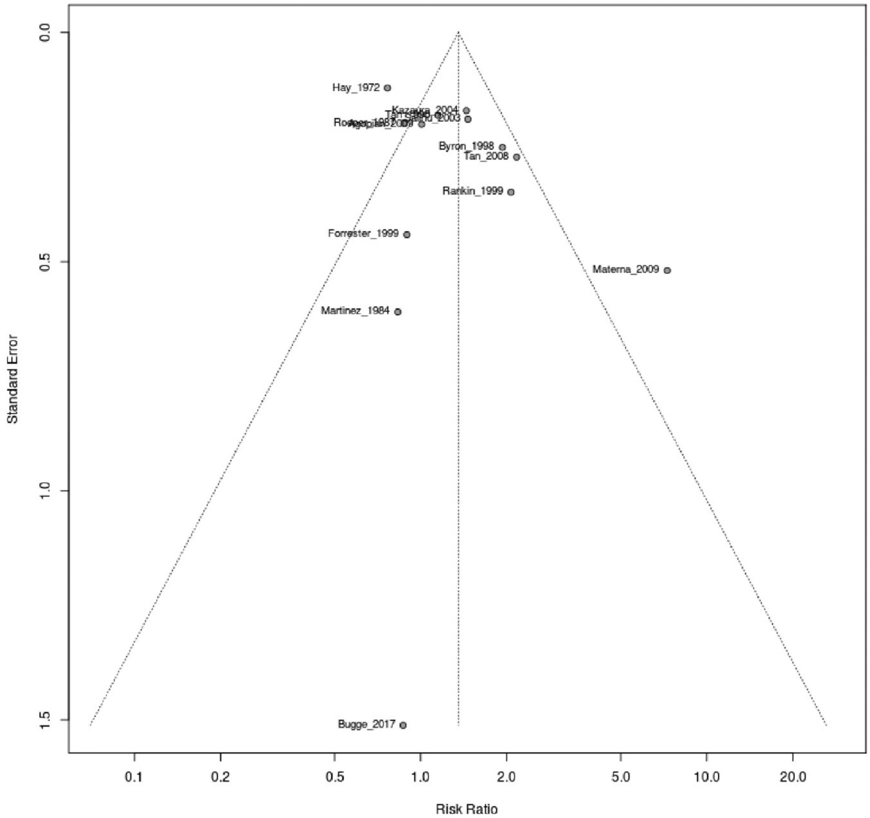
Funnel plot for the association between maternal age and *omphalocele* (ICD-10: Q79.2) (30—35 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

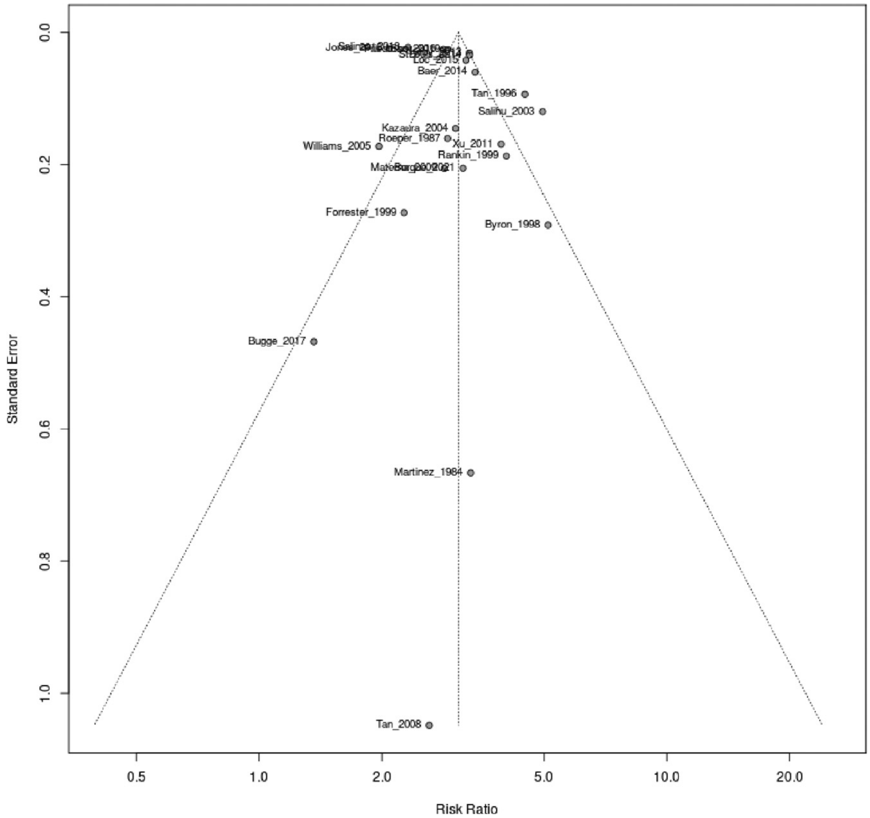
SUPPLEMENTAL FIGURE 32

Funnel plot for the association between maternal age and *omphalocele* (ICD-10: Q79.2) (35–40 vs 20–30 age groups)



ICD-10, International Classification of Diseases-10.

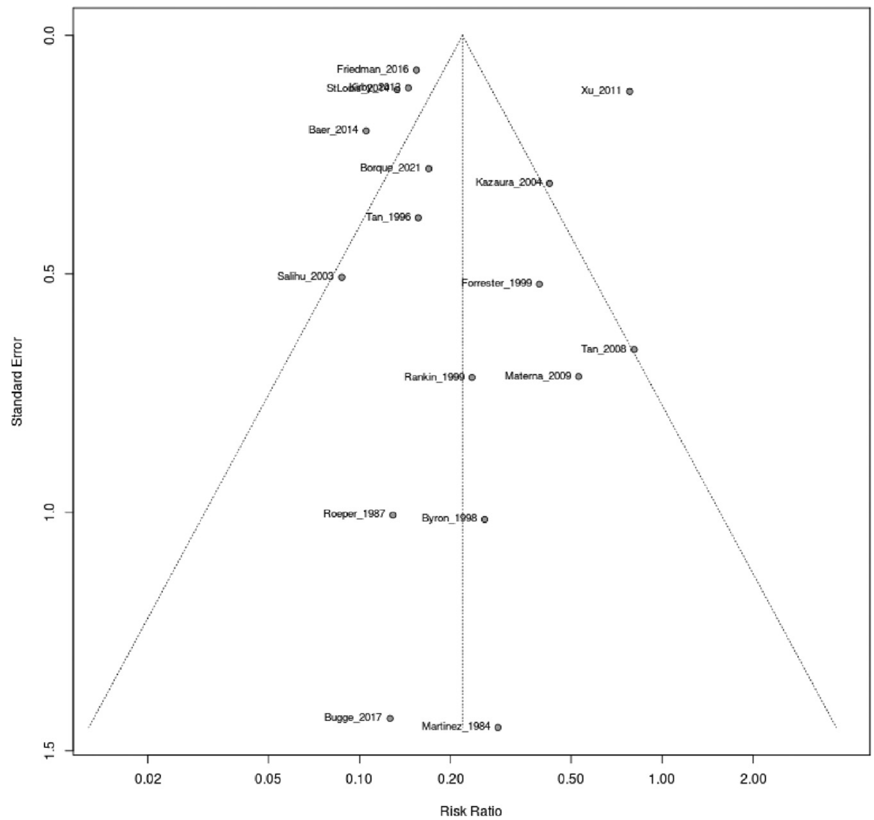
SUPPLEMENTAL FIGURE 33
Funnel plot for the association between maternal age and *gastroschisis* (ICD-10: Q79.3) (<20 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 34

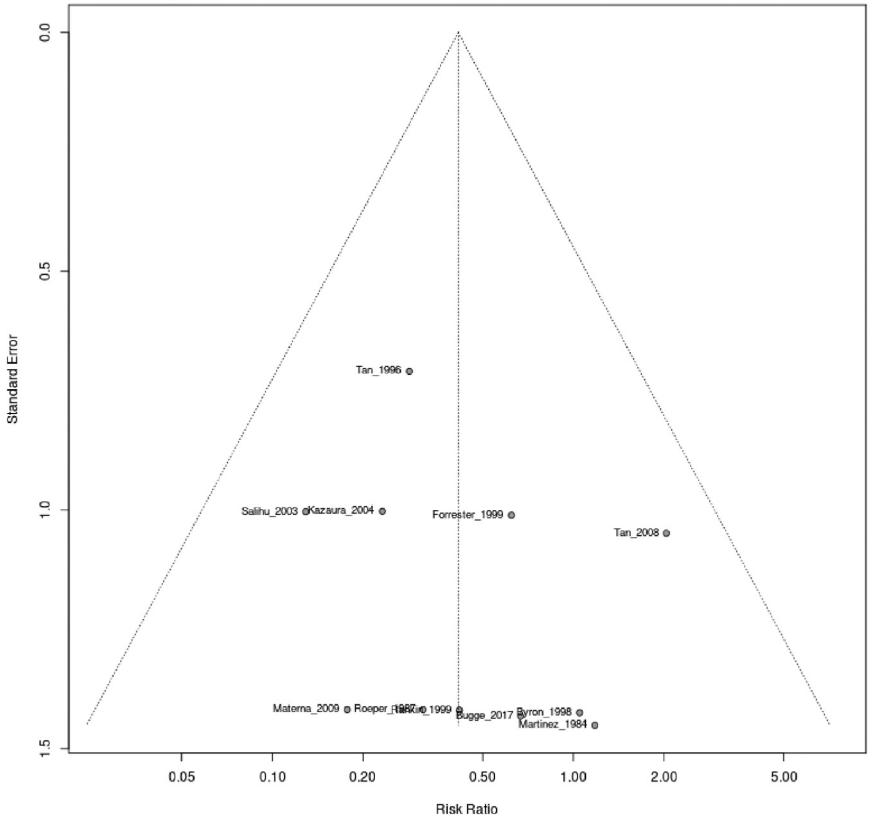
Funnel plot for the association between maternal age and *gastroschisis* (ICD-10: Q79.3) (>35 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 35

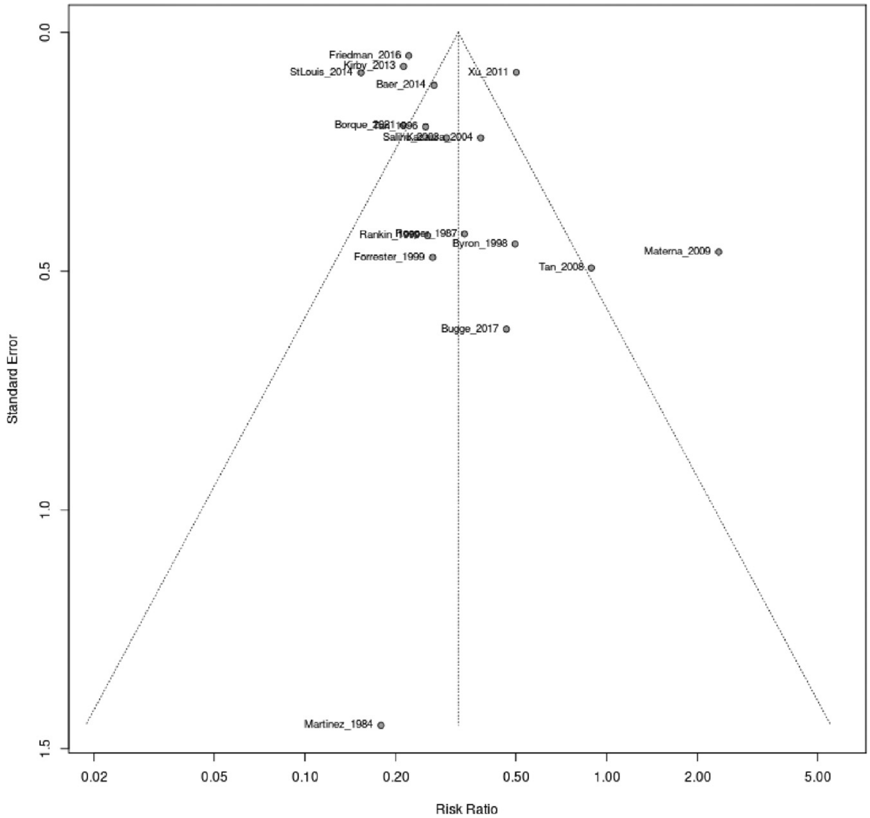
Funnel plot for the association between maternal age and *gastroschisis* (ICD-10: Q79.3) (>40 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 36

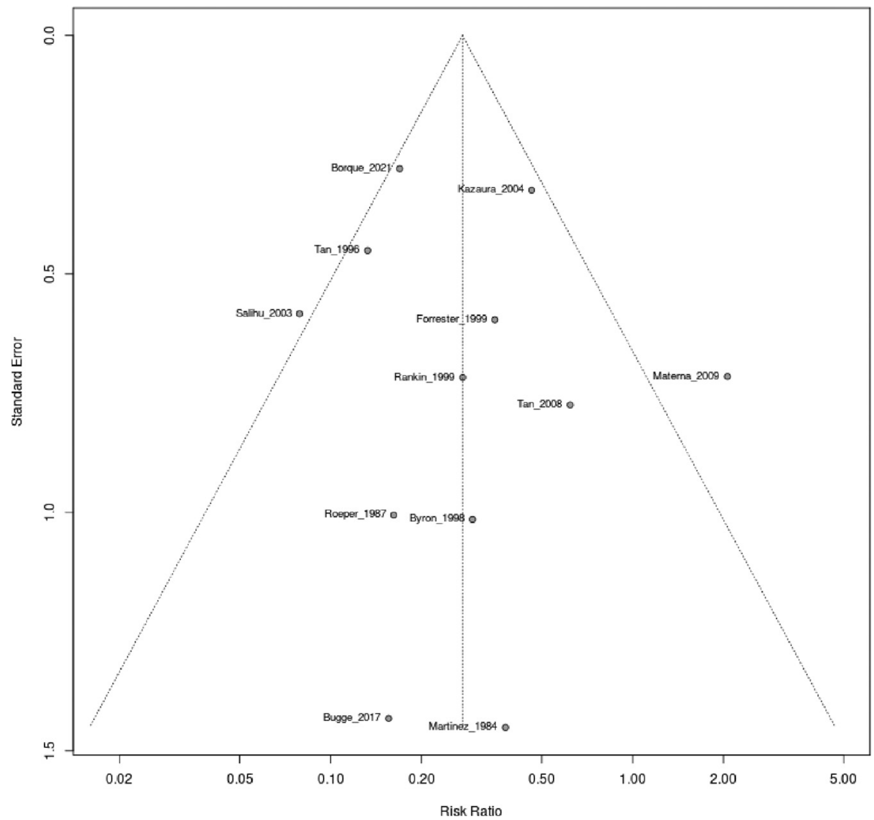
Funnel plot for the association between maternal age and *gastroschisis* (ICD-10: Q79.3) (30—35 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 37

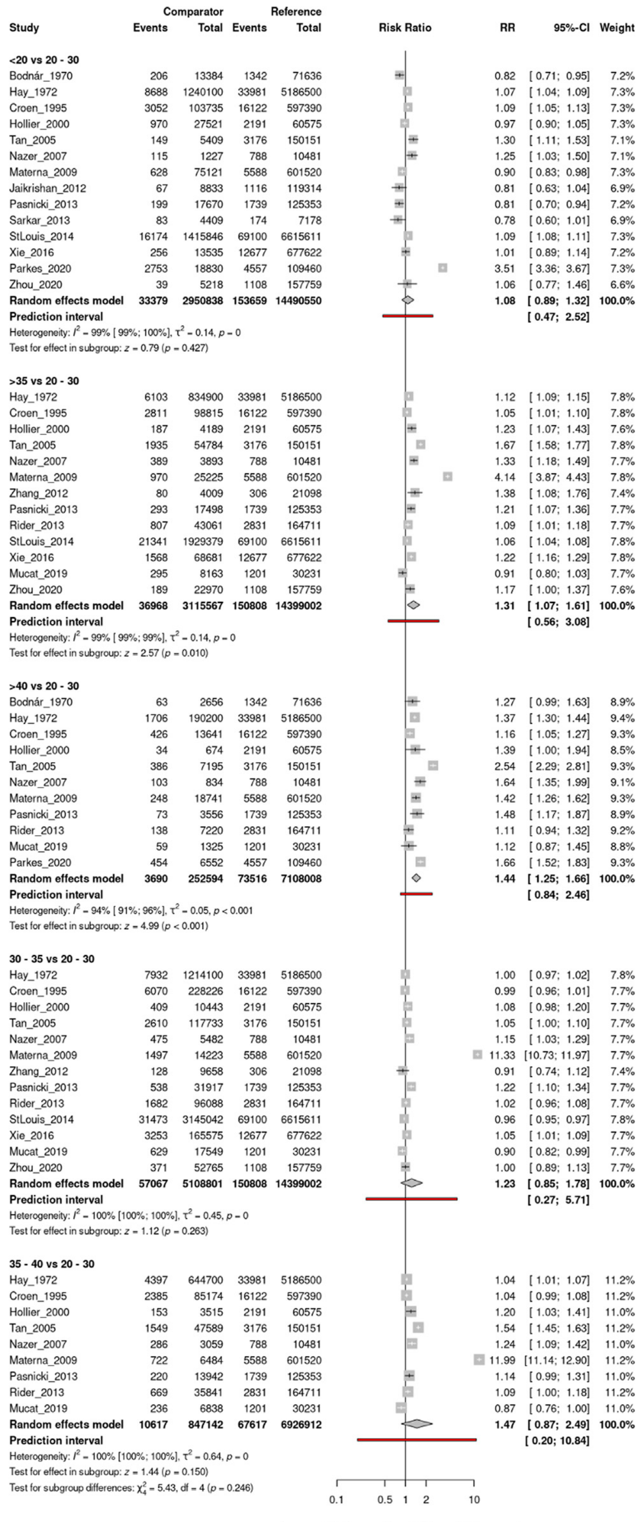
Funnel plot for the association between maternal age and *gastroschisis* (ICD-10: Q79.3) (35—40 vs 20—30 age groups)



ICD-10, International Classification of Diseases-10.

SUPPLEMENTAL FIGURE 38

Forest plot representing the RR with 95% CI of *all nonchromosomal anomalies* (ICD-10: Q00—Q89) in different age groups compared to the 20 to 30 age group and sorted by year of publication



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 39

Forest plot representing the RR with 95% CI of *all nonchromosomal anomalies (only studies excluding concomitant chromosomal anomalies)* (ICD-10: Q00—Q89) in different age groups compared to the 20 to 30 age group and sorted by year of publication

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Hollier_2000	970	27521	2191	60575	0.97	[0.90; 1.05]	20.0%
Materna_2009	628	75121	5588	601520	0.90	[0.83; 0.98]	20.0%
Pasnicki_2013	199	17670	1739	125353	0.81	[0.70; 0.94]	19.9%
StLouis_2014	16174	1415846	69100	6615611	1.09	[1.08; 1.11]	20.1%
Parkes_2020	1231	18830	2136	109460	3.35	[3.13; 3.59]	20.0%
Random effects model	**19202**	**1554988**	**80754**	**7512519**	**1.21**	**[0.59; 2.49]**	**100.0%**
Prediction interval						**[0.16; 9.09]**	

Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.33, p < 0.001
Test for effect in subgroup: t_4 = 0.74 (p = 0.498)

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
>35 vs 20 - 30							
Hollier_2000	187	4189	2191	60575	1.23	[1.07; 1.43]	16.6%
Materna_2009	970	25225	5588	601520	4.14	[3.87; 4.43]	16.7%
Pasnicki_2013	293	17498	1739	125353	1.21	[1.07; 1.36]	16.6%
Rider_2013	807	43061	2831	164711	1.09	[1.01; 1.18]	16.7%
StLouis_2014	21341	1929379	69100	6615611	1.06	[1.04; 1.08]	16.8%
Mucat_2019	295	8163	1201	30231	0.91	[0.80; 1.03]	16.6%
Random effects model	**23893**	**2027515**	**82650**	**7598001**	**1.37**	**[0.76; 2.45]**	**100.0%**
Prediction interval						**[0.26; 7.18]**	

Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.31, p = 0
Test for effect in subgroup: t_5 = 1.38 (p = 0.227)

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
>40 vs 20 - 30							
Hollier_2000	34	674	2191	60575	1.39	[1.00; 1.94]	16.2%
Materna_2009	248	18741	5588	601520	1.42	[1.26; 1.62]	17.0%
Pasnicki_2013	73	3556	1739	125353	1.48	[1.17; 1.87]	16.6%
Rider_2013	138	7220	2831	164711	1.11	[0.94; 1.32]	16.9%
Mucat_2019	59	1325	1201	30231	1.12	[0.87; 1.45]	16.5%
Parkes_2020	139	6552	2136	109460	1.09	[0.92; 1.29]	16.9%
Random effects model	**691**	**38068**	**15686**	**1091850**	**1.25**	**[1.08; 1.46]**	**100.0%**
Prediction interval						**[0.91; 1.73]**	

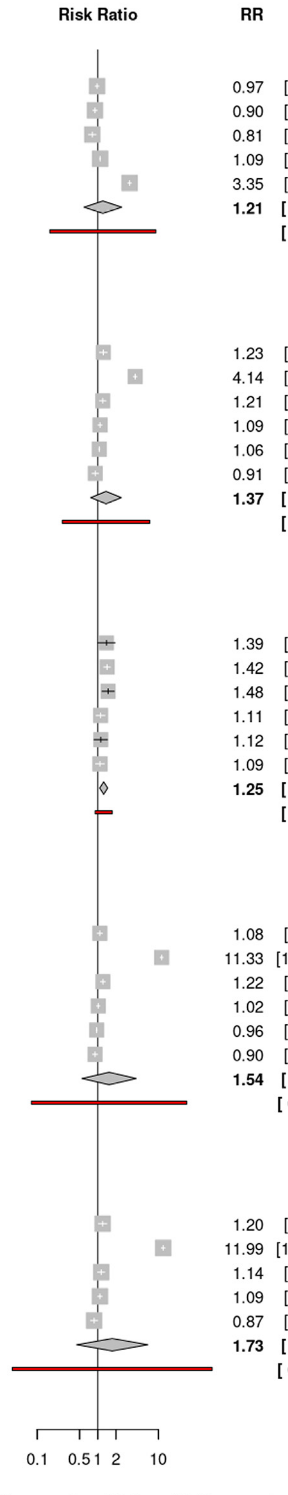
Heterogeneity: I^2 = 57% [0%; 83%], τ^2 = 0.01, p = 0.040
Test for effect in subgroup: t_5 = 3.81 (p = 0.013)

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
30 - 35 vs 20 - 30							
Hollier_2000	409	10443	2191	60575	1.08	[0.98; 1.20]	16.6%
Materna_2009	1497	14223	5588	601520	11.33	[10.73; 11.97]	16.7%
Pasnicki_2013	538	31917	1739	125353	1.22	[1.10; 1.34]	16.6%
Rider_2013	1682	96088	2831	164711	1.02	[0.96; 1.08]	16.7%
StLouis_2014	31473	3145042	69100	6615611	0.96	[0.95; 0.97]	16.7%
Mucat_2019	629	17549	1201	30231	0.90	[0.82; 0.99]	16.6%
Random effects model	**36228**	**3315262**	**82650**	**7598001**	**1.54**	**[0.55; 4.32]**	**100.0%**
Prediction interval						**[0.08; 29.38]**	

Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.97, p = 0
Test for effect in subgroup: t_5 = 1.07 (p = 0.334)

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
35 - 40 vs 20 - 30							
Hollier_2000	153	3515	2191	60575	1.20	[1.03; 1.41]	19.9%
Materna_2009	722	6484	5588	601520	11.99	[11.14; 12.90]	20.1%
Pasnicki_2013	220	13942	1739	125353	1.14	[0.99; 1.31]	20.0%
Rider_2013	669	35841	2831	164711	1.09	[1.00; 1.18]	20.1%
Mucat_2019	236	6838	1201	30231	0.87	[0.76; 1.00]	20.0%
Random effects model	**2000**	**66620**	**13550**	**982390**	**1.73**	**[0.45; 6.70]**	**100.0%**
Prediction interval						**[0.04; 77.01]**	

Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 1.18, p = 0
Test for effect in subgroup: t_4 = 1.13 (p = 0.323)
Test for subgroup differences: χ^2_4 = 0.82, df = 4 (p = 0.935)

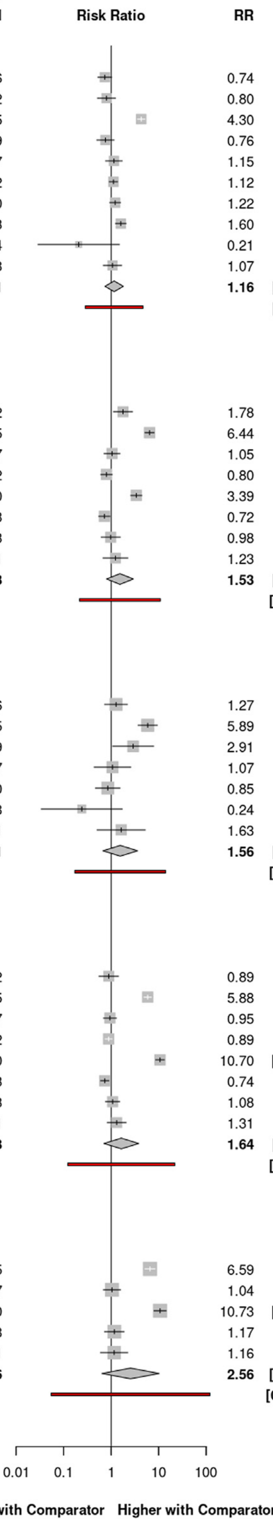


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 40

Forest plot representing the RR with 95% CI of *congenital anomalies of the nervous system* (ICD-10: Q00−Q07) in different age groups compared to the 20 to 30 age group and sorted by year of publication

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Bodnár_1970	38	13384	276	71636	0.74	[0.53; 1.03]	10.6%
Feldman_1982	24	29235	114	111052	0.80	[0.52; 1.24]	10.3%
Sever_1982	140	146173	586	2628305	4.30	[3.57; 5.17]	11.0%
Dudin_1997	30	7798	74	14619	0.76	[0.50; 1.16]	10.4%
Forrester_2000B	28	23026	134	126287	1.15	[0.76; 1.72]	10.4%
Rankin_2000	108	52816	580	317512	1.12	[0.91; 1.37]	10.9%
Materna_2009	63	75121	415	601520	1.22	[0.93; 1.58]	10.8%
Petrova_2009	68	28497	357	239383	1.60	[1.23; 2.07]	10.8%
Jaikrishan_2012	1	8833	65	119314	0.21	[0.03; 1.50]	4.4%
Pasnicki_2013	22	17670	146	125353	1.07	[0.68; 1.67]	10.3%
Random effects model	**522**	**402553**	**2747**	**4354981**	**1.16**	**[0.74; 1.81]**	**100.0%**
Prediction interval						**[0.29; 4.69]**	
Heterogeneity: I^2 = 95% [92%; 97%], τ^2 = 0.33, $p < 0.001$							
Test for effect in subgroup: t_9 = 0.74 (p = 0.478)							
>35 vs 20 - 30							
Feldman_1982	21	11508	114	111052	1.78	[1.12; 2.83]	12.2%
Sever_1982	88	61315	586	2628305	6.44	[5.15; 8.05]	13.0%
Forrester_2000B	31	27938	134	126287	1.05	[0.71; 1.55]	12.5%
Rankin_2000	53	36304	580	317512	0.80	[0.60; 1.06]	12.8%
Materna_2009	59	25225	415	601520	3.39	[2.58; 4.45]	12.9%
Petrova_2009	57	52941	357	239383	0.72	[0.55; 0.95]	12.8%
Pasnicki_2013	20	17498	146	125353	0.98	[0.62; 1.57]	12.2%
Mucat_2019	14	8163	42	30231	1.23	[0.67; 2.26]	11.6%
Random effects model	**343**	**240892**	**2374**	**4179643**	**1.53**	**[0.80; 2.94]**	**100.0%**
Prediction interval						**[0.22; 10.87]**	
Heterogeneity: I^2 = 97% [96%; 98%], τ^2 = 0.57, $p < 0.001$							
Test for effect in subgroup: t_7 = 1.56 (p = 0.164)							
>40 vs 20 - 30							
Bodnár_1970	13	2656	276	71636	1.27	[0.73; 2.21]	17.1%
Sever_1982	18	13696	586	2628305	5.89	[3.69; 9.42]	17.6%
Dudin_1997	4	272	74	14619	2.91	[1.07; 7.89]	13.8%
Forrester_2000B	5	4409	134	126287	1.07	[0.44; 2.61]	14.6%
Materna_2009	11	18741	415	601520	0.85	[0.47; 1.55]	16.8%
Pasnicki_2013	1	3556	146	125353	0.24	[0.03; 1.73]	7.7%
Mucat_2019	3	1325	42	30231	1.63	[0.51; 5.25]	12.5%
Random effects model	**55**	**44655**	**1673**	**3597951**	**1.56**	**[0.67; 3.62]**	**100.0%**
Prediction interval						**[0.17; 13.99]**	
Heterogeneity: I^2 = 84% [69%; 92%], τ^2 = 0.61, $p < 0.001$							
Test for effect in subgroup: t_6 = 1.28 (p = 0.248)							
30 - 35 vs 20 - 30							
Feldman_1982	20	21860	114	111052	0.89	[0.55; 1.43]	11.9%
Sever_1982	144	109762	586	2628305	5.88	[4.90; 7.06]	12.8%
Forrester_2000B	52	51844	134	126287	0.95	[0.69; 1.30]	12.5%
Rankin_2000	163	100773	580	317512	0.89	[0.74; 1.05]	12.8%
Materna_2009	105	14223	415	601520	10.70	[8.64; 13.25]	12.8%
Petrova_2009	125	113746	357	239383	0.74	[0.60; 0.90]	12.8%
Pasnicki_2013	40	31917	146	125353	1.08	[0.76; 1.53]	12.4%
Mucat_2019	32	17549	42	30231	1.31	[0.83; 2.08]	12.0%
Random effects model	**681**	**461674**	**2374**	**4179643**	**1.64**	**[0.70; 3.81]**	**100.0%**
Prediction interval						**[0.12; 21.90]**	
Heterogeneity: I^2 = 99% [98%; 99%], τ^2 = 1.00, $p < 0.001$							
Test for effect in subgroup: t_7 = 1.38 (p = 0.210)							
35 - 40 vs 20 - 30							
Sever_1982	70	47619	586	2628305	6.59	[5.15; 8.45]	21.0%
Forrester_2000B	26	23529	134	126287	1.04	[0.68; 1.58]	20.1%
Materna_2009	48	6484	415	601520	10.73	[7.97; 14.45]	20.8%
Pasnicki_2013	19	13942	146	125353	1.17	[0.73; 1.89]	19.7%
Mucat_2019	11	6838	42	30231	1.16	[0.60; 2.25]	18.4%
Random effects model	**174**	**98412**	**1323**	**3511696**	**2.56**	**[0.64; 10.32]**	**100.0%**
Prediction interval						**[0.05; 120.01]**	
Heterogeneity: I^2 = 97% [95%; 98%], τ^2 = 1.21, $p < 0.001$							
Test for effect in subgroup: t_4 = 1.87 (p = 0.134)							
Test for subgroup differences: χ^2_4 = 2.77, df = 4 (p = 0.598)							

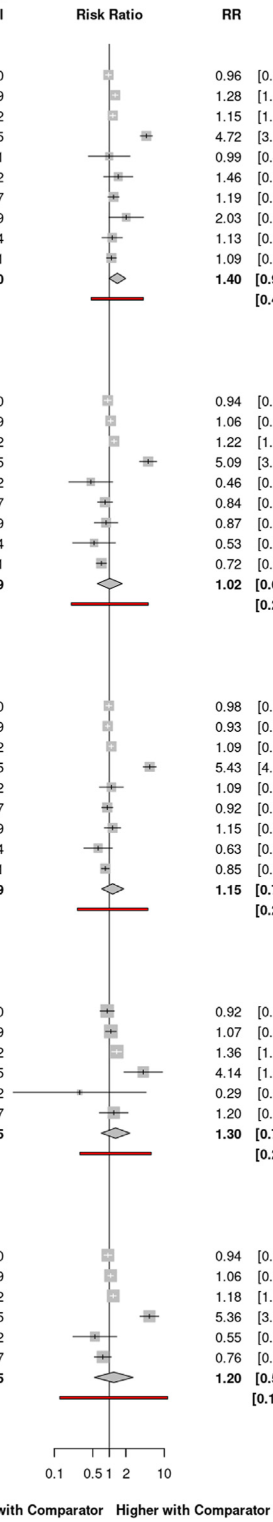


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 41

Forest plot representing the RR with 95% CI of *anencephaly* (ICD-10: Q00.0) in different age groups compared to the 20 to 30 age group and sorted by year of publication

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Hay_1972	309	1240100	1341	5186500	0.96	[0.85; 1.09]	11.3%
Janerich_1972	306	320794	1833	2457349	1.28	[1.13; 1.44]	11.3%
Fedrick_1976	286	103161	1765	735182	1.15	[1.02; 1.31]	11.3%
Sever_1982	73	146173	278	2628305	4.72	[3.65; 6.11]	10.8%
Borman_1986	6	6853	31	35211	0.99	[0.42; 2.38]	7.0%
Forrester_2000B	13	23009	49	126212	1.46	[0.79; 2.68]	8.7%
Canfield_2009	91	269890	284	1004687	1.19	[0.94; 1.51]	10.9%
Petrova_2009_Norway	8	7640	75	145219	2.03	[0.98; 4.20]	7.9%
Petrova_2009_Russia	26	20857	104	94164	1.13	[0.73; 1.73]	9.9%
StLouis_2014	115	1415846	492	6615611	1.09	[0.89; 1.34]	11.0%
Random effects model	**1233**	**3554323**	**6252**	**19028440**	**1.40**	**[0.98; 1.99]**	**100.0%**
Prediction interval						**[0.47; 4.17]**	
Heterogeneity: $I^2 = 93\%$ [89%; 95%], $\tau^2 = 0.20$, $p < 0.001$							
Test for effect in subgroup: $t_9 = 2.16$ ($p = 0.059$)							
>35 vs 20 - 30							
Hay_1972	202	834900	1341	5186500	0.94	[0.81; 1.08]	12.6%
Janerich_1972	391	495715	1833	2457349	1.06	[0.95; 1.18]	12.7%
Fedrick_1976	367	125433	1765	735182	1.22	[1.09; 1.36]	12.7%
Sever_1982	33	61315	278	2628305	5.09	[3.55; 7.30]	11.6%
Forrester_2000B	5	27996	49	126212	0.46	[0.18; 1.15]	7.6%
Canfield_2009	45	190264	284	1004687	0.84	[0.61; 1.15]	11.9%
Petrova_2009_Norway	20	44366	75	145219	0.87	[0.53; 1.43]	10.7%
Petrova_2009_Russia	5	8575	104	94164	0.53	[0.22; 1.29]	7.7%
StLouis_2014	103	1929379	492	6615611	0.72	[0.58; 0.89]	12.4%
Random effects model	**1171**	**3717943**	**6221**	**18993229**	**1.02**	**[0.60; 1.72]**	**100.0%**
Prediction interval						**[0.20; 5.11]**	
Heterogeneity: $I^2 = 92\%$ [87%; 95%], $\tau^2 = 0.41$, $p < 0.001$							
Test for effect in subgroup: $t_8 = 0.08$ ($p = 0.936$)							
30 - 35 vs 20 - 30							
Hay_1972	308	1214100	1341	5186500	0.98	[0.87; 1.11]	11.8%
Janerich_1972	560	803311	1833	2457349	0.93	[0.85; 1.03]	11.9%
Fedrick_1976	518	198537	1765	735182	1.09	[0.99; 1.20]	11.9%
Sever_1982	63	109762	278	2628305	5.43	[4.13; 7.13]	11.3%
Forrester_2000B	22	51887	49	126212	1.09	[0.66; 1.81]	9.9%
Canfield_2009	94	362254	284	1004687	0.92	[0.73; 1.16]	11.5%
Petrova_2009_Norway	57	96370	75	145219	1.15	[0.81; 1.62]	10.9%
Petrova_2009_Russia	12	17376	104	94164	0.63	[0.34; 1.14]	9.2%
StLouis_2014	198	3145042	492	6615611	0.85	[0.72; 1.00]	11.7%
Random effects model	**1832**	**5998639**	**6221**	**18993229**	**1.15**	**[0.72; 1.84]**	**100.0%**
Prediction interval						**[0.26; 5.04]**	
Heterogeneity: $I^2 = 95\%$ [92%; 97%], $\tau^2 = 0.35$, $p < 0.001$							
Test for effect in subgroup: $t_8 = 0.69$ ($p = 0.510$)							
>40 vs 20 - 30							
Hay_1972	45	190200	1341	5186500	0.92	[0.68; 1.23]	21.1%
Janerich_1972	78	98025	1833	2457349	1.07	[0.85; 1.34]	21.8%
Fedrick_1976	93	28490	1765	735182	1.36	[1.10; 1.67]	21.9%
Sever_1982	6	13696	278	2628305	4.14	[1.85; 9.30]	14.7%
Forrester_2000B	0	4411	49	126212	0.29	[0.02; 4.68]	3.0%
Canfield_2009	11	32324	284	1004687	1.20	[0.66; 2.20]	17.4%
Random effects model	**233**	**367146**	**5550**	**12138235**	**1.30**	**[0.71; 2.38]**	**100.0%**
Prediction interval						**[0.29; 5.77]**	
Heterogeneity: $I^2 = 68\%$ [24%; 86%], $\tau^2 = 0.23$, $p = 0.008$							
Test for effect in subgroup: $t_5 = 1.11$ ($p = 0.318$)							
35 - 40 vs 20 - 30							
Hay_1972	157	644700	1341	5186500	0.94	[0.80; 1.11]	18.3%
Janerich_1972	313	397690	1833	2457349	1.06	[0.94; 1.19]	18.5%
Fedrick_1976	274	96943	1765	735182	1.18	[1.04; 1.34]	18.5%
Sever_1982	27	47619	278	2628305	5.36	[3.61; 7.96]	16.6%
Forrester_2000B	5	23585	49	126212	0.55	[0.22; 1.37]	11.0%
Canfield_2009	34	157940	284	1004687	0.76	[0.53; 1.09]	17.0%
Random effects model	**810**	**1368477**	**5550**	**12138235**	**1.20**	**[0.53; 2.72]**	**100.0%**
Prediction interval						**[0.13; 11.51]**	
Heterogeneity: $I^2 = 93\%$ [88%; 96%], $\tau^2 = 0.56$, $p < 0.001$							
Test for effect in subgroup: $t_5 = 0.58$ ($p = 0.585$)							
Test for subgroup differences: $\chi^2_4 = 1.53$, df = 4 ($p = 0.822$)							

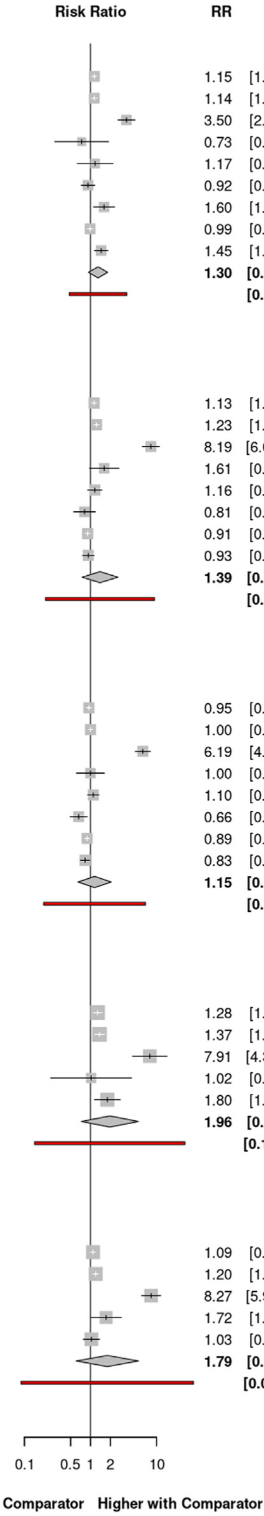


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 42

Forest plot representing the RR with 95% CI of *spina bifida* (ICD-10: Q05) in different age groups compared to the 20 to 30 age group and sorted by year of publication

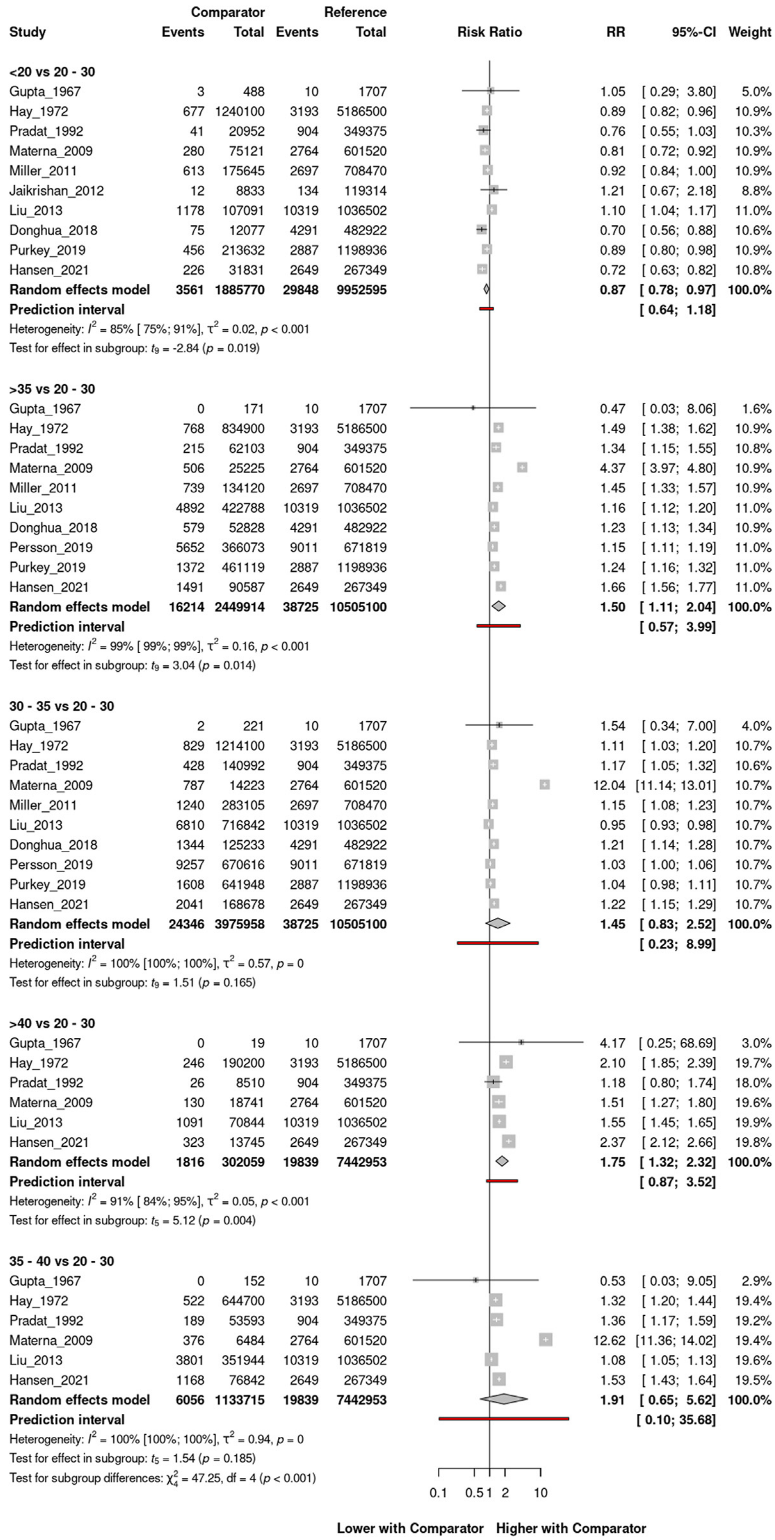
Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Hay_1972	952	1240100	3477	5186500	1.15	[1.07; 1.23]	12.1%
Janerich_1972	407	379484	2615	2780544	1.14	[1.03; 1.27]	12.0%
Sever_1982	52	146173	267	2628305	3.50	[2.60; 4.71]	11.5%
Borman_1986	5	6853	35	35211	0.73	[0.29; 1.87]	7.9%
Forrester_2000B	12	23033	56	126252	1.17	[0.63; 2.19]	9.8%
Canfield_2009	85	269890	345	1004687	0.92	[0.72; 1.16]	11.7%
Petrova_2009	34	28497	178	239383	1.60	[1.11; 2.32]	11.2%
StLouis_2014	435	1415846	2059	6615611	0.99	[0.89; 1.09]	12.0%
Liu_2019	81	209192	436	1633199	1.45	[1.14; 1.84]	11.7%
Random effects model	**2063**	**3719068**	**9468**	**20249692**	**1.30**	**[0.93; 1.82]**	**100.0%**
Prediction interval						**[0.48; 3.53]**	
Heterogeneity: $I^2 = 89\%$ [82%; 94%], $\tau^2 = 0.16$, $p < 0.001$							
Test for effect in subgroup: $t_8 = 1.81$ ($p = 0.109$)							
>35 vs 20 - 30							
Hay_1972	635	834900	3477	5186500	1.13	[1.04; 1.23]	13.0%
Janerich_1972	609	525904	2615	2780544	1.23	[1.13; 1.34]	13.0%
Sever_1982	51	61315	267	2628305	8.19	[6.07; 11.05]	12.4%
Forrester_2000B	20	27944	56	126252	1.61	[0.97; 2.69]	11.3%
Canfield_2009	76	190264	345	1004687	1.16	[0.91; 1.49]	12.6%
Petrova_2009	32	52941	178	239383	0.81	[0.56; 1.18]	12.0%
StLouis_2014	544	1929379	2059	6615611	0.91	[0.82; 1.00]	13.0%
Liu_2019	120	485278	436	1633199	0.93	[0.76; 1.13]	12.7%
Random effects model	**2087**	**4107925**	**9433**	**20214481**	**1.39**	**[0.75; 2.59]**	**100.0%**
Prediction interval						**[0.21; 9.29]**	
Heterogeneity: $I^2 = 97\%$ [95%; 98%], $\tau^2 = 0.53$, $p < 0.001$							
Test for effect in subgroup: $t_7 = 1.26$ ($p = 0.249$)							
30 - 35 vs 20 - 30							
Hay_1972	770	1214100	3477	5186500	0.95	[0.88; 1.02]	12.9%
Janerich_1972	819	869682	2615	2780544	1.00	[0.93; 1.08]	12.9%
Sever_1982	69	109762	267	2628305	6.19	[4.75; 8.06]	12.4%
Forrester_2000B	23	51919	56	126252	1.00	[0.61; 1.62]	11.3%
Canfield_2009	137	362254	345	1004687	1.10	[0.90; 1.34]	12.6%
Petrova_2009	56	113746	178	239383	0.66	[0.49; 0.89]	12.3%
StLouis_2014	870	3145042	2059	6615611	0.89	[0.82; 0.96]	12.9%
Liu_2019	221	1000093	436	1633199	0.83	[0.70; 0.97]	12.7%
Random effects model	**2965**	**6866598**	**9433**	**20214481**	**1.15**	**[0.65; 2.06]**	**100.0%**
Prediction interval						**[0.20; 6.80]**	
Heterogeneity: $I^2 = 97\%$ [95%; 98%], $\tau^2 = 0.47$, $p < 0.001$							
Test for effect in subgroup: $t_7 = 0.58$ ($p = 0.582$)							
>40 vs 20 - 30							
Hay_1972	163	190200	3477	5186500	1.28	[1.09; 1.50]	23.9%
Janerich_1972	134	104213	2615	2780544	1.37	[1.15; 1.63]	23.8%
Sever_1982	11	13696	267	2628305	7.91	[4.33; 14.45]	19.8%
Forrester_2000B	2	4415	56	126252	1.02	[0.25; 4.18]	10.9%
Canfield_2009	20	32324	345	1004687	1.80	[1.15; 2.83]	21.6%
Random effects model	**330**	**344848**	**6760**	**11726288**	**1.96**	**[0.72; 5.31]**	**100.0%**
Prediction interval						**[0.14; 26.88]**	
Heterogeneity: $I^2 = 88\%$ [75%; 94%], $\tau^2 = 0.55$, $p < 0.001$							
Test for effect in subgroup: $t_4 = 1.87$ ($p = 0.134$)							
35 - 40 vs 20 - 30							
Hay_1972	472	644700	3477	5186500	1.09	[0.99; 1.20]	21.0%
Janerich_1972	475	421691	2615	2780544	1.20	[1.09; 1.32]	21.0%
Sever_1982	40	47619	267	2628305	8.27	[5.93; 11.53]	19.8%
Forrester_2000B	18	23529	56	126252	1.72	[1.01; 2.93]	18.0%
Canfield_2009	56	157940	345	1004687	1.03	[0.78; 1.37]	20.2%
Random effects model	**1061**	**1295479**	**6760**	**11726288**	**1.79**	**[0.61; 5.31]**	**100.0%**
Prediction interval						**[0.09; 36.19]**	
Heterogeneity: $I^2 = 97\%$ [95%; 98%], $\tau^2 = 0.74$, $p < 0.001$							
Test for effect in subgroup: $t_4 = 1.50$ ($p = 0.209$)							
Test for subgroup differences: $\chi^2_4 = 2.10$, df = 4 ($p = 0.717$)							



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 43

Forest plot representing the RR with 95% CI of *congenital heart defects* (ICD-10: Q20—Q26) in different age groups compared to the 20 to 30 age group and sorted by year of publication

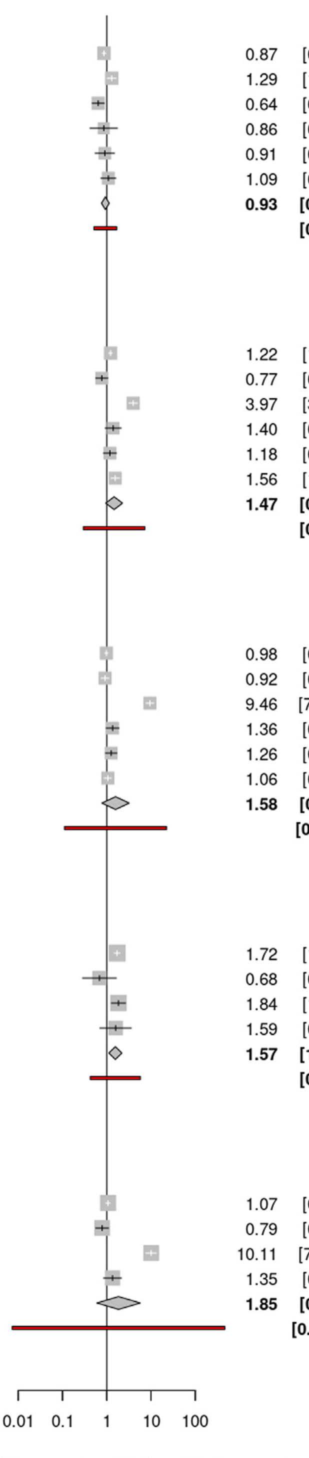


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 44

Forest plot representing the RR with 95% CI of *cleft lip and cleft palate* (ICD-10: Q35—Q37) in different age groups compared to the 20 to 30 age group and sorted by year of publication

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Hay_1972	556	1240100	2680	5186500	0.87	[0.79; 0.95]	18.2%
DeRoo_2003	84	31617	357	173893	1.29	[1.02; 1.64]	17.7%
Materna_2009	42	75121	523	601520	0.64	[0.47; 0.88]	17.3%
Jaikrishan_2012	8	8833	126	119314	0.86	[0.42; 1.75]	14.1%
Pasnicki_2013	17	17670	133	125353	0.91	[0.55; 1.50]	15.9%
Jaruratanasirikul_2016	32	22265	126	95535	1.09	[0.74; 1.61]	16.8%
Random effects model	**739**	**1395606**	**3945**	**6302115**	**0.93**	**[0.76; 1.14]**	**100.0%**
Prediction interval						**[0.52; 1.68]**	
Heterogeneity: I^2 = 67% [20%; 86%], τ^2 = 0.03, p = 0.011							
Test for effect in subgroup: z = -0.69 (p = 0.490)							
>35 vs 20 - 30							
Hay_1972	526	834900	2680	5186500	1.22	[1.11; 1.34]	17.4%
DeRoo_2003	43	27067	357	173893	0.77	[0.56; 1.06]	16.5%
Materna_2009	87	25225	523	601520	3.97	[3.16; 4.98]	17.0%
Pasnicki_2013	26	17498	133	125353	1.40	[0.92; 2.13]	15.8%
Jaruratanasirikul_2016	45	28891	126	95535	1.18	[0.84; 1.66]	16.4%
Luo_2019	100	55368	273	235136	1.56	[1.24; 1.96]	16.9%
Random effects model	**827**	**988949**	**4092**	**6417937**	**1.47**	**[0.95; 2.28]**	**100.0%**
Prediction interval						**[0.30; 7.24]**	
Heterogeneity: I^2 = 95% [92%; 97%], τ^2 = 0.28, p < 0.001							
Test for effect in subgroup: z = 1.71 (p = 0.087)							
30 - 35 vs 20 - 30							
Hay_1972	617	1214100	2680	5186500	0.98	[0.90; 1.07]	17.1%
DeRoo_2003	123	65218	357	173893	0.92	[0.75; 1.13]	16.8%
Materna_2009	117	14223	523	601520	9.46	[7.75; 11.55]	16.8%
Pasnicki_2013	46	31917	133	125353	1.36	[0.97; 1.90]	16.1%
Jaruratanasirikul_2016	66	39702	126	95535	1.26	[0.94; 1.70]	16.3%
Luo_2019	175	142086	273	235136	1.06	[0.88; 1.28]	16.8%
Random effects model	**1144**	**1507246**	**4092**	**6417937**	**1.58**	**[0.77; 3.22]**	**100.0%**
Prediction interval						**[0.11; 22.44]**	
Heterogeneity: I^2 = 99% [98%; 99%], τ^2 = 0.78, p < 0.001							
Test for effect in subgroup: z = 1.26 (p = 0.209)							
>40 vs 20 - 30							
Hay_1972	169	190200	2680	5186500	1.72	[1.47; 2.01]	29.7%
DeRoo_2003	5	3559	357	173893	0.68	[0.28; 1.65]	20.7%
Materna_2009	30	18741	523	601520	1.84	[1.27; 2.66]	27.9%
Pasnicki_2013	6	3556	133	125353	1.59	[0.70; 3.60]	21.7%
Random effects model	**210**	**216056**	**3693**	**6087266**	**1.57**	**[1.11; 2.20]**	**100.0%**
Prediction interval						**[0.43; 5.75]**	
Heterogeneity: I^2 = 30% [0%; 75%], τ^2 = 0.06, p = 0.230							
Test for effect in subgroup: z = 2.58 (p = 0.010)							
35 - 40 vs 20 - 30							
Hay_1972	357	644700	2680	5186500	1.07	[0.96; 1.20]	26.3%
DeRoo_2003	38	23508	357	173893	0.79	[0.56; 1.10]	24.9%
Materna_2009	57	6484	523	601520	10.11	[7.70; 13.27]	25.4%
Pasnicki_2013	20	13942	133	125353	1.35	[0.85; 2.16]	23.5%
Random effects model	**472**	**688634**	**3693**	**6087266**	**1.85**	**[0.59; 5.75]**	**100.0%**
Prediction interval						**[0.01; 465.66]**	
Heterogeneity: I^2 = 99% [98%; 99%], τ^2 = 1.32, p < 0.001							
Test for effect in subgroup: z = 1.06 (p = 0.290)							
Test for subgroup differences: χ^2_4 = 9.94, df = 4 (p = 0.041)							

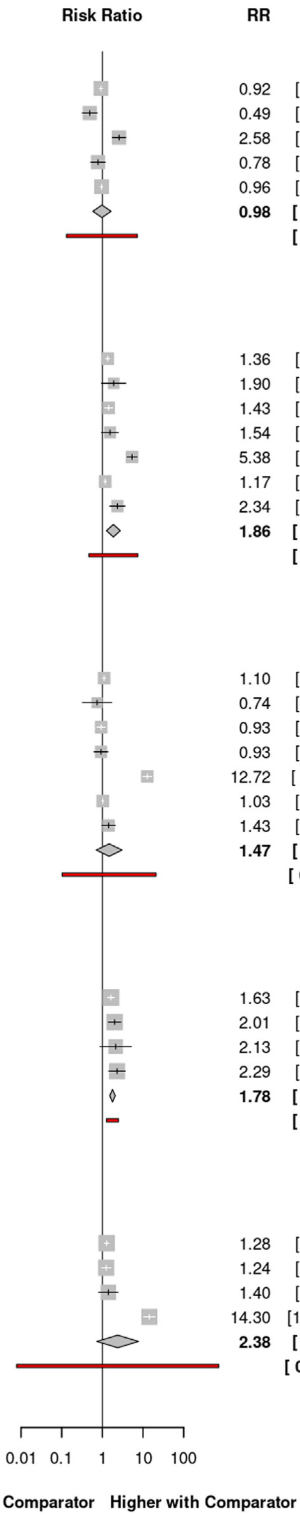


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 45

Forest plot representing the RR with 95% CI of *cleft palate* (ICD-10: Q35) in different age groups compared to the 20 to 30 age group and sorted by year of publication

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Hay_1972	411	1240100	1861	5186500	0.92	[0.83; 1.03]	20.8%
Shields_1981	23	205752	334	1463671	0.49	[0.32; 0.75]	19.3%
Baird_1994	33	34274	145	387862	2.58	[1.77; 3.76]	19.6%
Materna_2009	26	75121	266	601520	0.78	[0.52; 1.17]	19.4%
StLouis_2014	742	1415846	3626	6615611	0.96	[0.88; 1.03]	20.8%
Random effects model	**1235**	**2971093**	**6232**	**14255164**	**0.98**	**[0.58; 1.64]**	**100.0%**
Prediction interval						**[0.13; 7.25]**	
Heterogeneity: $I^2 = 89\%$ [78%; 95%], $\tau^2 = 0.33$, $p < 0.001$							
Test for effect in subgroup: $z = -0.09$ ($p = 0.925$)							
>35 vs 20 - 30							
Hay_1972	406	834900	1861	5186500	1.36	[1.22; 1.51]	15.1%
Beckman_1976	15	8335	18	19008	1.90	[0.96; 3.77]	12.5%
Shields_1981	98	300245	334	1463671	1.43	[1.14; 1.79]	14.8%
Baird_1994	19	32993	145	387862	1.54	[0.96; 2.48]	13.7%
Materna_2009	60	25225	266	601520	5.38	[4.07; 7.12]	14.7%
StLouis_2014	1240	1929379	3626	6615611	1.17	[1.10; 1.25]	15.2%
Luo_2019	32	55368	58	235136	2.34	[1.52; 3.61]	14.0%
Random effects model	**1870**	**3186445**	**6308**	**14509308**	**1.86**	**[1.26; 2.76]**	**100.0%**
Prediction interval						**[0.47; 7.43]**	
Heterogeneity: $I^2 = 95\%$ [92%; 97%], $\tau^2 = 0.25$, $p < 0.001$							
Test for effect in subgroup: $z = 3.10$ ($p = 0.002$)							
30 - 35 vs 20 - 30							
Hay_1972	481	1214100	1861	5186500	1.10	[1.00; 1.22]	15.1%
Beckman_1976	8	11388	18	19008	0.74	[0.32; 1.71]	11.5%
Shields_1981	93	436986	334	1463671	0.93	[0.74; 1.17]	14.9%
Baird_1994	30	86632	145	387862	0.93	[0.63; 1.37]	14.2%
Materna_2009	80	14223	266	601520	12.72	[9.91; 16.32]	14.8%
StLouis_2014	1770	3145042	3626	6615611	1.03	[0.97; 1.09]	15.2%
Luo_2019	50	142086	58	235136	1.43	[0.98; 2.08]	14.3%
Random effects model	**2512**	**5050457**	**6308**	**14509308**	**1.47**	**[0.71; 3.04]**	**100.0%**
Prediction interval						**[0.10; 20.94]**	
Heterogeneity: $I^2 = 98\%$ [98%; 99%], $\tau^2 = 0.93$, $p < 0.001$							
Test for effect in subgroup: $z = 1.03$ ($p = 0.304$)							
>40 vs 20 - 30							
Hay_1972	111	190200	1861	5186500	1.63	[1.34; 1.97]	27.5%
Shields_1981	34	74260	334	1463671	2.01	[1.41; 2.86]	26.5%
Baird_1994	5	6288	145	387862	2.13	[0.87; 5.19]	20.5%
Materna_2009	19	18741	266	601520	2.29	[1.44; 3.65]	25.5%
Random effects model	**169**	**289489**	**2606**	**7639553**	**1.78**	**[1.52; 2.07]**	**100.0%**
Prediction interval						**[1.26; 2.50]**	
Heterogeneity: $I^2 = 0\%$ [0%; 85%], $\tau^2 = 0$, $p = 0.460$							
Test for effect in subgroup: $z = 7.22$ ($p < 0.001$)							
35 - 40 vs 20 - 30							
Hay_1972	295	644700	1861	5186500	1.28	[1.13; 1.44]	26.2%
Shields_1981	64	225985	334	1463671	1.24	[0.95; 1.62]	25.5%
Baird_1994	14	26705	145	387862	1.40	[0.81; 2.43]	23.2%
Materna_2009	41	6484	266	601520	14.30	[10.30; 19.85]	25.1%
Random effects model	**414**	**903874**	**2606**	**7639553**	**2.38**	**[0.73; 7.70]**	**100.0%**
Prediction interval						**[0.01; 725.04]**	
Heterogeneity: $I^2 = 98\%$ [97%; 99%], $\tau^2 = 1.41$, $p < 0.001$							
Test for effect in subgroup: $z = 1.44$ ($p = 0.149$)							
Test for subgroup differences: $\chi^2_4 = 5.36$, df = 4 ($p = 0.253$)							

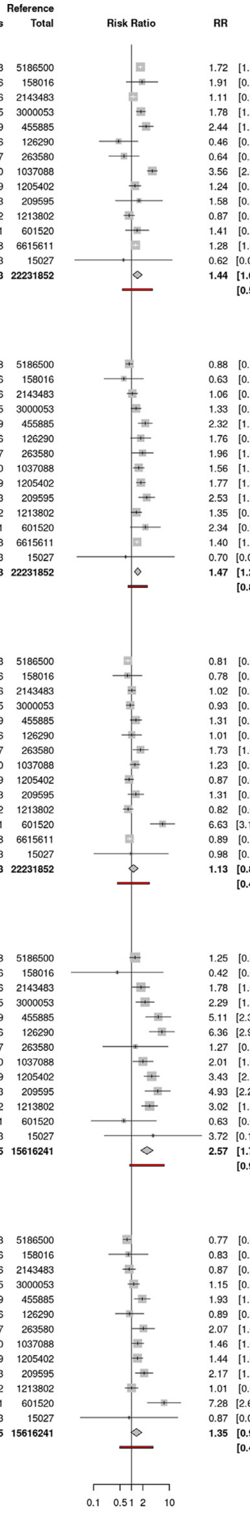


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 46

Forest plot representing the RR with 95% CI of *omphalocele* (ICD-10: Q79.2) in different age groups compared to the 20 to 30 age group and sorted by year of publication

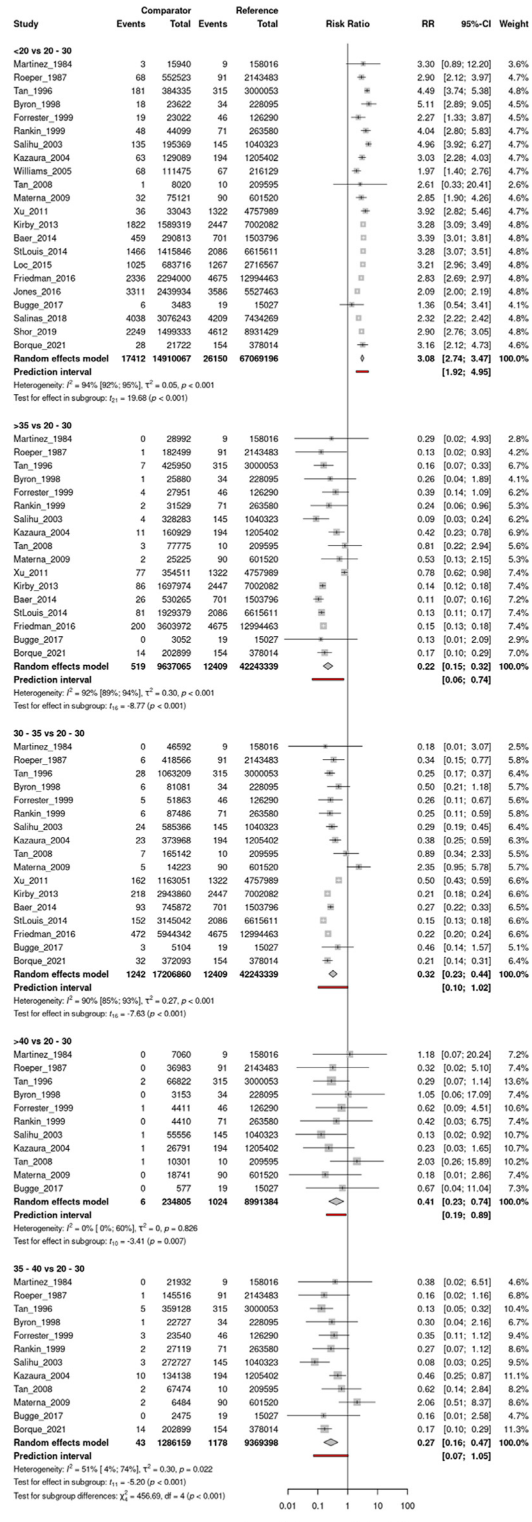
Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Hay_1972	325	1240100	788	5186500	1.72	[1.52; 1.96]	10.3%
Martinez_1984	5	15940	26	158016	1.91	[0.73; 4.96]	4.8%
Roeper_1987	131	552523	456	2143483	1.11	[0.92; 1.35]	10.1%
Tan_1996	58	384335	255	3000053	1.78	[1.34; 2.36]	9.5%
Byron_1998	25	47215	99	455885	2.44	[1.57; 3.78]	8.5%
Forrester_1999	3	23022	36	126290	0.46	[0.14; 1.48]	3.8%
Rankin_1999	5	44099	47	263580	0.64	[0.25; 1.60]	5.0%
Salihu_2003	67	195335	100	1037088	3.56	[2.61; 4.85]	9.4%
Kazaura_2004	33	129089	249	1205402	1.24	[0.86; 1.78]	9.0%
Tan_2008	2	8020	33	209595	1.58	[0.38; 6.60]	2.9%
Agopian_2009	42	322274	182	1213802	0.87	[0.62; 1.22]	9.2%
Materna_2009	9	75121	51	601520	1.41	[0.70; 2.87]	6.4%
StLouis_2014	175	1415846	638	6615611	1.28	[1.08; 1.51]	10.2%
Bugge_2017	0	3483	3	15027	0.62	[0.03; 11.93]	0.9%
Random effects model	**880**	**4456402**	**2963**	**22231852**	**1.44**	**[1.08; 1.92]**	**100.0%**
Prediction interval						**[0.58; 3.60]**	
Heterogeneity: $I^2 = 82\%$ [71%; 89%], $\tau^2 = 0.16$, $p < 0.001$							
Test for effect in subgroup: $t_{13} = 2.77$ ($p = 0.016$)							
>35 vs 20 - 30							
Hay_1972	111	834900	788	5186500	0.88	[0.72; 1.07]	9.4%
Martinez_1984	3	28992	26	158016	0.63	[0.19; 2.08]	3.5%
Roeper_1987	41	182499	456	2143483	1.06	[0.77; 1.45]	8.7%
Tan_1996	48	425950	255	3000053	1.33	[0.97; 1.80]	8.8%
Byron_1998	26	51653	99	455885	2.32	[1.51; 3.57]	7.9%
Forrester_1999	14	27951	36	126290	1.76	[0.95; 3.26]	6.6%
Rankin_1999	11	31529	47	263580	1.96	[1.01; 3.77]	6.3%
Salihu_2003	50	333297	100	1037088	1.56	[1.11; 2.18]	8.6%
Kazaura_2004	59	160929	249	1205402	1.77	[1.34; 2.36]	8.9%
Tan_2008	31	77775	33	209595	2.53	[1.55; 4.13]	7.5%
Agopian_2009	47	231666	182	1213802	1.35	[0.98; 1.86]	8.7%
Materna_2009	5	25225	51	601520	2.34	[0.93; 5.86]	4.7%
StLouis_2014	261	1929379	638	6615611	1.40	[1.21; 1.62]	9.6%
Bugge_2017	0	3052	3	15027	0.70	[0.04; 13.61]	0.8%
Random effects model	**707**	**4344797**	**2963**	**22231852**	**1.47**	**[1.20; 1.79]**	**100.0%**
Prediction interval						**[0.82; 2.64]**	
Heterogeneity: $I^2 = 69\%$ [47%; 82%], $\tau^2 = 0.06$, $p < 0.001$							
Test for effect in subgroup: $t_{13} = 4.18$ ($p = 0.001$)							
30 - 35 vs 20 - 30							
Hay_1972	149	1214100	788	5186500	0.81	[0.68; 0.96]	8.9%
Martinez_1984	6	46592	26	158016	0.78	[0.32; 1.90]	4.6%
Roeper_1987	91	418566	456	2143483	1.02	[0.82; 1.28]	8.7%
Tan_1996	84	1063209	255	3000053	0.93	[0.73; 1.19]	8.6%
Byron_1998	46	161414	99	455885	1.31	[0.93; 1.86]	8.0%
Forrester_1999	15	51863	36	126290	1.01	[0.56; 1.85]	6.3%
Rankin_1999	27	87486	47	263580	1.73	[1.08; 2.78]	7.2%
Salihu_2003	70	588235	100	1037088	1.23	[0.91; 1.67]	8.3%
Kazaura_2004	67	373968	249	1205402	0.87	[0.66; 1.14]	8.5%
Tan_2008	34	165142	33	209595	1.31	[0.81; 2.11]	7.1%
Agopian_2009	54	440737	182	1213802	0.82	[0.60; 1.11]	8.3%
Materna_2009	8	14223	51	601520	6.63	[3.15; 13.98]	5.4%
StLouis_2014	269	3145042	638	6615611	0.89	[0.77; 1.02]	9.0%
Bugge_2017	1	5104	3	15027	0.98	[0.10; 9.43]	1.2%
Random effects model	**921**	**7775681**	**2963**	**22231852**	**1.13**	**[0.85; 1.50]**	**100.0%**
Prediction interval						**[0.43; 2.99]**	
Heterogeneity: $I^2 = 72\%$ [52%; 84%], $\tau^2 = 0.18$, $p < 0.001$							
Test for effect in subgroup: $t_{13} = 0.94$ ($p = 0.365$)							
>40 vs 20 - 30							
Hay_1972	36	190200	788	5186500	1.25	[0.89; 1.74]	13.0%
Martinez_1984	0	7060	26	158016	0.42	[0.03; 6.93]	1.3%
Roeper_1987	14	36983	456	2143483	1.78	[1.05; 3.03]	10.9%
Tan_1996	13	66822	255	3000053	2.29	[1.31; 4.00]	10.6%
Byron_1998	7	6307	99	455885	5.11	[2.38; 11.00]	8.4%
Forrester_1999	8	4411	36	126290	6.36	[2.96; 13.68]	8.5%
Rankin_1999	1	4410	47	263580	1.27	[0.18; 9.21]	2.5%
Salihu_2003	11	56701	100	1037088	2.01	[1.08; 3.75]	9.9%
Kazaura_2004	19	26791	249	1205402	3.43	[2.15; 5.47]	11.6%
Tan_2008	8	10301	33	209595	4.93	[2.28; 10.68]	8.4%
Agopian_2009	18	39751	182	1213802	3.02	[1.86; 4.90]	11.4%
Materna_2009	1	18741	51	601520	0.63	[0.09; 4.55]	2.5%
Bugge_2017	0	577	3	15027	3.72	[0.19; 71.88]	1.2%
Random effects model	**136**	**469055**	**2325**	**15616241**	**2.57**	**[1.77; 3.73]**	**100.0%**
Prediction interval						**[0.90; 7.30]**	
Heterogeneity: $I^2 = 67\%$ [41%; 82%], $\tau^2 = 0.20$, $p < 0.001$							
Test for effect in subgroup: $t_{12} = 5.51$ ($p < 0.001$)							
35 - 40 vs 20 - 30							
Hay_1972	75	644700	788	5186500	0.77	[0.60; 0.97]	10.7%
Martinez_1984	3	21932	26	158016	0.83	[0.25; 2.75]	4.1%
Roeper_1987	27	145516	456	2143483	0.87	[0.59; 1.29]	9.6%
Tan_1996	35	359128	255	3000053	1.15	[0.81; 1.63]	9.9%
Byron_1998	19	45346	99	455885	1.93	[1.18; 3.15]	8.8%
Forrester_1999	6	23540	36	126290	0.89	[0.38; 2.12]	5.9%
Rankin_1999	10	27119	47	263580	2.07	[1.05; 4.09]	7.2%
Salihu_2003	39	276596	100	1037088	1.46	[1.01; 2.12]	9.8%
Kazaura_2004	40	134138	249	1205402	1.44	[1.03; 2.02]	10.1%
Tan_2008	23	67474	33	209595	2.17	[1.27; 3.69]	8.4%
Agopian_2009	29	191915	182	1213802	1.01	[0.68; 1.49]	9.6%
Materna_2009	4	6484	51	601520	7.28	[2.63; 20.13]	4.9%
Bugge_2017	0	2475	3	15027	0.87	[0.04; 16.78]	0.9%
Random effects model	**310**	**1946363**	**2325**	**15616241**	**1.35**	**[0.98; 1.87]**	**100.0%**
Prediction interval						**[0.49; 3.73]**	
Heterogeneity: $I^2 = 72\%$ [51%; 84%], $\tau^2 = 0.19$, $p < 0.001$							
Test for effect in subgroup: $t_{12} = 2.03$ ($p = 0.065$)							
Test for subgroup differences: $\chi^2_4 = 14.97$, df = 4 ($p = 0.005$)							



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 47

Forest plot representing the RR with 95% CI of *gastroschisis* (ICD-10: Q79.3) in different age groups compared to the 20 to 30 age group and sorted by year of publication

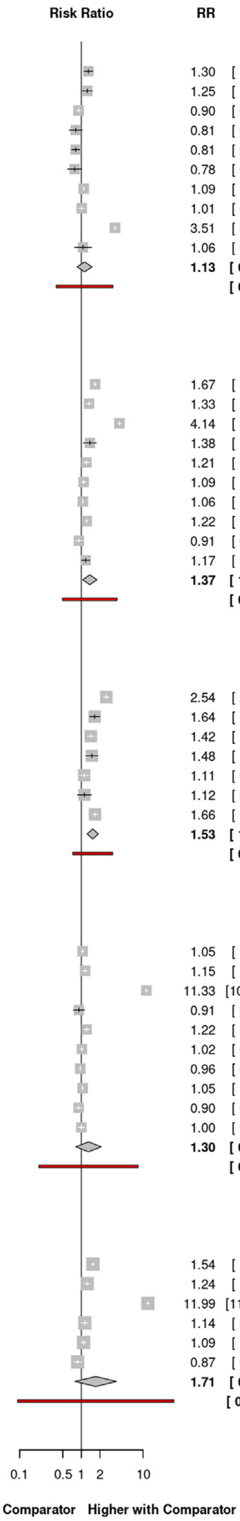


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 48

Forest plot representing the RR with 95% CI of *all nonchromosomal anomalies* (ICD-10: Q00—Q89) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Tan_2005	149	5409	3176	150151	1.30	[1.11; 1.53]	10.0%
Nazer_2007	115	1227	788	10481	1.25	[1.03; 1.50]	10.0%
Materna_2009	628	75121	5588	601520	0.90	[0.83; 0.98]	10.2%
Jaikrishan_2012	67	8833	1116	119314	0.81	[0.63; 1.04]	9.8%
Pasnicki_2013	199	17670	1739	125353	0.81	[0.70; 0.94]	10.1%
Sarkar_2013	83	4409	174	7178	0.78	[0.60; 1.01]	9.8%
StLouis_2014	16174	1415846	69100	6615611	1.09	[1.08; 1.11]	10.2%
Xie_2016	256	13535	12677	677622	1.01	[0.89; 1.14]	10.1%
Parkes_2020	2753	18830	4557	109460	3.51	[3.36; 3.67]	10.2%
Zhou_2020	39	5218	1108	157759	1.06	[0.77; 1.46]	9.5%
Random effects model	**20463**	**1566098**	**100023**	**8574449**	**1.13**	**[0.85; 1.49]**	**100.0%**
Prediction interval						**[0.39; 3.24]**	
Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.19, p = 0							
Test for effect in subgroup: z = 0.84 (p = 0.399)							
>35 vs 20 - 30							
Tan_2005	1935	54784	3176	150151	1.67	[1.58; 1.77]	10.1%
Nazer_2007	389	3893	788	10481	1.33	[1.18; 1.49]	10.0%
Materna_2009	970	25225	5588	601520	4.14	[3.87; 4.43]	10.1%
Zhang_2012	80	4009	306	21098	1.38	[1.08; 1.76]	9.7%
Pasnicki_2013	293	17498	1739	125353	1.21	[1.07; 1.36]	10.0%
Rider_2013	807	43061	2831	164711	1.09	[1.01; 1.18]	10.1%
StLouis_2014	21341	1929379	69100	6615611	1.06	[1.04; 1.08]	10.1%
Xie_2016	1568	68681	12677	677622	1.22	[1.16; 1.29]	10.1%
Mucat_2019	295	8163	1201	30231	0.91	[0.80; 1.03]	10.0%
Zhou_2020	189	22970	1108	157759	1.17	[1.00; 1.37]	9.9%
Random effects model	**27867**	**2177663**	**98514**	**8554537**	**1.37**	**[1.05; 1.78]**	**100.0%**
Prediction interval						**[0.50; 3.79]**	
Heterogeneity: I^2 = 99% [99%; 100%], τ^2 = 0.18, p = 0							
Test for effect in subgroup: z = 2.34 (p = 0.019)							
>40 vs 20 - 30							
Tan_2005	386	7195	3176	150151	2.54	[2.29; 2.81]	14.5%
Nazer_2007	103	834	788	10481	1.64	[1.35; 1.99]	14.2%
Materna_2009	248	18741	5588	601520	1.42	[1.26; 1.62]	14.4%
Pasnicki_2013	73	3556	1739	125353	1.48	[1.17; 1.87]	14.1%
Rider_2013	138	7220	2831	164711	1.11	[0.94; 1.32]	14.3%
Mucat_2019	59	1325	1201	30231	1.12	[0.87; 1.45]	13.9%
Parkes_2020	454	6552	4557	109460	1.66	[1.52; 1.83]	14.5%
Random effects model	**1461**	**45423**	**19880**	**1191907**	**1.53**	**[1.24; 1.89]**	**100.0%**
Prediction interval						**[0.73; 3.22]**	
Heterogeneity: I^2 = 94% [90%; 96%], τ^2 = 0.07, p < 0.001							
Test for effect in subgroup: z = 3.97 (p < 0.001)							
30 - 35 vs 20 - 30							
Tan_2005	2610	117733	3176	150151	1.05	[1.00; 1.10]	10.1%
Nazer_2007	475	5482	788	10481	1.15	[1.03; 1.29]	10.0%
Materna_2009	1497	14223	5588	601520	11.33	[10.73; 11.97]	10.0%
Zhang_2012	128	9658	306	21098	0.91	[0.74; 1.12]	9.8%
Pasnicki_2013	538	31917	1739	125353	1.22	[1.10; 1.34]	10.0%
Rider_2013	1682	96088	2831	164711	1.02	[0.96; 1.08]	10.0%
StLouis_2014	31473	3145042	69100	6615611	0.96	[0.95; 0.97]	10.1%
Xie_2016	3253	165575	12677	677622	1.05	[1.01; 1.09]	10.1%
Mucat_2019	629	17549	1201	30231	0.90	[0.82; 0.99]	10.0%
Zhou_2020	371	52765	1108	157759	1.00	[0.89; 1.13]	10.0%
Random effects model	**42656**	**3656032**	**98514**	**8554537**	**1.30**	**[0.81; 2.10]**	**100.0%**
Prediction interval						**[0.20; 8.30]**	
Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.59, p = 0							
Test for effect in subgroup: z = 1.09 (p = 0.274)							
35 - 40 vs 20 - 30							
Tan_2005	1549	47589	3176	150151	1.54	[1.45; 1.63]	16.8%
Nazer_2007	286	3059	788	10481	1.24	[1.09; 1.42]	16.6%
Materna_2009	722	6484	5588	601520	11.99	[11.14; 12.90]	16.7%
Pasnicki_2013	220	13942	1739	125353	1.14	[0.99; 1.31]	16.6%
Rider_2013	669	35841	2831	164711	1.09	[1.00; 1.18]	16.7%
Mucat_2019	236	6838	1201	30231	0.87	[0.76; 1.00]	16.6%
Random effects model	**3682**	**113753**	**15323**	**1082447**	**1.71**	**[0.78; 3.72]**	**100.0%**
Prediction interval						**[0.09; 31.53]**	
Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.95, p = 0							
Test for effect in subgroup: z = 1.35 (p = 0.179)							
Test for subgroup differences: χ^2_4 = 3.32, df = 4 (p = 0.506)							

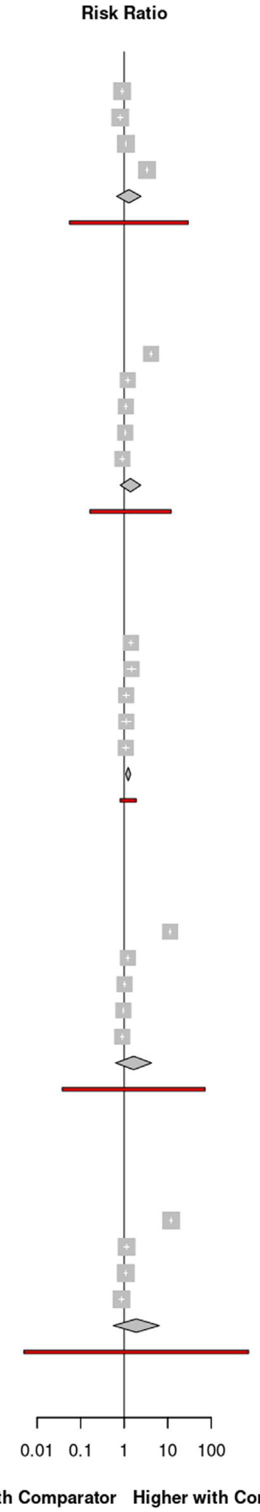


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 49

Forest plot representing the RR with 95% CI of *all nonchromosomal anomalies (only studies excluding concomitant chromosomal anomalies)* (ICD-10: Q00−Q89) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Materna_2009	628	75121	5588	601520	0.90	[0.83; 0.98]	25.0%
Pasnicki_2013	199	17670	1739	125353	0.81	[0.70; 0.94]	24.9%
StLouis_2014	16174	1415846	69100	6615611	1.09	[1.08; 1.11]	25.1%
Parkes_2020	1231	18830	2136	109460	3.35	[3.13; 3.59]	25.0%
Random effects model	**18232**	**1527467**	**78563**	**7451944**	**1.28**	**[0.67; 2.43]**	**100.0%**
Prediction interval						**[0.06; 29.56]**	
Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.43, p < 0.001							
Test for effect in subgroup: z = 0.76 (p = 0.449)							
>35 vs 20 - 30							
Materna_2009	970	25225	5588	601520	4.14	[3.87; 4.43]	20.0%
Pasnicki_2013	293	17498	1739	125353	1.21	[1.07; 1.36]	19.9%
Rider_2013	807	43061	2831	164711	1.09	[1.01; 1.18]	20.0%
StLouis_2014	21341	1929379	69100	6615611	1.06	[1.04; 1.08]	20.1%
Mucat_2019	295	8163	1201	30231	0.91	[0.80; 1.03]	19.9%
Random effects model	**23706**	**2023326**	**80459**	**7537426**	**1.39**	**[0.81; 2.40]**	**100.0%**
Prediction interval						**[0.16; 11.95]**	
Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 0.38, p = 0							
Test for effect in subgroup: z = 1.20 (p = 0.229)							
>40 vs 20 - 30							
Materna_2009	248	18741	5588	601520	1.42	[1.26; 1.62]	20.2%
Pasnicki_2013	73	3556	1739	125353	1.48	[1.17; 1.87]	19.9%
Rider_2013	138	7220	2831	164711	1.11	[0.94; 1.32]	20.1%
Mucat_2019	59	1325	1201	30231	1.12	[0.87; 1.45]	19.8%
Parkes_2020	139	6552	2136	109460	1.09	[0.92; 1.29]	20.1%
Random effects model	**657**	**37394**	**13495**	**1031275**	**1.24**	**[1.09; 1.41]**	**100.0%**
Prediction interval						**[0.81; 1.89]**	
Heterogeneity: I^2 = 64% [7%; 86%], τ^2 = 0.01, p = 0.024							
Test for effect in subgroup: z = 3.19 (p = 0.001)							
30 - 35 vs 20 - 30							
Materna_2009	1497	14223	5588	601520	11.33	[10.73; 11.97]	20.0%
Pasnicki_2013	538	31917	1739	125353	1.22	[1.10; 1.34]	20.0%
Rider_2013	1682	96088	2831	164711	1.02	[0.96; 1.08]	20.0%
StLouis_2014	31473	3145042	69100	6615611	0.96	[0.95; 0.97]	20.0%
Mucat_2019	629	17549	1201	30231	0.90	[0.82; 0.99]	20.0%
Random effects model	**35819**	**3304819**	**80459**	**7537426**	**1.65**	**[0.64; 4.26]**	**100.0%**
Prediction interval						**[0.04; 71.98]**	
Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 1.17, p = 0							
Test for effect in subgroup: z = 1.03 (p = 0.303)							
35 - 40 vs 20 - 30							
Materna_2009	722	6484	5588	601520	11.99	[11.14; 12.90]	25.1%
Pasnicki_2013	220	13942	1739	125353	1.14	[0.99; 1.31]	24.9%
Rider_2013	669	35841	2831	164711	1.09	[1.00; 1.18]	25.1%
Mucat_2019	236	6838	1201	30231	0.87	[0.76; 1.00]	24.9%
Random effects model	**1847**	**63105**	**11359**	**921815**	**1.90**	**[0.56; 6.37]**	**100.0%**
Prediction interval						**[0.00; 721.32]**	
Heterogeneity: I^2 = 100% [100%; 100%], τ^2 = 1.52, p = 0							
Test for effect in subgroup: z = 1.03 (p = 0.301)							
Test for subgroup differences: χ^2_4 = 0.95, df = 4 (p = 0.917)							

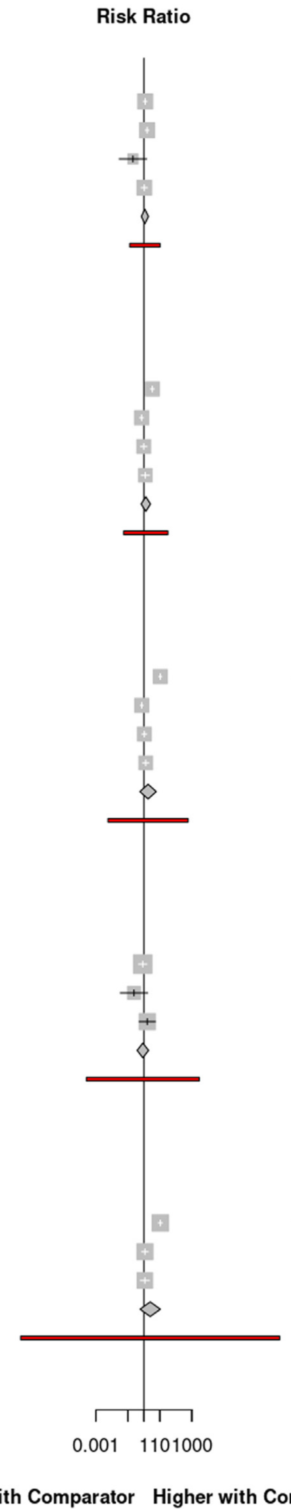


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 50

Forest plot representing the RR with 95% CI of *congenital anomalies of the nervous system* (ICD-10: Q00—Q07) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Materna_2009	63	75121	415	601520	1.22	[0.93; 1.58]	29.4%
Petrova_2009	68	28497	357	239383	1.60	[1.23; 2.07]	29.4%
Jaikrishan_2012	1	8833	65	119314	0.21	[0.03; 1.50]	13.0%
Pasnicki_2013	22	17670	146	125353	1.07	[0.68; 1.67]	28.2%
Random effects model	**154**	**130121**	**983**	**1085570**	**1.16**	**[0.70; 1.94]**	**100.0%**
Prediction interval						**[0.13; 10.24]**	
Heterogeneity: $I^2 = 55\%$ [0%; 85%], $\tau^2 = 0.19$, $p = 0.082$							
Test for effect in subgroup: $z = 0.58$ ($p = 0.565$)							
>35 vs 20 - 30							
Materna_2009	59	25225	415	601520	3.39	[2.58; 4.45]	25.9%
Petrova_2009	57	52941	357	239383	0.72	[0.55; 0.95]	25.8%
Pasnicki_2013	20	17498	146	125353	0.98	[0.62; 1.57]	24.7%
Mucat_2019	14	8163	42	30231	1.23	[0.67; 2.26]	23.6%
Random effects model	**150**	**103827**	**960**	**996487**	**1.32**	**[0.67; 2.60]**	**100.0%**
Prediction interval						**[0.06; 31.70]**	
Heterogeneity: $I^2 = 95\%$ [91%; 98%], $\tau^2 = 0.43$, $p < 0.001$							
Test for effect in subgroup: $z = 0.82$ ($p = 0.415$)							
30 - 35 vs 20 - 30							
Materna_2009	105	14223	415	601520	10.70	[8.64; 13.25]	25.5%
Petrova_2009	125	113746	357	239383	0.74	[0.60; 0.90]	25.5%
Pasnicki_2013	40	31917	146	125353	1.08	[0.76; 1.53]	24.9%
Mucat_2019	32	17549	42	30231	1.31	[0.83; 2.08]	24.2%
Random effects model	**302**	**177435**	**960**	**996487**	**1.83**	**[0.56; 5.99]**	**100.0%**
Prediction interval						**[0.01; 586.65]**	
Heterogeneity: $I^2 = 99\%$ [99%; 99%], $\tau^2 = 1.43$, $p < 0.001$							
Test for effect in subgroup: $z = 1.00$ ($p = 0.315$)							
>40 vs 20 - 30							
Materna_2009	11	18741	415	601520	0.85	[0.47; 1.55]	44.3%
Pasnicki_2013	1	3556	146	125353	0.24	[0.03; 1.73]	21.6%
Mucat_2019	3	1325	42	30231	1.63	[0.51; 5.25]	34.0%
Random effects model	**15**	**23622**	**603**	**757104**	**0.86**	**[0.38; 1.98]**	**100.0%**
Prediction interval						**[0.00; 2940.14]**	
Heterogeneity: $I^2 = 27\%$ [0%; 92%], $\tau^2 = 0.23$, $p = 0.254$							
Test for effect in subgroup: $z = -0.34$ ($p = 0.730$)							
35 - 40 vs 20 - 30							
Materna_2009	48	6484	415	601520	10.73	[7.97; 14.45]	35.0%
Pasnicki_2013	19	13942	146	125353	1.17	[0.73; 1.89]	33.5%
Mucat_2019	11	6838	42	30231	1.16	[0.60; 2.25]	31.4%
Random effects model	**78**	**27264**	**603**	**757104**	**2.49**	**[0.58; 10.71]**	**100.0%**
Prediction interval						**[0.00; 314094609.14]**	
Heterogeneity: $I^2 = 97\%$ [95%; 99%], $\tau^2 = 1.60$, $p < 0.001$							
Test for effect in subgroup: $z = 1.22$ ($p = 0.221$)							
Test for subgroup differences: $\chi^2_4 = 2.12$, df = 4 ($p = 0.714$)							

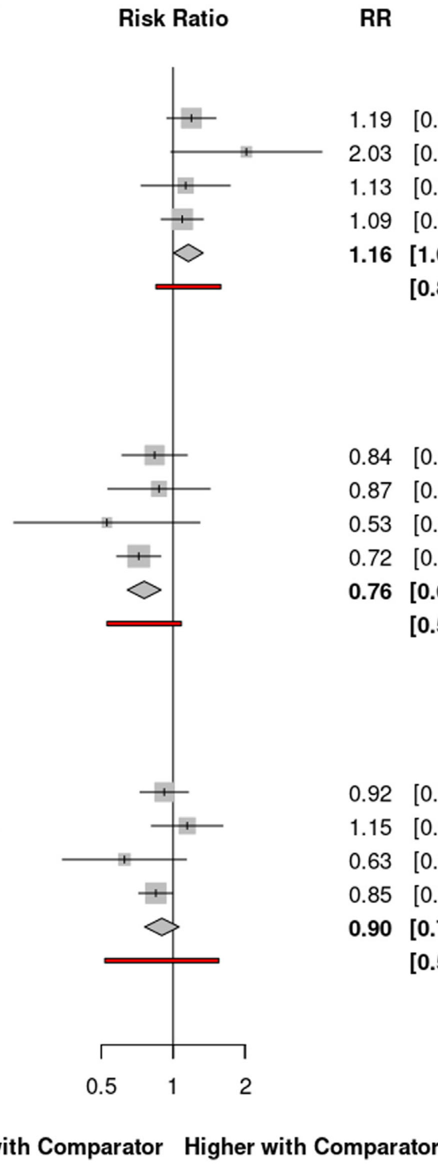


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 51

Forest plot representing the RR with 95% CI of *anencephaly* (ICD-10: Q00.0) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Canfield_2009	91	269890	284	1004687	1.19	[0.94; 1.51]	33.9%
Petrova_2009_Norway	8	7640	75	145219	2.03	[0.98; 4.20]	9.5%
Petrova_2009_Russia	26	20857	104	94164	1.13	[0.73; 1.73]	19.9%
StLouis_2014	115	1415846	492	6615611	1.09	[0.89; 1.34]	36.7%
Random effects model	**240**	**1714233**	**955**	**7859681**	**1.16**	**[1.01; 1.34]**	**100.0%**
Prediction interval						**[0.85; 1.58]**	
Heterogeneity: $I^2 = 0\%$ [0%; 85%], $\tau^2 = 0$, $p = 0.446$							
Test for effect in subgroup: $z = 2.03$ ($p = 0.042$)							
>35 vs 20 - 30							
Canfield_2009	45	190264	284	1004687	0.84	[0.61; 1.15]	31.6%
Petrova_2009_Norway	20	44366	75	145219	0.87	[0.53; 1.43]	19.3%
Petrova_2009_Russia	5	8575	104	94164	0.53	[0.22; 1.29]	7.7%
StLouis_2014	103	1929379	492	6615611	0.72	[0.58; 0.89]	41.4%
Random effects model	**173**	**2172584**	**955**	**7859681**	**0.76**	**[0.64; 0.89]**	**100.0%**
Prediction interval						**[0.53; 1.08]**	
Heterogeneity: $I^2 = 0\%$ [0%; 85%], $\tau^2 = 0$, $p = 0.666$							
Test for effect in subgroup: $z = -3.36$ ($p < 0.001$)							
30 - 35 vs 20 - 30							
Canfield_2009	94	362254	284	1004687	0.92	[0.73; 1.16]	30.4%
Petrova_2009_Norway	57	96370	75	145219	1.15	[0.81; 1.62]	22.5%
Petrova_2009_Russia	12	17376	104	94164	0.63	[0.34; 1.14]	11.5%
StLouis_2014	198	3145042	492	6615611	0.85	[0.72; 1.00]	35.7%
Random effects model	**361**	**3621042**	**955**	**7859681**	**0.90**	**[0.76; 1.06]**	**100.0%**
Prediction interval						**[0.52; 1.55]**	
Heterogeneity: $I^2 = 22\%$ [0%; 88%], $\tau^2 = < 0.01$, $p = 0.281$							
Test for effect in subgroup: $z = -1.28$ ($p = 0.199$)							
Test for subgroup differences: $\chi^2_2 = 15.44$, df = 2 ($p < 0.001$)							

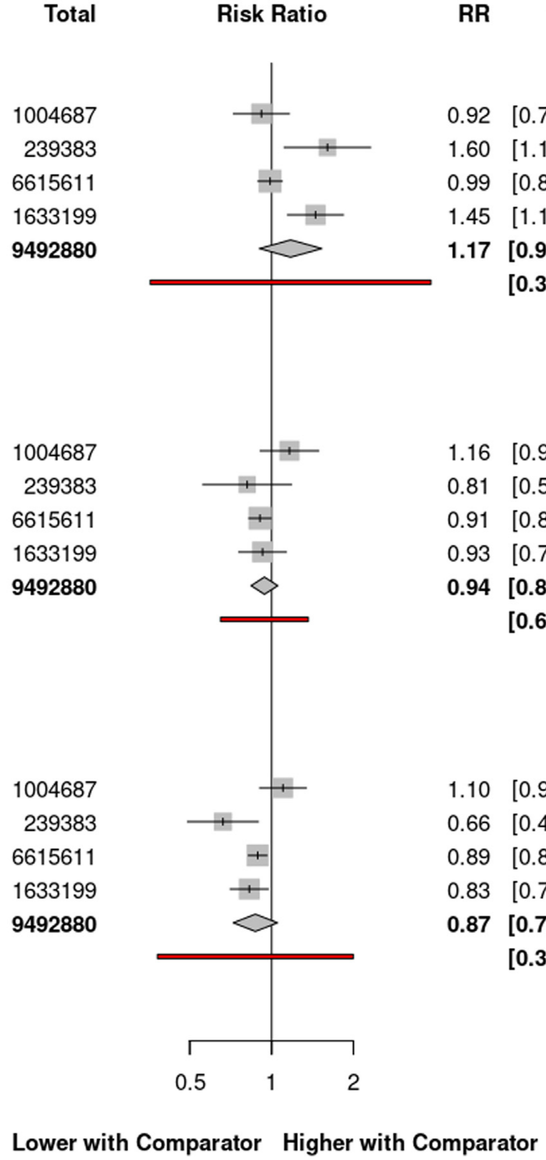


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 52

Forest plot representing the RR with 95% CI of *spina bifida* (ICD-10: Q05) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Canfield_2009	85	269890	345	1004687	0.92	[0.72; 1.16]	24.9%
Petrova_2009	34	28497	178	239383	1.60	[1.11; 2.32]	18.1%
StLouis_2014	435	1415846	2059	6615611	0.99	[0.89; 1.09]	32.0%
Liu_2019	81	209192	436	1633199	1.45	[1.14; 1.84]	25.0%
Random effects model	**635**	**1923425**	**3018**	**9492880**	**1.17**	**[0.90; 1.53]**	**100.0%**
Prediction interval						**[0.36; 3.85]**	
Heterogeneity: $I^2 = 80\%$ [47%; 92%], $\tau^2 = 0.06$, $p = 0.002$							
Test for effect in subgroup: $z = 1.19$ ($p = 0.234$)							
>35 vs 20 - 30							
Canfield_2009	76	190264	345	1004687	1.16	[0.91; 1.49]	24.0%
Petrova_2009	32	52941	178	239383	0.81	[0.56; 1.18]	17.4%
StLouis_2014	544	1929379	2059	6615611	0.91	[0.82; 1.00]	31.9%
Liu_2019	120	485278	436	1633199	0.93	[0.76; 1.13]	26.6%
Random effects model	**772**	**2657862**	**3018**	**9492880**	**0.94**	**[0.84; 1.05]**	**100.0%**
Prediction interval						**[0.65; 1.36]**	
Heterogeneity: $I^2 = 23\%$ [0%; 88%], $\tau^2 = < 0.01$, $p = 0.272$							
Test for effect in subgroup: $z = -1.05$ ($p = 0.292$)							
30 - 35 vs 20 - 30							
Canfield_2009	137	362254	345	1004687	1.10	[0.90; 1.34]	24.6%
Petrova_2009	56	113746	178	239383	0.66	[0.49; 0.89]	19.4%
StLouis_2014	870	3145042	2059	6615611	0.89	[0.82; 0.96]	29.7%
Liu_2019	221	1000093	436	1633199	0.83	[0.70; 0.97]	26.4%
Random effects model	**1284**	**4621135**	**3018**	**9492880**	**0.87**	**[0.72; 1.05]**	**100.0%**
Prediction interval						**[0.38; 2.00]**	
Heterogeneity: $I^2 = 66\%$ [2%; 89%], $\tau^2 = 0.03$, $p = 0.030$							
Test for effect in subgroup: $z = -1.43$ ($p = 0.151$)							
Test for subgroup differences: $\chi^2_2 = 3.30$, df = 2 ($p = 0.192$)							

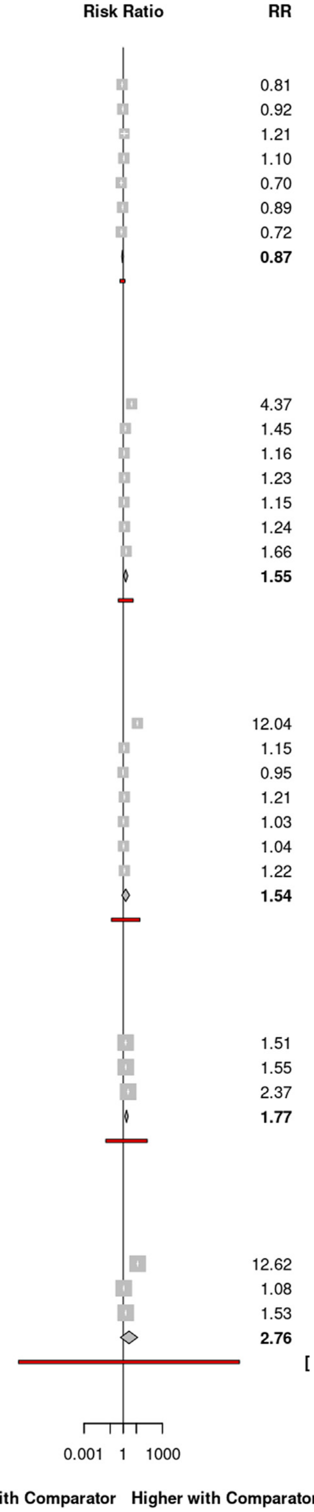


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 53

Forest plot representing the RR with 95% CI of *congenital heart defects* (ICD-10: Q20−Q26) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Materna_2009	280	75121	2764	601520	0.81	[0.72; 0.92]	14.6%
Miller_2011	613	175645	2697	708470	0.92	[0.84; 1.00]	14.7%
Jaikrishan_2012	12	8833	134	119314	1.21	[0.67; 2.18]	12.5%
Liu_2013	1178	107091	10319	1036502	1.10	[1.04; 1.17]	14.7%
Donghua_2018	75	12077	4291	482922	0.70	[0.56; 0.88]	14.3%
Purkey_2019	456	213632	2887	1198936	0.89	[0.80; 0.98]	14.6%
Hansen_2021	226	31831	2649	267349	0.72	[0.63; 0.82]	14.6%
Random effects model	**2840**	**624230**	**25741**	**4415013**	**0.87**	**[0.76; 0.99]**	**100.0%**
Prediction interval						**[0.56; 1.35]**	
Heterogeneity: $I^2 = 90\%$ [81%; 94%], $\tau^2 = 0.02$, $p < 0.001$							
Test for effect in subgroup: $z = -2.05$ ($p = 0.041$)							
>35 vs 20 - 30							
Materna_2009	506	25225	2764	601520	4.37	[3.97; 4.80]	14.3%
Miller_2011	739	134120	2697	708470	1.45	[1.33; 1.57]	14.3%
Liu_2013	4892	422788	10319	1036502	1.16	[1.12; 1.20]	14.3%
Donghua_2018	579	52828	4291	482922	1.23	[1.13; 1.34]	14.3%
Persson_2019	5652	366073	9011	671819	1.15	[1.11; 1.19]	14.3%
Purkey_2019	1372	461119	2887	1198936	1.24	[1.16; 1.32]	14.3%
Hansen_2021	1491	90587	2649	267349	1.66	[1.56; 1.77]	14.3%
Random effects model	**15231**	**1552740**	**34618**	**4967518**	**1.55**	**[1.09; 2.20]**	**100.0%**
Prediction interval						**[0.42; 5.69]**	
Heterogeneity: $I^2 = 99\%$ [99%; 99%], $\tau^2 = 0.22$, $p < 0.001$							
Test for effect in subgroup: $z = 2.43$ ($p = 0.015$)							
30 - 35 vs 20 - 30							
Materna_2009	787	14223	2764	601520	12.04	[11.14; 13.01]	14.3%
Miller_2011	1240	283105	2697	708470	1.15	[1.08; 1.23]	14.3%
Liu_2013	6810	716842	10319	1036502	0.95	[0.93; 0.98]	14.3%
Donghua_2018	1344	125233	4291	482922	1.21	[1.14; 1.28]	14.3%
Persson_2019	9257	670616	9011	671819	1.03	[1.00; 1.06]	14.3%
Purkey_2019	1608	641948	2887	1198936	1.04	[0.98; 1.11]	14.3%
Hansen_2021	2041	168678	2649	267349	1.22	[1.15; 1.29]	14.3%
Random effects model	**23087**	**2620645**	**34618**	**4967518**	**1.54**	**[0.79; 3.03]**	**100.0%**
Prediction interval						**[0.13; 18.80]**	
Heterogeneity: $I^2 = 100\%$ [100%; 100%], $\tau^2 = 0.83$, $p = 0$							
Test for effect in subgroup: $z = 1.26$ ($p = 0.207$)							
>40 vs 20 - 30							
Materna_2009	130	18741	2764	601520	1.51	[1.27; 1.80]	33.1%
Liu_2013	1091	70844	10319	1036502	1.55	[1.45; 1.65]	33.5%
Hansen_2021	323	13745	2649	267349	2.37	[2.12; 2.66]	33.4%
Random effects model	**1544**	**103330**	**15732**	**1905371**	**1.77**	**[1.33; 2.36]**	**100.0%**
Prediction interval						**[0.05; 67.78]**	
Heterogeneity: $I^2 = 95\%$ [90%; 98%], $\tau^2 = 0.06$, $p < 0.001$							
Test for effect in subgroup: $z = 3.90$ ($p < 0.001$)							
35 - 40 vs 20 - 30							
Materna_2009	376	6484	2764	601520	12.62	[11.36; 14.02]	33.2%
Liu_2013	3801	351944	10319	1036502	1.08	[1.05; 1.13]	33.4%
Hansen_2021	1168	76842	2649	267349	1.53	[1.43; 1.64]	33.4%
Random effects model	**5345**	**435270**	**15732**	**1905371**	**2.76**	**[0.61; 12.39]**	**100.0%**
Prediction interval						**[0.00; 791881552.74]**	
Heterogeneity: $I^2 = 100\%$ [100%; 100%], $\tau^2 = 1.76$, $p = 0$							
Test for effect in subgroup: $z = 1.32$ ($p = 0.186$)							
Test for subgroup differences: $\chi^2_4 = 27.89$, df = 4 ($p < 0.001$)							

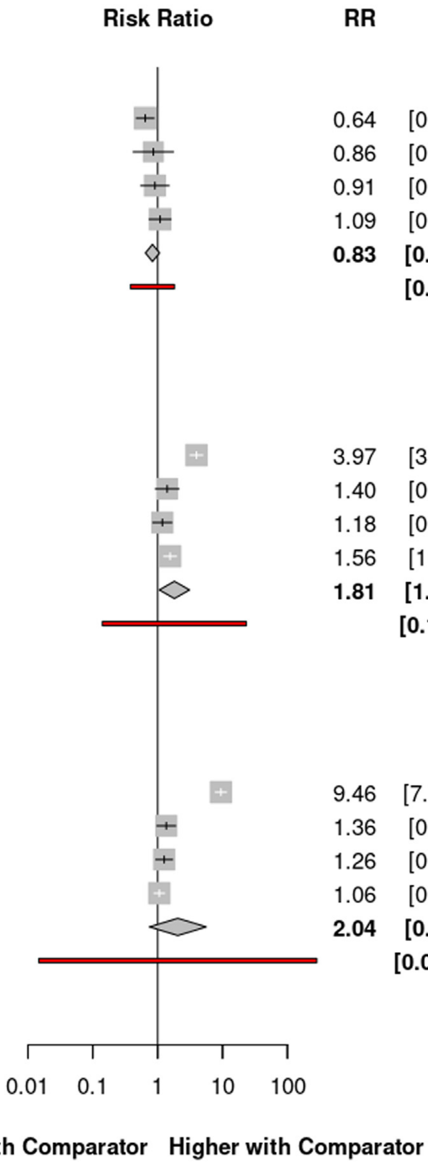


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 54

Forest plot representing the RR with 95% CI of *cleft lip and cleft palate* (ICD-10: Q35—Q37) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Materna_2009	42	75121	523	601520	0.64	[0.47; 0.88]	26.7%
Jaikrishan_2012	8	8833	126	119314	0.86	[0.42; 1.75]	22.3%
Pasnicki_2013	17	17670	133	125353	0.91	[0.55; 1.50]	24.9%
Jaruratanasirikul_2016	32	22265	126	95535	1.09	[0.74; 1.61]	26.1%
Random effects model	**99**	**123889**	**908**	**941722**	**0.83**	**[0.65; 1.07]**	**100.0%**
Prediction interval						**[0.38; 1.81]**	
Heterogeneity: I^2 = 34% [0%; 77%], τ^2 = 0.02, p = 0.209							
Test for effect in subgroup: z = -1.44 (p = 0.150)							
>35 vs 20 - 30							
Materna_2009	87	25225	523	601520	3.97	[3.16; 4.98]	25.6%
Pasnicki_2013	26	17498	133	125353	1.40	[0.92; 2.13]	24.1%
Jaruratanasirikul_2016	45	28891	126	95535	1.18	[0.84; 1.66]	24.8%
Luo_2019	100	55368	273	235136	1.56	[1.24; 1.96]	25.6%
Random effects model	**258**	**126982**	**1055**	**1057544**	**1.81**	**[1.06; 3.10]**	**100.0%**
Prediction interval						**[0.14; 23.25]**	
Heterogeneity: I^2 = 94% [88%; 97%], τ^2 = 0.28, p < 0.001							
Test for effect in subgroup: z = 2.16 (p = 0.031)							
30 - 35 vs 20 - 30							
Materna_2009	117	14223	523	601520	9.46	[7.75; 11.55]	25.4%
Pasnicki_2013	46	31917	133	125353	1.36	[0.97; 1.90]	24.5%
Jaruratanasirikul_2016	66	39702	126	95535	1.26	[0.94; 1.70]	24.8%
Luo_2019	175	142086	273	235136	1.06	[0.88; 1.28]	25.4%
Random effects model	**404**	**227928**	**1055**	**1057544**	**2.04**	**[0.74; 5.62]**	**100.0%**
Prediction interval						**[0.01; 283.11]**	
Heterogeneity: I^2 = 99% [98%; 99%], τ^2 = 1.05, p < 0.001							
Test for effect in subgroup: z = 1.38 (p = 0.166)							
Test for subgroup differences: χ^2_2 = 8.64, df = 2 (p = 0.013)							

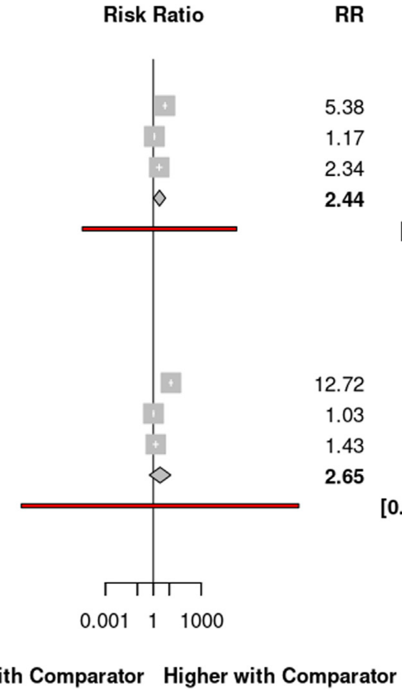


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 55

Forest plot representing the RR with 95% CI of *cleft palate* (ICD-10: Q35) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

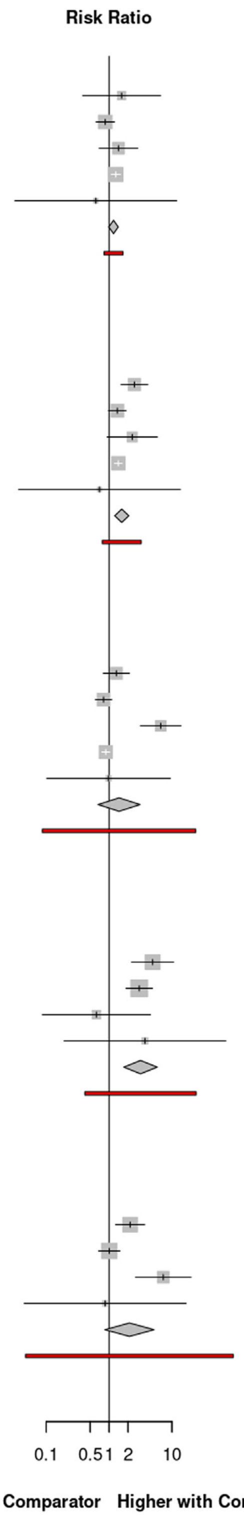
Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
>35 vs 20 - 30							
Materna_2009	60	25225	266	601520	5.38	[4.07; 7.12]	33.4%
StLouis_2014	1240	1929379	3626	6615611	1.17	[1.10; 1.25]	34.1%
Luo_2019	32	55368	58	235136	2.34	[1.52; 3.61]	32.5%
Random effects model	**1332**	**2009972**	**3950**	**7452267**	**2.44**	**[1.02; 5.82]**	**100.0%**
Prediction interval						**[0.00; 166984.46]**	
Heterogeneity: $I^2 = 98\%$ [97%; 99%], $\tau^2 = 0.57$, $p < 0.001$							
Test for effect in subgroup: $z = 2.00$ ($p = 0.045$)							
30 - 35 vs 20 - 30							
Materna_2009	80	14223	266	601520	12.72	[9.91; 16.32]	33.4%
StLouis_2014	1770	3145042	3626	6615611	1.03	[0.97; 1.09]	33.9%
Luo_2019	50	142086	58	235136	1.43	[0.98; 2.08]	32.7%
Random effects model	**1900**	**3301351**	**3950**	**7452267**	**2.65**	**[0.56; 12.48]**	**100.0%**
Prediction interval						**[0.00; 1307435733.36]**	
Heterogeneity: $I^2 = 99\%$ [99%; 100%], $\tau^2 = 1.86$, $p < 0.001$							
Test for effect in subgroup: $z = 1.23$ ($p = 0.218$)							
Test for subgroup differences: $\chi^2_1 = 0.01$, df = 1 ($p = 0.926$)							



SUPPLEMENTAL FIGURE 56

Forest plot representing the RR with 95% CI of *omphalocele* (ICD-10: Q79.2) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Tan_2008	2	8020	33	209595	1.58	[0.38; 6.60]	11.1%
Agopian_2009	42	322274	182	1213802	0.87	[0.62; 1.22]	30.2%
Materna_2009	9	75121	51	601520	1.41	[0.70; 2.87]	22.4%
StLouis_2014	175	1415846	638	6615611	1.28	[1.08; 1.51]	32.7%
Bugge_2017	0	3483	3	15027	0.62	[0.03; 11.93]	3.5%
Random effects model	**228**	**1824744**	**907**	**8655555**	**1.18**	**[0.99; 1.40]**	**100.0%**
Prediction interval						**[0.83; 1.66]**	
Heterogeneity: I^2 = 15% [0%; 82%], τ^2 = < 0.01, p = 0.321							
Test for effect in subgroup: z = 1.85 (p = 0.064)							
>35 vs 20 - 30							
Tan_2008	31	77775	33	209595	2.53	[1.55; 4.13]	24.2%
Agopian_2009	47	231666	182	1213802	1.35	[0.98; 1.86]	27.2%
Materna_2009	5	25225	51	601520	2.34	[0.93; 5.86]	16.3%
StLouis_2014	261	1929379	638	6615611	1.40	[1.21; 1.62]	29.3%
Bugge_2017	0	3052	3	15027	0.70	[0.04; 13.61]	3.1%
Random effects model	**344**	**2267097**	**907**	**8655555**	**1.59**	**[1.23; 2.06]**	**100.0%**
Prediction interval						**[0.78; 3.24]**	
Heterogeneity: I^2 = 39% [0%; 78%], τ^2 = 0.03, p = 0.159							
Test for effect in subgroup: z = 3.54 (p < 0.001)							
30 - 35 vs 20 - 30							
Tan_2008	34	165142	33	209595	1.31	[0.81; 2.11]	23.1%
Agopian_2009	54	440737	182	1213802	0.82	[0.60; 1.11]	26.0%
Materna_2009	8	14223	51	601520	6.63	[3.15; 13.98]	18.3%
StLouis_2014	269	3145042	638	6615611	0.89	[0.77; 1.02]	27.8%
Bugge_2017	1	5104	3	15027	0.98	[0.10; 9.43]	4.7%
Random effects model	**366**	**3770248**	**907**	**8655555**	**1.44**	**[0.66; 3.12]**	**100.0%**
Prediction interval						**[0.09; 23.90]**	
Heterogeneity: I^2 = 87% [71%; 94%], τ^2 = 0.62, p < 0.001							
Test for effect in subgroup: z = 0.93 (p = 0.354)							
>40 vs 20 - 30							
Tan_2008	8	10301	33	209595	4.93	[2.28; 10.68]	36.0%
Agopian_2009	18	39751	182	1213802	3.02	[1.86; 4.90]	46.4%
Materna_2009	1	18741	51	601520	0.63	[0.09; 4.55]	11.7%
Bugge_2017	0	577	3	15027	3.72	[0.19; 71.88]	5.9%
Random effects model	**27**	**69370**	**269**	**2039944**	**3.16**	**[1.71; 5.84]**	**100.0%**
Prediction interval						**[0.41; 24.24]**	
Heterogeneity: I^2 = 22% [0%; 88%], τ^2 = 0.13, p = 0.277							
Test for effect in subgroup: z = 3.67 (p < 0.001)							
35 - 40 vs 20 - 30							
Tan_2008	23	67474	33	209595	2.17	[1.27; 3.69]	34.8%
Agopian_2009	29	191915	182	1213802	1.01	[0.68; 1.49]	38.7%
Materna_2009	4	6484	51	601520	7.28	[2.63; 20.13]	22.0%
Bugge_2017	0	2475	3	15027	0.87	[0.04; 16.78]	4.6%
Random effects model	**56**	**268348**	**269**	**2039944**	**2.11**	**[0.86; 5.18]**	**100.0%**
Prediction interval						**[0.05; 94.32]**	
Heterogeneity: I^2 = 80% [48%; 93%], τ^2 = 0.57, p = 0.002							
Test for effect in subgroup: z = 1.62 (p = 0.105)							
Test for subgroup differences: χ^2_4 = 12.25, df = 4 (p = 0.016)							

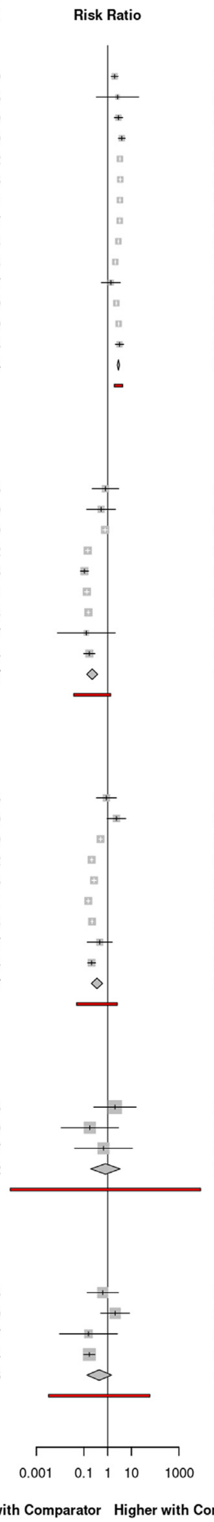


CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL FIGURE 57

Forest plot representing the RR with 95% CI of *gastroschisis* (ICD-10: Q79.3) in different age groups compared to the 20 to 30 age group and sorted by year of publication but only including studies published since 2005

Study	Comparator Events	Comparator Total	Reference Events	Reference Total	RR	95%-CI	Weight
<20 vs 20 - 30							
Williams_2005	68	111475	67	216129	1.97	[1.40; 2.76]	7.4%
Tan_2008	1	8020	10	209595	2.61	[0.33; 20.41]	4.2%
Materna_2009	32	75121	90	601520	2.85	[1.90; 4.26]	7.3%
Xu_2011	36	33043	1322	4757989	3.92	[2.82; 5.46]	7.4%
Kirby_2013	1822	1589319	2447	7002082	3.28	[3.09; 3.49]	7.5%
Baer_2014	459	290813	701	1503796	3.39	[3.01; 3.81]	7.5%
StLouis_2014	1466	1415846	2086	6615611	3.28	[3.07; 3.51]	7.5%
Loc_2015	1025	683716	1267	2716567	3.21	[2.96; 3.49]	7.5%
Friedman_2016	2336	2294000	4675	12994463	2.83	[2.69; 2.97]	7.5%
Jones_2016	3311	2439934	3586	5527463	2.09	[2.00; 2.19]	7.5%
Bugge_2017	6	3483	19	15027	1.36	[0.54; 3.41]	6.5%
Salinas_2018	4038	3076243	4209	7434269	2.32	[2.22; 2.42]	7.5%
Shor_2019	2249	1499333	4612	8931429	2.90	[2.76; 3.05]	7.5%
Borque_2021	28	21722	154	378014	3.16	[2.12; 4.73]	7.3%
Random effects model	**16877**	**13542068**	**25245**	**58903954**	**2.84**	**[2.54; 3.18]**	**100.0%**
Prediction interval						**[1.89; 4.28]**	
Heterogeneity: $I^2 = 95\%$ [94%; 97%], $\tau^2 = 0.03$, $p < 0.001$							
Test for effect in subgroup: $z = 18.28$ ($p < 0.001$)							
>35 vs 20 - 30							
Tan_2008	3	77775	10	209595	0.81	[0.22; 2.94]	9.8%
Materna_2009	2	25225	90	601520	0.53	[0.13; 2.15]	9.4%
Xu_2011	77	354511	1322	4757989	0.78	[0.62; 0.98]	12.7%
Kirby_2013	86	1697974	2447	7002082	0.14	[0.12; 0.18]	12.7%
Baer_2014	26	530265	701	1503796	0.11	[0.07; 0.16]	12.5%
StLouis_2014	81	1929379	2086	6615611	0.13	[0.11; 0.17]	12.7%
Friedman_2016	200	3603972	4675	12994463	0.15	[0.13; 0.18]	12.8%
Bugge_2017	0	3052	19	15027	0.13	[0.01; 2.09]	5.2%
Borque_2021	14	202899	154	378014	0.17	[0.10; 0.29]	12.2%
Random effects model	**489**	**8425052**	**11504**	**34078097**	**0.22**	**[0.13; 0.38]**	**100.0%**
Prediction interval						**[0.04; 1.34]**	
Heterogeneity: $I^2 = 96\%$ [94%; 97%], $\tau^2 = 0.50$, $p < 0.001$							
Test for effect in subgroup: $z = -5.57$ ($p < 0.001$)							
30 - 35 vs 20 - 30							
Tan_2008	7	165142	10	209595	0.89	[0.34; 2.33]	10.1%
Materna_2009	5	14223	90	601520	2.35	[0.95; 5.78]	10.3%
Xu_2011	162	1163051	1322	4757989	0.50	[0.43; 0.59]	11.8%
Kirby_2013	218	2943860	2447	7002082	0.21	[0.18; 0.24]	11.8%
Baer_2014	93	745872	701	1503796	0.27	[0.22; 0.33]	11.7%
StLouis_2014	152	3145042	2086	6615611	0.15	[0.13; 0.18]	11.8%
Friedman_2016	472	5944342	4675	12994463	0.22	[0.20; 0.24]	11.8%
Bugge_2017	3	5104	19	15027	0.46	[0.14; 1.57]	9.3%
Borque_2021	32	372093	154	378014	0.21	[0.14; 0.31]	11.5%
Random effects model	**1144**	**14498729**	**11504**	**34078097**	**0.35**	**[0.21; 0.61]**	**100.0%**
Prediction interval						**[0.05; 2.55]**	
Heterogeneity: $I^2 = 95\%$ [92%; 96%], $\tau^2 = 0.62$, $p < 0.001$							
Test for effect in subgroup: $z = -3.72$ ($p < 0.001$)							
>40 vs 20 - 30							
Tan_2008	1	10301	10	209595	2.03	[0.26; 15.89]	40.7%
Materna_2009	0	18741	90	601520	0.18	[0.01; 2.86]	29.8%
Bugge_2017	0	577	19	15027	0.67	[0.04; 11.04]	29.5%
Random effects model	**1**	**29619**	**119**	**826142**	**0.80**	**[0.19; 3.34]**	**100.0%**
Prediction interval						**[0.00; 8220.45]**	
Heterogeneity: $I^2 = 0\%$ [0%; 90%], $\tau^2 = 0$, $p = 0.380$							
Test for effect in subgroup: $z = -0.30$ ($p = 0.765$)							
35 - 40 vs 20 - 30							
Tan_2008	2	67474	10	209595	0.62	[0.14; 2.84]	25.1%
Materna_2009	2	6484	90	601520	2.06	[0.51; 8.37]	26.3%
Bugge_2017	0	2475	19	15027	0.16	[0.01; 2.58]	14.6%
Borque_2021	14	202899	154	378014	0.17	[0.10; 0.29]	34.0%
Random effects model	**18**	**279332**	**273**	**1204156**	**0.44**	**[0.13; 1.46]**	**100.0%**
Prediction interval						**[0.00; 59.87]**	
Heterogeneity: $I^2 = 75\%$ [32%; 91%], $\tau^2 = 0.93$, $p = 0.007$							
Test for effect in subgroup: $z = -1.34$ ($p = 0.180$)							
Test for subgroup differences: $\chi^2_4 = 143.19$, df = 4 ($p < 0.001$)							



CI, confidence interval; *ICD-10*, International Classification of Diseases-10; *RR*, risk ratio.

SUPPLEMENTAL TABLE 1
PRISMA checklist

Section and topic	Item #	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review.	
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	

(continued)

SUPPLEMENTAL TABLE 1
PRISMA checklist *(continued)*

Section and topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item #5]).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (see Figure 1).	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	

(continued)

SUPPLEMENTAL TABLE 1
PRISMA checklist *(continued)*

Section and topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
Other information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or nonfinancial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

SUPPLEMENTAL TABLE 2

Basic characteristics of the included studies

Author (year)	Ref	Country	Study period	Total	Cases	Age category	Congenital anomalies
Agopian 2009	1	Texas (USA)	1999—2004	2,208,758	325	<20, 20—24, 25—29, 30—34, 35—39, ≥40	Omhalocele
Baer 2014	2	California (USA)	2005—2010	3,070,957	1279	<19, 20—24, 25—29, 30—34, ≥35	Gastroschisis
Beckman 1976	3	Sweden	1950—1973	61,061	280	<24, 25—29, 30—34, ≥35	Cleft palate, cleft lip with or without cleft palate, polydaycytly, syndactyly, clubfoot
Bergman 2015	4	Europe	2001—2010	5,871,855	10,929	<20, 20—24, 25—29, 30—34, 35—39, ≥40	Hypospadiasis
Baird 1994	5	Canada	1966—1981	576,815	702	<20, 20—24, 25—29, 30—34, 35—39, ≥40	Isolated cleft palate, cleft lip and cleft palate
Bodnár 1970	6	Hungary	1958—1967	115,215	2100	<19, 20—24, 25—29, 30—39, ≥40	All NCAs, nervous system, circulatory system, urogenital anomalies, musculoskeletal system, digestive system
Borman 1986	7	New Zeland	1978	52,143	104	<20, 20—24, 25—29, ≥30	Anencephlaus, spina bifida
Borque 2021	8	Canada	2012—2018	1,001,080	231	<20, 20—24, 25—29, 30—34, 35—39, ≥40	Gastroschisis
Bugge 2017	9	Greenland	1989—2015	26,666	33	<20, 20—24, 25—29, 30—34, 35—39, 40—44, ≥45	Gastroschisis, omphalocele
Byron 1998	10	Australia	1980—1990	358,679	59; 104	<20, 20—24, 25—29, 30—34, 35—39, ≥40	Gastroschisis, omphalocele
Canfield 2009	11	Texas (USA)	1999—2003	1,827,317	514; 643	<20, 20—24, 25—29, 30—34, 35—39, ≥40	Anencephlaus, spina bifida
Canon 2012	12	Arkansas (USA)	1998—2007	196,050	1455	<20, 20—24, 25—29, 30—34, ≥35	Hypospadiasis
Croen 1995	13	California (USA)	1983—1988	1,028,255	29,848	<20, 20—24, 25—29, 30—34, 35—39, ≥40	All NCAs
DeRoo 2003	14	Washington (USA)	1987—1990	298,138	608	<20, 20—24, 25—29, 30—34, 35—39, ≥40	Cleft lip and cleft palate
Dott 2003	15	Metropolitan Atlanta (USA)	1968—1999	1,029,143	249	<20, 20—24, 25—34, ≥35	Diaphragmatic hernia
Dudin 1997	16	Palestina	1986—1993	26,934	148	15—19, 20—24, 25—29, 30—39, ≥40	Neural tube defects
Fedrick 1976	17	Scotland	1961—1972	1,162,939	3246	<20, 20—24, 25—29, 30—34, 35—39, 40—44, ≥45	Anencephlaus
Feldman 1982	18	New York, Brooklyn (USA)	1968—1976	173,670	179	<20, 20—24, 25—29, 30—34, ≥35	Neural tube defects
Forrester 2004	19	Hawaii (USA)	1986—2000	281,866	544	<19, 20—24, 25—29, 30—34, 35—39, ≥40	Cleft lip and cleft palate
Forrester 1999	20	Hawaii (USA)	1986—1997	229,584	150	19≥, 20—24, 25—29, 30—34, 35—39, ≥40	Omphalocele, gastoschisis
Forrester 2000	21	Hawaii (USA)	1986—1997	246,231	245	19≥, 20—24, 25—29, 30—34, 35—39, ≥40	Anencephaly, spina bifida, encephalocele
Friedman 2016	22	USA	2005—2013	24,836,777	5985	<20, 20—24, 25—29, 30—34, ≥35	Gastroschisis

(continued)

SUPPLEMENTAL TABLE 2

Basic characteristics of the included studies *(continued)*

Author (year)	Ref	Country	Study period	Total	Cases	Age category	Congenital anomalies
Gupta 1967	23	Nigeria	1964	4220	15	15–19 20–24, 25–29, 30–34, 35–39, 40–44	CHD
Hansen 2021	24	Australia	1990–2016	765,419	8173	<20, 20–24, 25–29, 30–34, 35–39, ≥40	CHD
Hay 1972	25	USA	1961–1966	8,475,600	1063	<20, 20–24, 25–29, 30–34, 35–39, ≥40	Anencephlay, spina bifida, hydrocephalus, congenital heart defects, cleft lip without cleft palate, cleft lip and palate, cleft palate without cleft lift, tracheoesophageal fistula and other esophageal defects, omhalocele, imperforate anus and other anorectal defects, hypospadias, position foot defects, polydactyly, syndactyly, reduction deformities
Hollier 2000	26	Dallas (Texas, USA)	1988–1994	102,728	3466	<20, 20–24, 25–29, 30–34, 35–39, ≥40	All NCAs
Jaikrishan 2012	27	India	1995–2011	141,540	1370	15–19, 20–29, ≥30	Clubfood, CHD, cleft palate/lip, NTD, hypospadias
Janerich 1972	28	New York State (USA)	1945–1970	4,555,614	4450	15–19; 20–24; 25–29; 30–34; 35–39; 40–44	Spina bifida
Janerich 1972	29	New York State (USA)	1945–1967	4,074,079	3090	15–19; 20–24; 25–29; 30–34; 35–39; 40–44	Anencephaly
Jaruratanasirikul 2016	30	Southern Thailand	2009–2013	186,393	269	<20; 20–<25; 25–<30; 30–<35; ≥35	Oral clefts
Jones 2016	31	USA	1995–2012	21,040,437	8866	<20; 20–24; 25–29; 30–34; 35<	Gastroschisis
Kazaura 2004	32	Norway	1967–1998	1,869,388	699	<20; 20–24; 25–29; 30–34; 35–39; ≥40	Gastroschisis, omphalocele
Kirby 2013	33	USA	1995–2005	13,233,235	4713	<20; 20–24; 25–29; 30–34; 35<	Gastroschisis
Liu 2013	34	Canada	2002–2010	2,283,223	26,488	<19; 20–24; 25–29; 30–34; 35–39; 40<	CHD
Liu 2019	35	Canada	2004–2015	3,327,762	1517	<19; 20–24; 25–29; 30–34; 35–39; 40<	Spina bifida, anencephaly/encephalocele
Li 2019	36	Zhejiang Province (China, People's Republic of)	2010–2016	1,748,023	2790	<20; 20–25; 30–35; ≥35	Kidney and urinary tract defects
Loc-Uyen 2015	37	USA-Texas	1999–2011	4,970,525	2549	<19; 20–24; 25–29; 30<	Gastroschisis
Luo 2019	38	China-Shenzhen	2003–2017	591,024	777	<25; 25–; 30–; 35<	Cleft lip and palate
Martinez-Frias 1984	39	Spain	1976	264,502	52	<19; 20–24; 25–29; 30–34; 35–39; 40<	Gastroschisis, omphalocele

(continued)

SUPPLEMENTAL TABLE 2

Basic characteristics of the included studies *(continued)*

Author (year)	Ref	Country	Study period	Total	Cases	Age category	Congenital anomalies
Materna-Kiryluk 2009	40	Poland	1998–2002	716,089	8683	<19; 20–24; 25–29; 30–34; 35–39; 40<	All NCAs (excluded muskuloskeletal defects),diaphragmatic hernia, gastroschisis, omphalocele, neural tube defects, microcephalus, hydrocephalus, congenital heart defects, hypospadias, renal agenesis or hypoplasia, cystic kidney disease, hydronephrosis, cleft palate, cleft lip with or without cleft palate, oesophageal atresia, small intestinal/ large intestinal atresia or stenosis, anal atresia or stenosis
McGivern 2015	41	Europe	1980–2009	11,478,586	3373	<20; 20–24; 25–29; 30–34; 35<	Diaphragmatic hernia
Miller 2011	42	Atlanta (Georgia, USA)	1968–2005	1,301,340	5289	<35; 35<	CHD
Mucat 2019	43	Malta	2000–2014	55,943		20–24; 25–29; 30–34; 35–39; 40<	All NCAs, nervous system, eye, ear, face, neck, circulatory system, respiratory system, digestive system, genital organs, urinary system, muskoloskeletal system
Nazer 2007	44	Chile	1996–2005	21,083	1767	<15; 15–19; 20–24; 25–29; 30–34; 35–39; 40–44; 45<	All NCAs
Nazer 2013	45	Chile	2002–2011	15,636	1174	<15; 15–19; 20–24; 25–29; 30–34; 35–39; 40–44; 45<	All NCAs
Parkes 2020	46	England, Scotland (UK)	2003–2010	219,486		<19; 20–29; 30–39; 40<	All NCAs
Pasnicki 2013	47	Poland	1988–2007	192,438	2769	<18; 20–24; 25–29; 30–34; 35–39; 40<	All NCAs, nervous system, circulatory system, cleft lip and cleft palate, digestive system, genital organs, urinary system, muskoloskeletal system, other
Persson 2019	48	Sweden	1992–2012	2,050,491	28,628	>24; 25–29; 30–34; 35<	CHD
Petrova 2009	49	Norway and Arkhangelskaja Oblast (Russia)	1995–2004	434,567	615	<19; 20–24; 25–29; 30–34; 35<	Neural tube defects: anencephalus, spina bifida
Pradat 1992	50	Sweden	1981–1986	573,422	1605	<20; 20–24; 25–29; 30–34; 35–39; 40–44; >44	CHD
Purkey 2019	51	California (USA)	2008–2012	2,054,516	6325	<19; 20–24; 25–29; 30–34; 35<	CHD
Rankin 1999	52	North of England	1986–1996	426,694	296	11–19; 20–24; 25–29; 30–34; 35–39; >40	Gastroschisis, omphalocele, omphalocele

(continued)

SUPPLEMENTAL TABLE 2

Basic characteristics of the included studies *(continued)*

Author (year)	Ref	Country	Study period	Total	Cases	Age category	Congenital anomalies
Rankin 2000	53	North of England	1984—1996	507,405	934	11—19; 20—24; 25—29; 30—34; 35—39; >40	Neural tube defects
Rider 2013	54	Utah (USA)	1999—2008	480,125	8510	<24; 25—29; 30—34; 35—39; 40—60	All NCAs
Roeper 1987	55	California (USA)	1968—1977	3,297,071	166	<19; 20—24; 25—29; 30—34; 35—39; 40<	Gastroschisis, omphalocele
Salihu 2003	56	NewYork State (USA)	1992—1999	2,153,955; 2,149,340	595	<19; 20—24; 25—29; 30—34; 35—39; 40<	Omphalocele, gastroschisis
Salim 2019	57	Brazil	1996—2014	4,270,114	5062	<19; 20—29; 30—34; 35—39; 40<	Circulatory system
Sarkar 2013	58	India	2011—2012	12,896	286	<20; 20—30; 30<	All NCAs
Sever 1982	59	Los Angeles County (California, USA)	1966—1972	2,945,555	962	<14; 15—19; 20—24; 25—29; 30—34; 35—39; 40—44; 45<	Anencephalus, spina bifida, encephalocele, neural tube defects, all NCAs
Shields 1981	60	Denmark	1940—1971	2,406,654	548	<19; 20—24; 25—29; 30—34; 35—39; 40—44; 45<	Cleft palate
Short 2019	61	USA	2006—2015	17,686,317	3489	<19; 20—24; 25—29; 30<	Gastroschisis
StLouis 2017	62	USA	1999—2007	13,105,878	138,999	<19; 20—24; 25—29; 30—34; 35<	All NCAs, anencephalus, spina bifida, encephalocele, anotia/microtia, common truncus CHD, transposition of the great arteries, tetralogy of fallot, atrioventricular septal defect without down syndrome, hypoplastic left heart syndrome, coarctation of the aorta, aortic valve stenosis, cleft palate without cleft lip, cleft lip with and without cleft palate, esophageal atresia/tracheoesophageal fistula, pyloric stenosis, rectal and large intestinal atresia/stenosis, hypospadiasis, upper limb deficiency, lower limb deficiency, any limb deficiency, diaphragmatic hernia, gastroschisis, omphalocele
Tan 1996	63	England, Wales (UK)	1987—1993	4,873,547	1043	<20; 20—24; 25—29; 30—34; 35—39; >40	Gastroschisis, omphalocele
Tan 2005	64	Singapore	1994—2000	328,077	7870	<20; 20—24; 25—29; 30—34; 35—39; >40	All NCAs
Tan 2008	65	Singapore	1993—2002	460,532	121	<20; 20—24; 25—29; 30—34; 35—39; >40	Gastroschisis, omphalocele
Williams 2005	66	Atlanta (USA)	1968—2000	877,604	211	<20; 20—24; 24<	Gastroschisis
Xie 2016	67	China-Hunan Province	2005—2014	925,413	17,753	<20; 20—24; 25—29; 30—34; 35<	All NCAs
Xie 2018	68	China (People's Republic of)	2012—2016	673,060	6289	<20, 20—24, 25—29, 30—34, ≥35	Congenital heart defects

(continued)

SUPPLEMENTAL TABLE 2

Basic characteristics of the included studies *(continued)*

Author (year)	Ref	Country	Study period	Total	Cases	Age category	Congenital anomalies
Xu 2011	[69]	China (People's Republic of)	1996–2007	6,308,594	1601	<19; 20–24; 25–29; 30–34; 35<	Gastroschisis
Zhang 2012	[70]	China (People's Republic of)	2012	62,526	976	<25; 25–30; 35<	All NCAs
Yang 2006	[71]	California (USA)	1989–1997	2,506,188	550	<20; 20–24; 25–29; 30–34; 35–39; 40–55	Diaphragmatic hernia
Zhou 2020	[72]	China (People's Republic of), Southern Jiangsu	2014–2018	238,712	1707	<19; 20–24; 25–29; 30–34; 35<	All NCAs

CHD, congenital heart defect; *NCAs*, nonchromosomal congenital anomalies; *NTD*, neural tube defect.

SUPPLEMENTAL TABLE 3

Risk of bias assessment using the QUIPS tool

Code	D1	D2	D3	D4	D5	D6	
	Low-risk: table or detailed text about population Moderate: moderate information about population High risk: limited information about study population	Low risk: population—based study—whole country/region/ hospital Moderate risk: case-control study—high-case numbers High risk: case-control study—low case numbers or just descriptive information about cases	Low risk: clear and detailed age categories covering all age groups Moderate risk: clear categories, but some age groups are missing High risk: only 1 group is examined	Low risk: clear definition of outcome—exact ICD-10 category Moderate risk: can be matched to ICD-10 category High risk: unclear definition	Low risk: clear information about confounders/ multivariate models Moderate risk: limited informationHigh risk: no information about relevant confounders	Low risk: clear, raw data; no or negligible contradiction Moderate risk: needs some calculation or reading from graph; minor contradiction High risk: only approximate data can be obtained; serious contradiction	High quality: max. + + Acceptable: max. + + +/+ Low quality: + + or more
Code	Study population	Study design	Prognostic factor measurment	Outcome	Study confounding	Data Quality—statistics	Overall rate
Agopian_2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Baer_2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Beckman_1976	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk	Acceptable
Bergman_2015	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Baird_1994	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk	Acceptable
Bodnár_1970	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk	Acceptable
Borman_1986	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Borque_2021	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Acceptable
Bugge_2017	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Byron_1998	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk	High quality
Canfield_2009	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Canon_2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Croen_1995	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Moderate risk	Acceptable
DeRoo_2003	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	High quality
Donghua_2018	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk	High quality
Dott_2003	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Acceptable
Dudin_1997	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Fedrick_1976	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality

(continued)

SUPPLEMENTAL TABLE 3

Risk of bias assessment using the QUIPS tool *(continued)*

	D1	D2	D3	D4	D5	D6	
	Low-risk: table or detailed text about population Moderate: moderate information about population High risk: limited information about study population	Low risk: population—based study—whole country/region/hospital Moderate risk: case-control study—high-case numbers High risk: case-control study—low case numbers or just descriptive information about cases	Low risk: clear and detailed age categories covering all age groups Moderate risk: clear categories, but some age groups are missing High risk: only 1 group is examined	Low risk: clear definition of outcome—exact ICD-10 category Moderate risk: can be matched to ICD-10 category High risk: unclear definition	Low risk: clear information about confounders/multivariate models Moderate risk: limited informationHigh risk: no information about relevant confounders	Low risk: clear, raw data; no or negligible contradiction Moderate risk: needs some calculation or reading from graph; minor contradiction High risk: only approximate data can be obtained; serious contradiction	High quality: max. ++ Acceptable: max. ++ +/+ Low quality: ++ or more
Code	**Study population**	**Study design**	**Prognostic factor measurment**	**Outcome**	**Study confounding**	**Data Quality—statistics**	**Overall rate**
Feldman_1982	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Forrester_2004C	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk	High quality
Forrester_1999	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Forrester_2000	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Friedman_2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Gupta_1967	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Hansen_2021	Low risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	High quality
Hay_1972	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk	High quality
Hollier_2000	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	High quality
Jaikrishan_2012	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk	High quality
Janerich_1972	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Janerich_1972	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Jaruratanasirikul_2016	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Jones_2016	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Acceptable
Kazaura_2004	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Kirby_2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Liu_2013	Low risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	High quality
Liu_2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality

(continued)

SUPPLEMENTAL TABLE 3

Risk of bias assessment using the QUIPS tool *(continued)*

Code	D1: Low-risk: table or detailed text about population Moderate: moderate information about population High risk: limited information about study population — Study population	D2: Low risk: population—based study—whole country/region/ hospital Moderate risk: case-control study—high-case numbers High risk: case-control study—low case numbers or just descriptive information about cases — Study design	D3: Low risk: clear and detailed age categories covering all age groups Moderate risk: clear categories, but some age groups are missing High risk: only 1 group is examined — Prognostic factor measurment	D4: Low risk: clear definition of outcome—exact ICD-10 category Moderate risk: can be matched to ICD-10 category High risk: unclear definition — Outcome	D5: Low risk: clear information about confounders/ multivariate models Moderate risk: limited informationHigh risk: no information about relevant confounders — Study confounding	D6: Low risk: clear, raw data; no or negligible contradiction Moderate risk: needs some calculation or reading from graph; minor contradiction High risk: only approximate data can be obtained; serious contradiction — Data Quality—statistics	High quality: max. ++ Acceptable: max. ++ +/+ Low quality: ++ or more — Overall rate
Liz_2019	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Loc_2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Luo_2019	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	High quality
Martinez_1984	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk	High quality
Materna_2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
McGivern_2015	Low risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	High quality
Miller_2011	Low risk	Low risk	Low risk	Moderate risk	Low risk	Moderate risk	High quality
Mucat_2019	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Low risk	High quality
Nazer_2007	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Parkes_2020	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Pasnicki_2013	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Persson_2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Petrova_2009	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Pradat_1992	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Purkey_2019	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Rankin_1999	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Rankin_2000	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Rider_2013	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	High quality

(continued)

SUPPLEMENTAL TABLE 3

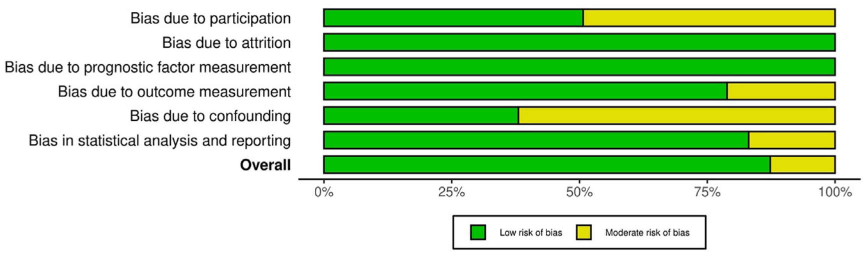
Risk of bias assessment using the QUIPS tool *(continued)*

	D1	D2	D3	D4	D5	D6	
	Low-risk: table or detailed text about population Moderate: moderate information about population High risk: limited information about study population	Low risk: population—based study—whole country/region/ hospital Moderate risk: case-control study—high-case numbers High risk: case-control study—low case numbers or just descriptive information about cases	Low risk: clear and detailed age categories covering all age groups Moderate risk: clear categories, but some age groups are missing High risk: only 1 group is examined	Low risk: clear definition of outcome—exact ICD-10 category Moderate risk: can be matched to ICD-10 category High risk: unclear definition	Low risk: clear information about confounders/ multivariate models Moderate risk: limited informationHigh risk: no information about relevant confounders	Low risk: clear, raw data; no or negligible contradiction Moderate risk: needs some calculation or reading from graph; minor contradiction High risk: only approximate data can be obtained; serious contradiction	High quality: max. + + Acceptable: max. + + +/+ Low quality: + + or more
Code	**Study population**	**Study design**	**Prognostic factor measurment**	**Outcome**	**Study confounding**	**Data Quality—statistics**	**Overall rate**
Roeper_1987	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	High quality
Salihu_2003	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Acceptable
Salim_2019	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Salinas_2018	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Sarkar_2013	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Sever_1982	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Shields_1981	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Short_2019	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Acceptable
StLouis_2014	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Tan_2008	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Tan_2005	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Tan_1996	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Williams_2005	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Xie_2016	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Xu_2011	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Yang_2006	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Zhang_2012	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality
Zhou_2020	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	High quality

Colors represent: Green: low risk of bias, Yellow: moderate risk of bias, Red: high risk of bias.

ICD-10, International Classification of Diseases-10; *QUIPS*, Quality in Prognostic Studies.

SUPPLEMENTAL TABLE 4
Overall risk of bias including all studies using the Risk-of-Bias VISualization tool



SUPPLEMENTAL TABLE 5
Comparison of the "all NCAs" (ICD-10: Q00—Q89) risk ratio outcomes: studies with concomitant CAs excluded vs studies with concomitant CAs included

Risk groups	Excluding cases with concomitant CAs	Including cases with concomitant CAs
<20 vs 20—30	1.21 [0.59—2.49; n=5]	1.08 [0.89—1.32; n=14]
>35 vs 20—30	1.37 [0.76—2.45; n=6]	1.31 [1.07—1.61; n=13]
>40 vs 20—30	1.25 [1.08—1.46; n=6]	1.44 [1.25—1.66; n=11]
30—35 vs 20—30	1.54 [0.55—4.32; n=6]	1.23 [0.85—1.78; n=13]
35—40 vs 20—30	1.73 [0.45—6.70; n=5]	1.47 [0.87—2.49; n=9]

CAs, chromosomal abnormalities.

SUPPLEMENTAL TABLE 6
Summary of effect of year of publication on the maternal age dependence of risk of congenital anomalies

ICD-10 NCA categories	<20		>35		30–35		>40		35–40	
	Trend	Subset	Trend	Subset	Trend	Subset	Trend	Subset	Trend	Subset
Q00–Q89 all nonchromosomal anomalies	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
Q00–Q89[j] all nonchromosomal anomalies[j]	✘	✘	✔[a]	✘	✔[a]	✘	✔[b]	✘	✔[a]	✘
Q00–Q07 malformations of the nervous system	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
Q00.0 anencephaly	✘	✔[c]	✘	✔[d]	✘	✘	✘	—	✘	—
Q05 spina bifida	✘	✘	✘	✘	✘	✘	✘	—	✘	—
Q20–Q26 malformations of the circulatory system	✘	✘	✘	✘	✘	✘	✘	✘	✘	✘
Q35–Q37 cleft lip and cleft palate	✘	✘	✘	✔[e]	✘	✘	✘	—	✘	—
Q35 cleft palate	✘	—	✘	✔[f]	✘	✘	✔[g]	—	✘	—
Q79.2 exomphalos	✘	✔[h]	✘	✘	✘	✘	✘	✘	✘	✘
Q79.3 gastroschisis	✘	✘	✘	✘	✘	✘[i]	✘	✔[h]	✘	✔[h]

The "trend" column shows if any trend could be detected visually in the study-level effect sizes of the full set of studies sorted by date of publication. The "subset" column shows if the subset of studies published since 2005 yielded a different pooled effect size compared to that of the full set of studies. ✘: no trend or difference detected. ✔: some trend or difference was detected. —: too few articles to analyze the subset.

[a] Slight nonsignificant negative trend; [b] Moderate nonsignificant negative trend; [c] Full set is just nonsignificant, subset is just significant; [d] Full set is nonsignificant risk effect, subset is significant protective effect; [e] Full set is nonsignificant, subset is significant; [f] The risk has increased; [g] Slight nonsignificant positive trend; [h] Full set is significant, subset is nonsignificant; [i] subset is less significant as the full set; [j] Only studies where concomitant chromosomal abnormality cases were excluded.