

PARENTAL CONSANGUINITY AND ADVERSE PREGNANCY OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF MAJOR CONGENITAL ANOMALIES

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ABSTRACT

Background: Consanguineous unions remain common in several populations in South Asia, the Middle East and North Africa, as well as in migrant communities originating from these regions. Parental biological relatedness increases the probability that an offspring inherits two copies of a deleterious recessive variant, although observed pregnancy outcomes are also shaped by maternal health, socioeconomic conditions and access to antenatal care. This review evaluated associations between consanguinity and major congenital anomalies, pregnancy loss, stillbirth, preterm birth, low birth weight and neonatal mortality.

Methods: Comparative observational studies involving consanguineous and non-consanguineous couples were identified from PubMed/MEDLINE, PubMed Central, publisher repositories and reference lists through 31 July 2026. Adjusted estimates were preferred. For the primary outcome, risk-ratio-type estimates were converted to odds ratios using the reported non-consanguineous baseline risk. Odds ratios were pooled using a restricted maximum-likelihood random-effects model with Hartung-Knapp confidence intervals. Heterogeneity was summarized using Q, I², tau² and a prediction interval. Other clinically distinct outcomes were synthesized narratively.

Results: Twenty-six comparative studies contributed to the qualitative synthesis, and four studies contributed compatible adjusted estimates for major congenital anomalies. The pooled odds ratio was 1.90 (95% CI 1.02-3.56), with substantial heterogeneity (I² = 85.1%; tau² = 0.133). The 95% prediction interval was wide (0.32-11.32), indicating marked variation across populations and settings. Leave-one-out estimates ranged from 1.63 to 2.12, although confidence intervals widened when only three studies remained. Earlier quantitative evidence suggested a modest association with low birth weight, whereas findings for miscarriage, stillbirth, preterm birth and neonatal mortality were less consistent.

Conclusion: Consanguinity was associated with higher odds of major congenital anomalies, but the magnitude was not uniform and the certainty of the pooled evidence was very low because of observational designs, substantial heterogeneity and limited numbers of compatible studies. Clinical responses should emphasize individualized pedigree assessment, targeted carrier testing, appropriate fetal evaluation, and culturally respectful counselling rather than generalized or coercive messages.

KEYWORDS: consanguinity; first-cousin marriage; congenital anomalies; pregnancy loss; stillbirth; preterm birth; low birth weight; neonatal mortality; systematic review; meta-analysis

1. INTRODUCTION

Consanguinity refers to biological relatedness between partners who share one or more recent common ancestors. In clinical genetics, a union between second cousins or closer is generally classified as consanguineous because the expected inbreeding coefficient in the offspring is at least 0.0156. First cousins share, on average, one eighth of their inherited genetic material, and their offspring are expected to be homozygous by descent at approximately one sixteenth of autosomal loci. These values are population averages. Realized autozygosity may be greater when related unions recur over several generations or when marriage occurs within a small endogamous population [9-14].

Consanguineous marriage is unevenly distributed worldwide. It remains common in parts of Pakistan, India, Bangladesh, Afghanistan, Iran, the Arabian Peninsula and North Africa, and it is also encountered in migrant populations in Europe, North America and Australia [10-14]. Its social meaning varies between communities and may include family solidarity, perceived marital compatibility, preservation of property, familiarity between households and expectations of support within the extended family. These considerations are clinically important because counselling that reduces a family practice to a biomedical hazard may be experienced as stigmatizing and can weaken trust in genetic and maternity services [10,13-15].

The clearest biological consequence of parental relatedness is an increase in homozygosity for variants inherited from a common ancestor. When both partners carry the same pathogenic autosomal recessive variant, each pregnancy has a 25%

probability of producing an affected child. This mechanism is relevant to many metabolic, neurological, sensory, skeletal and developmental disorders. It can also contribute to structural anomalies, including selected cardiac and central nervous system defects [9,11-18]. Genomic analyses support this model: rare deleterious homozygous variants are substantially more frequent in offspring of related parents, whereas the effect of consanguinity on common-variant burden is much smaller [19-22].

Pregnancy outcomes cannot, however, be attributed to genetic relatedness alone. Maternal age, parity, nutrition, anaemia, diabetes, obesity, tobacco exposure, education, household wealth, residence and antenatal-care use may differ between consanguineous and non-consanguineous couples. Prenatal diagnosis and pregnancy termination may also alter the measured prevalence of congenital anomalies among live births. Consequently, unadjusted hospital series, referral cohorts and live-birth-only analyses are not directly comparable [16,17,23,31-33].

Previous reviews have consistently suggested an excess of congenital anomalies, while findings for miscarriage, stillbirth, prematurity and neonatal death have been less uniform [16-18]. Recent population studies from India, Pakistan and Qatar have added contemporary evidence and have highlighted the influence of maternal healthcare and social conditions [23,32,33]. A 2026 ECLAMC analysis from Venezuela also linked parental consanguinity with selected anomalies, illustrating that the population impact depends on both exposure prevalence and local ancestry structure [53]. The present review therefore aimed to quantify the association between parental consanguinity and major congenital anomalies and to synthesize the evidence for other pregnancy and neonatal outcomes.

2. MATERIALS AND METHODS

2.1 Review design and protocol status

This review was structured as a systematic synthesis of comparative observational evidence and was revised in accordance with PRISMA 2020 and MOOSE reporting principles [1,2]. Random allocation to consanguineous marriage is neither feasible nor ethical; therefore, eligible evidence comprised cohort, registry, case-control, survey and comparative cross-sectional studies. No prospectively registered protocol was available. This absence was treated as a methodological limitation, and the revised analysis plan was stated explicitly before recalculation of the pooled estimate.

2.2 Eligibility criteria

Studies were eligible when they included pregnancies, births, neonates or offspring for whom parental biological relatedness was documented and a non-consanguineous comparison group was available. The exposure could be reported as any consanguineous union or by relationship degree, including first cousins, first cousins once removed, second cousins or closer unions. Eligible studies reported at least one reproductive, fetal, birth or neonatal outcome. Case reports, single-family descriptions, disease-specific case series without a population comparator, studies without pregnancy or neonatal outcomes, duplicate publications and reports with irretrievable numerical data were excluded. Reviews were used for citation searching but were not treated as primary datasets.

2.3 Information sources and search strategy

The available search record documented searches of PubMed/MEDLINE, PubMed Central, publisher repositories and reference lists for reports available through 31 July 2026. Search concepts combined terms for consanguinity (consanguinity, consanguineous marriage, cousin marriage, first cousin, inbreeding and parental relatedness) with terms for pregnancy and neonatal outcomes (congenital anomaly, birth defect, miscarriage, spontaneous abortion, stillbirth, preterm birth, low birth weight, fetal growth restriction, perinatal mortality and neonatal mortality). The PubMed search syntax is reproduced in Appendix 2. Because record-level exports were not retained, the search could not be independently audited during this revision. A full submission-stage rerun in MEDLINE, Embase, Scopus and Web of Science is required to confirm completeness.

2.4 Study selection and data extraction

The aggregate screening summary indicated that 107 records were identified, 25 duplicates were removed, 82 titles or abstracts were screened, 39 reports underwent full-text assessment, and 26 studies were included in the qualitative synthesis. Thirteen full-text reports were excluded for absence of a non-consanguineous comparator, absence of a pregnancy or neonatal outcome, restriction to a selected disease series, overlapping data or insufficient numerical information. These counts were reconstructed from the available manuscript summary; the individual exclusion ledger was not available. Study characteristics, population, relationship degree, outcome definition, effect estimate, confidence interval and adjustment variables were extracted. Adjusted estimates were preferred because social and maternal characteristics can confound observed associations.

2.5 Outcomes

The primary outcome was any major congenital anomaly diagnosed prenatally, at birth, during the neonatal period or through a congenital-anomaly registry. When possible, major anomalies were distinguished from minor variants and chromosomal conditions. Secondary outcomes were spontaneous abortion, stillbirth, preterm birth, low birth weight, fetal growth restriction or small-for-gestational-age birth, perinatal mortality and neonatal death. Low birth weight, prematurity and fetal growth restriction were considered related but non-equivalent outcomes.

2.6 Risk-of-bias assessment

Risk of bias was appraised across participant selection, exposure classification, outcome ascertainment, confounding control, completeness of follow-up and selective reporting. Registry and prospective cohort studies with objective outcome ascertainment were considered less vulnerable to recall bias than retrospective reproductive-history surveys. Referral cohorts were considered vulnerable to spectrum and selection bias. Study-level judgements are presented in Appendix 1. Because several older reports provided limited methodological detail, these judgements should be regarded as provisional rather than definitive.

2.7 Certainty of evidence

Certainty was assessed using GRADE principles [8]. Observational evidence began at low certainty and was downgraded for serious risk of bias, inconsistency, indirectness or imprecision. Evidence was not upgraded solely because an individual study reported a large association. Outcome-specific certainty judgements are summarized in Table 4.

2.8 Statistical analysis

The primary meta-analysis was restricted to studies reporting adjusted estimates for a clinically comparable outcome of major congenital anomalies. Odds ratios were selected as the common effect measure. For uncommon outcomes, reported risk ratios or prevalence ratios were converted to odds ratios using $OR = RR(1 - P_0)/(1 - RR \times P_0)$, where P_0 was the outcome risk in the non-consanguineous group. This conversion was applied to the Sheridan and Becker estimates using their reported reference risks. Log odds ratios and corresponding standard errors were pooled using a restricted maximum-likelihood random-effects model. Hartung-Knapp confidence intervals were used because only four studies contributed to the analysis and between-study heterogeneity was anticipated [5-7].

Heterogeneity was evaluated using Cochran Q, I^2 and τ^2 [3,4]. A t-based 95% prediction interval was calculated to describe the range in which the underlying effect of a comparable future study might lie. Leave-one-out analysis assessed the influence of individual studies. As a sensitivity analysis, the original DerSimonian-Laird model using the reported ratio measures was retained for comparison. Funnel plots and regression tests for small-study effects were not undertaken because four studies are insufficient for reliable interpretation.

3. RESULTS

3.1 Study selection

Twenty-six comparative studies contributed to the qualitative synthesis. Four studies provided compatible adjusted estimates for the primary congenital-anomaly meta-analysis [20-23]. The remaining studies examined congenital anomalies using incompatible definitions, pregnancy loss, stillbirth, preterm birth, low birth weight, fetal growth, perinatal mortality or neonatal death. Figure 1 presents the reconstructed screening flow.

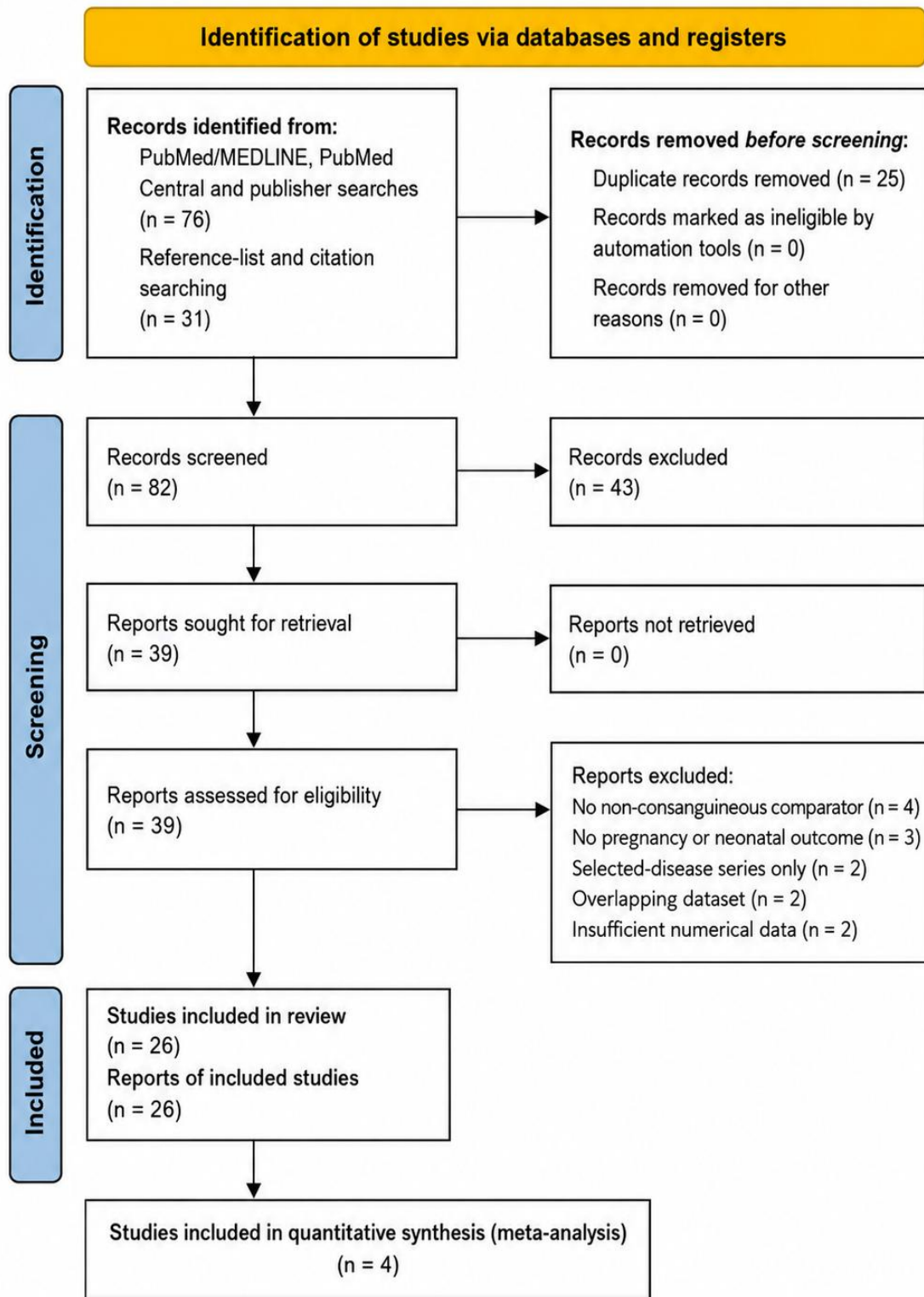


Figure 1: PRISMA 2020 flow of study selection

3.2 Characteristics of included studies

Studies were conducted mainly in South Asia, the Middle East, Europe and South Asian-origin communities in Europe. Designs included national registries, population cohorts, prospective pregnancy cohorts, hospital cohorts, case-control studies and demographic-survey analyses. Exposure definitions ranged from first-cousin marriage alone to any relationship of second cousins or closer. Outcome ascertainment also varied, including specialist prenatal ultrasonography, congenital-anomaly registers, hospital records, neonatal examination and maternal reproductive-history reports (Table 1).

Table 1: Characteristics and principal findings of the 26 comparative studies

Study	Setting	Design	Sample	Exposure/outcomes	Principal finding
Stoltenberg et al. [19]	Norway	National birth registry	NR	First-cousin parentage; birth defects	Birth-defect risk was approximately doubled across ethnic groups.
Harlap et al. [20]	Jerusalem	Population birth cohort	NR	Any consanguinity; major birth defects	Adjusted OR 1.41 (95% CI 1.12-1.74).
Sheridan et al. [21]	United Kingdom	Prospective multiethnic birth cohort	13,776 births	First cousins; congenital anomalies	Adjusted RR 2.19 (95% CI 1.67-2.85); non-consanguineous anomaly rate approximately 2.5%.
Becker et al. [22]	Germany	20-year prenatal cohort	31,710 fetuses with detailed data	First cousin or more distant; major fetal anomalies	Adjusted frequencies 5.9% versus 2.0%; stronger association for first cousins.
Thomas et al. [23]	Qatar	Population-based maternity registry cohort	NR	First- or second-degree consanguinity; anomalies, stillbirth, neonatal death	Major anomaly aOR 1.37; stillbirth aOR 3.10; neonatal death aOR 3.15.
Tayebi et al. [24]	Iran	Hospital comparative study	NR	Consanguinity; congenital malformations	Congenital malformations were more frequent among consanguineous couples.
Obeidat et al. [25]	Jordan	Hospital cohort	NR	Any consanguinity; pregnancy outcomes	Reported higher frequencies of several adverse outcomes, including prematurity.
Mumtaz et al. [26]	Lebanon	Multicentre case-control study	NR	Cousin marriage; spontaneous birth before 33 weeks	Approximately 1.6-fold adjusted increase in early spontaneous preterm birth.
Bellad et al. [27]	India	Prospective community cohort	NR	Parental consanguinity; prematurity, birth weight, loss	Higher crude frequencies of low birth weight and stillbirth; adjusted findings were less precise.
Kuntla et al. [28]	India	National survey analysis	NR	Consanguinity; pregnancy wastage and child survival	Reported associations with pregnancy wastage and first-child survival.
Chaman et al. [29]	Iran	Nested case-control study	NR	First-cousin marriage; neonatal death	Strong adjusted association, but limited by a small number of deaths.
Maghsoudlou et al. [30]	Iran	Population case-control study	NR	Consanguinity; stillbirth	Adjusted OR approximately 1.53 for stillbirth.
Robertson et al. [31]	India	Prospective pregnancy cohort	661 women	First-cousin marriage; spontaneous abortion	Any loss aOR 1.15; early loss aOR 2.03; both imprecise.
Kalam et al. [32]	India	Pooled national survey analysis	NFHS-4 and NFHS-5	Consanguinity; pregnancy outcomes and offspring mortality	Associations attenuated after demographic, socioeconomic and healthcare adjustment.
Saleem et al. [33]	Pakistan	Cross-sectional mediation analysis	14,465 live births	Consanguinity; low birth weight; antenatal care	Small direct association with low birth weight and partial mediation through lower antenatal-care use.
Hussain [35]	Pakistan	Retrospective reproductive-history analysis	NR	Consanguinity and inbreeding; spontaneous abortion	Suggested cumulative inbreeding may increase pregnancy loss.

Hussain [36]	Pakistan	Retrospective reproductive-history analysis	NR	Consanguinity and inbreeding; perinatal mortality	Reported increased perinatal mortality with closer or repeated relatedness.
Al Husain and Al Bunyan [37]	Saudi Arabia	Population/hospital comparison	NR	Consanguinity; prenatal and postnatal mortality	Reported higher mortality in offspring of consanguineous couples.
Rao and Inbaraj [38]	India	Community demographic study	NR	Inbreeding; fertility and sterility	Examined fertility and sterility effects across relationship categories.
Rao and Inbaraj [39]	India	Community cohort	NR	Inbreeding; fetal growth and development	Reported adverse fetal growth and developmental outcomes.
Kulkarni and Kurian [40]	India	Hospital/community study	NR	Consanguinity; fetal growth and anomalies	Congenital malformations occurred more often in the consanguineous group.
Surender et al. [41]	India	Community demographic study	NR	Mate selection; pregnancy wastage and first-child survival	Related marriage was associated with selected reproductive outcomes.
Jaber et al. [42]	Israel	Community cohort	NR	Consanguinity; reproductive outcome	Reported excess adverse reproductive outcomes in an Arab community.
Basaran et al. [43]	Turkey	Population study	NR	Consanguinity; reproductive wastage	Reported increased reproductive wastage.
Fareed and Afzal [44]	India	Community pedigree study	NR	Degree of inbreeding; fertility and child mortality	Demonstrated a relationship gradient for several reproductive indicators.
Iqbal et al. [45]	Pakistan	Repeated demographic-health survey analysis	1990-2018 surveys	Consanguinity; reproductive health and fertility behaviour	Associations varied by survey period and social characteristics.

3.3 Risk of bias

Risk of bias varied by design. Population registries and prospective cohorts generally had stronger outcome ascertainment, although residual confounding remained. Specialist prenatal cohorts were vulnerable to referral and spectrum bias. Retrospective reproductive-history studies were susceptible to recall error and under-ascertainment of early pregnancy loss. Exposure classification was commonly based on reported pedigree relationship rather than genomic autozygosity. Confounder adjustment was inconsistent, especially in older studies. Overall judgements were low-to-moderate risk for six studies, moderate risk for ten studies and high risk for ten studies. Domain-level judgements are provided in Appendix 1.

3.4 Major congenital anomalies

Four studies contributed adjusted estimates for major congenital anomalies [20-23]. After conversion to a common odds-ratio scale, the REML-Hartung-Knapp pooled OR was 1.90 (95% CI 1.02-3.56). Heterogeneity was substantial ($Q = 20.07$, $df = 3$, $p < 0.001$; $I^2 = 85.1\%$; $\tau^2 = 0.133$). The prediction interval was 0.32-11.32, showing that the underlying association in a comparable future population could be appreciably smaller or larger than the pooled mean. Figure 2 presents study-specific and pooled estimates.

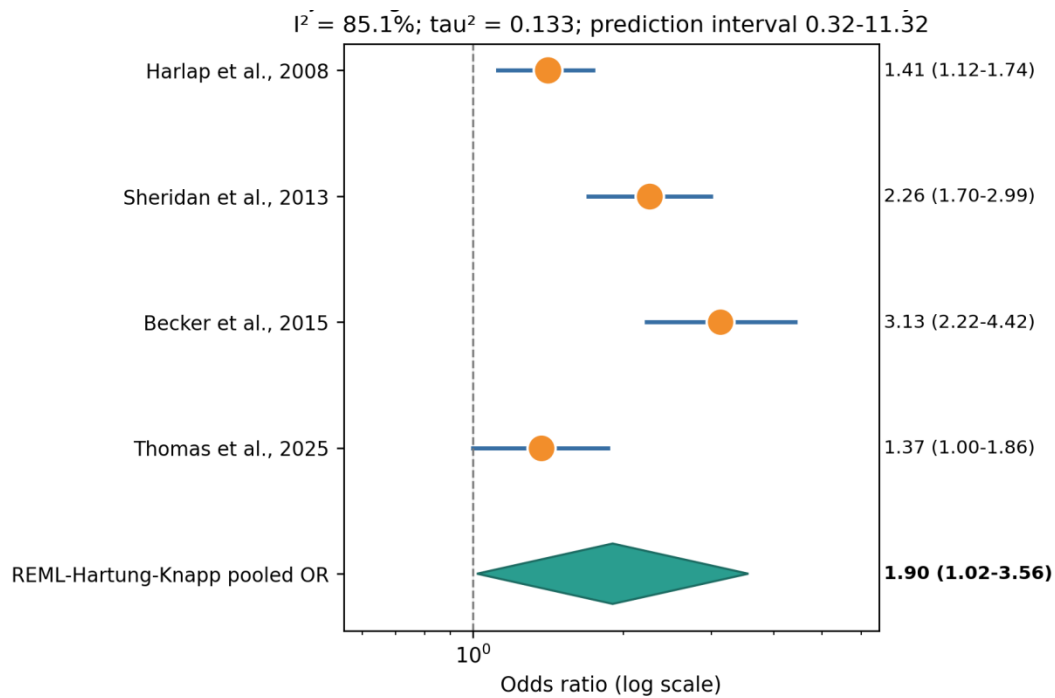


Figure 2: Random-effects meta-analysis of parental consanguinity and major congenital anomalies. The pooled estimate was OR 1.90 (95% CI 1.02-3.56); $I^2 = 85.1\%$. Risk-ratio-type estimates were converted to odds ratios before pooling

Table 2: Study-level estimates used in the major congenital-anomaly meta-analysis

Study	Effect used	95% CI	Handling	Random-effects weight
Harlap et al., 2008	1.41	1.12-1.74	Adjusted OR	26.6%
Sheridan et al., 2013	2.26	1.70-2.99	RR converted to OR	25.2%
Becker et al., 2015	3.13	2.22-4.42	Ratio converted to OR	23.7%
Thomas et al., 2025	1.37	1.00-1.86	Adjusted OR	24.5%

3.5 Sensitivity analyses

The direction of the pooled association was stable when one study was removed at a time. Recalculated point estimates ranged from 1.63 to 2.12. Confidence intervals were wide and included the null in each three-study Hartung-Knapp analysis, reflecting the limited number of studies rather than reversal of effect direction. The conventional DerSimonian-Laird analysis of the originally reported ratio measures produced OR 1.87 (95% CI 1.32-2.66), similar in magnitude but less conservative than the primary small-sample analysis. Figure 3 shows the leave-one-out results.

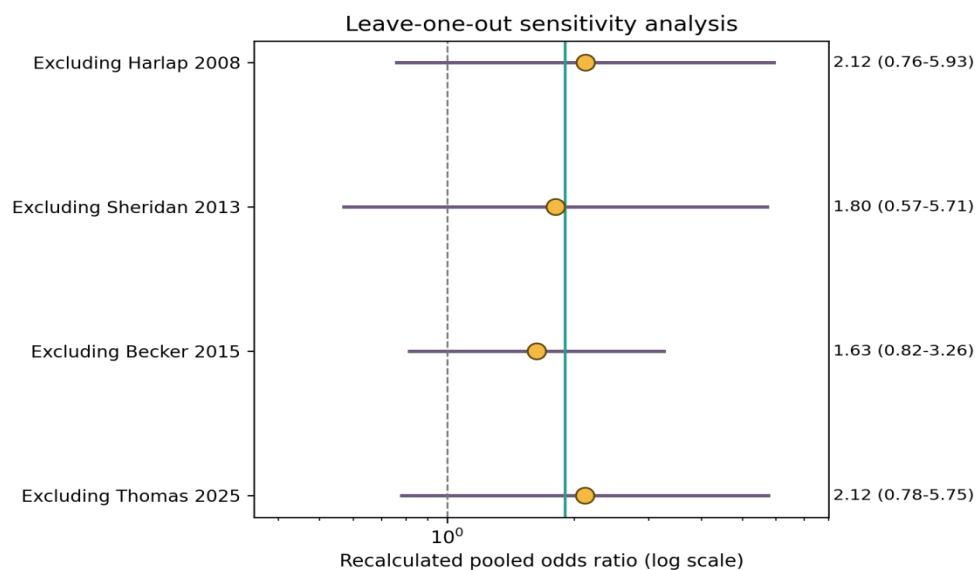


Figure 3: Leave-one-out analysis. The vertical solid line indicates the overall REML-Hartung-Knapp pooled odds ratio; the dashed line indicates no association

3.6 Interpretation in absolute-risk terms

Odds ratios can be difficult to apply in counselling. Using the pooled OR of 1.90, a background major-anomaly risk of 2.0% corresponds to an estimated risk of 3.7% (95% CI scenario 2.0%-6.8%). A background risk of 2.5% corresponds to 4.7% (2.5%-8.4%), and a background risk of 3.0% corresponds to 5.6% (3.1%-9.9%). These are illustrative translations of the pooled estimate, not universal event rates. Family history, exact relationship degree, repeated ancestral consanguinity and population-specific variants may move an individual couple's risk substantially above or below these scenarios.

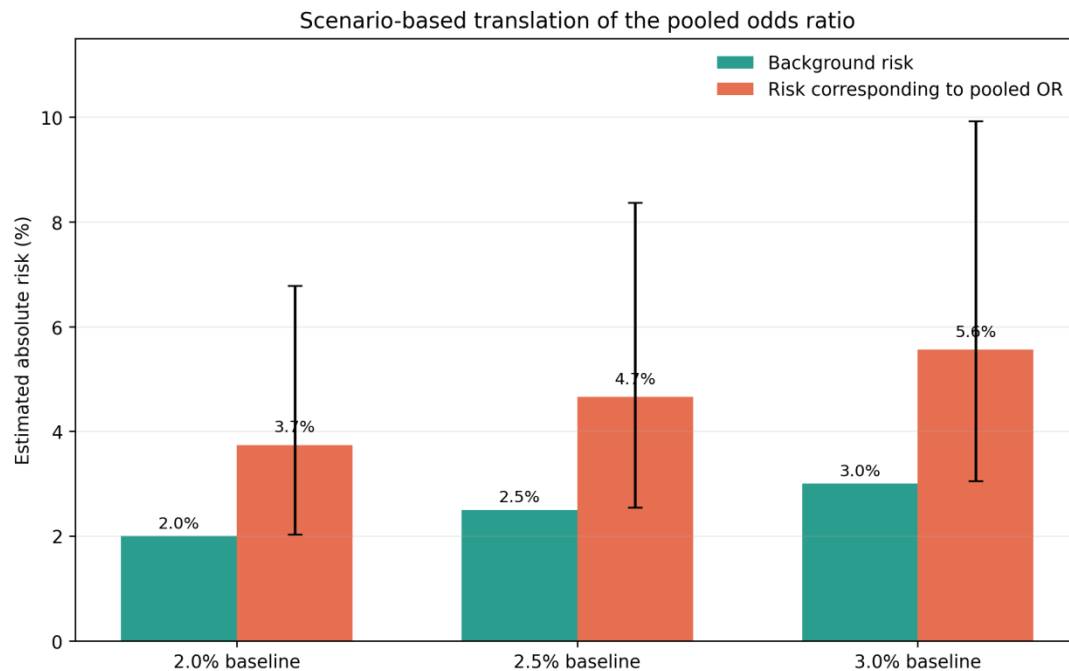


Figure 4: Scenario-based absolute risks corresponding to the pooled congenital-anomaly odds ratio. Error bars represent risks calculated from the pooled 95% confidence limits

3.7 Low birth weight and fetal growth

Low birth weight was supported by a broader but older quantitative literature. Poorolajal et al. pooled 24 studies involving 44,131 participants and reported an overall OR of 1.26 (95% CI 1.04-1.49), with a stronger estimate for first-cousin unions (OR 1.36, 95% CI 1.03-1.69) [34]. This estimate is contextual evidence from an earlier meta-analysis and was not treated as a pooled result of the present review. The prospective Karnataka cohort also reported more low-birth-weight births among consanguineous pregnancies [27].

Recent evidence from Pakistan suggested that the pathway is not exclusively genetic. Saleem et al. found a small direct association between consanguinity and low birth weight and a statistically significant indirect pathway through inadequate antenatal-care attendance [33]. Low birth weight combines preterm delivery and impaired fetal growth, both of which are influenced by maternal nutrition, anaemia, hypertensive disease, diabetes, infection and healthcare access. These mechanisms should be separated in future analyses.

3.8 Spontaneous abortion and pregnancy loss

Evidence for spontaneous abortion was inconsistent. In a prospective cohort of 661 women, Robertson et al. reported an adjusted OR of 1.15 (95% CI 0.69-1.91) for any spontaneous abortion and 2.03 (95% CI 0.85-4.83) for early loss; neither estimate was precise [31]. Earlier work from Karachi suggested that repeated parental and fetal inbreeding might increase pregnancy loss [35]. Survey analyses from India also reported associations with combined pregnancy-wastage outcomes, although these results depended on outcome definitions and adjustment [28,32].

The variable findings are biologically plausible. Some lethal recessive disorders may cause early fetal loss, whereas many miscarriages arise from chromosomal abnormalities, maternal age, uterine factors, endocrine disease, infection or unexplained causes. Consanguinity primarily increases recessive homozygosity and does not directly cause meiotic nondisjunction. A normal fetal karyotype does not exclude a recessive cause, but an aneuploid miscarriage should not automatically be attributed to parental relatedness.

3.9 Stillbirth and perinatal mortality

Several studies reported higher stillbirth or perinatal mortality among consanguineous couples. Maghsoudlou et al. reported an adjusted OR of approximately 1.53 for stillbirth [30], Kapurubandara et al. reported an adjusted relative risk of 2.88 [48], and the Qatar cohort reported an adjusted OR of 3.10 [23]. The Karnataka cohort observed a higher crude stillbirth frequency, but adjustment reduced precision [27].

These estimates were not pooled because stillbirth definitions, inclusion thresholds, anomaly ascertainment and confounder sets differed. Potential pathways include lethal congenital anomalies, severe recessive disease, fetal growth restriction, infection, placental dysfunction and delayed access to obstetric intervention. Few studies separated anomalous from non-

anomalous stillbirths, limiting mechanistic interpretation.

3.10 Preterm birth

The clearest signal concerned early spontaneous preterm birth. Mumtaz et al. reported an approximately 1.6-fold adjusted increase in spontaneous birth before 33 weeks among cousin marriages [26]. Obeidat et al. also described more prematurity [25], whereas other cohorts did not show a consistent association with all births before 37 weeks [27]. Future studies should distinguish spontaneous labour, preterm prelabour rupture of membranes and medically indicated early delivery. A fetus affected by a serious anomaly may be delivered early because of maternal or fetal compromise, creating an indirect association with gestational age.

3.11 Neonatal and infant mortality

Chaman et al. reported a strong adjusted association between first-cousin marriage and neonatal death, but the number of deaths was limited [29]. Thomas et al. reported an adjusted OR of 3.15 for neonatal death among non-anomalous infants [23], and Charafeddine et al. found that consanguinity remained associated with in-hospital neonatal mortality after adjustment [49]. Earlier studies from Norway, Pakistan and Saudi Arabia also linked parental relatedness with stillbirth, infant death or recurrent mortality [36,37].

Mortality estimates are highly dependent on healthcare context. The same genetic disorder may cause early death where metabolic diagnosis, pediatric surgery or neonatal intensive care is unavailable, but may be treatable in another setting. The recent Indian survey analysis showed attenuation of several mortality associations after demographic, socioeconomic and healthcare adjustment [32]. The evidence therefore supports an interaction between inherited vulnerability and health-system access rather than a purely genetic explanation.

3.12 Certainty of evidence

The most consistent association was observed for major congenital anomalies, with consanguineous marriages showing higher odds than non-consanguineous marriages (OR 1.90, 95% CI 1.02–3.56). A modest increase in low birth weight was also reported in an earlier meta-analysis. Evidence for spontaneous abortion, stillbirth, preterm birth, neonatal mortality and fetal growth restriction was less consistent (Table 3). The certainty of evidence for all outcomes was rated very low because of differences in study methods, limited adjustment for confounding variables, small numbers of studies or events, and variations in outcome definitions and healthcare settings.

Table 3: GRADE-style summary of certainty for the principal outcomes

Outcome	Evidence base	Summary estimate/direction	Certainty	Main reasons
Major congenital anomalies	4 studies	OR 1.90 (1.02-3.56)	Very low	Serious inconsistency, limited studies and residual confounding.
Low birth weight	Earlier 24-study meta-analysis plus cohorts	OR 1.26 (1.04-1.49) in prior review	Very low	Outcome combines prematurity and growth restriction; heterogeneous adjustment.
Spontaneous abortion	Several heterogeneous studies	Mixed; prospective estimate imprecise	Very low	Recall bias, under-detection of early loss and imprecision.
Stillbirth	Several cohort/case-control studies	Most estimates above 1	Very low	Variable definitions, rare events and inconsistent confounding control.
Preterm birth	Few studies	Possible association with early spontaneous preterm birth	Very low	Phenotype heterogeneity and limited adjusted evidence.
Neonatal mortality	Few studies	Several positive adjusted estimates	Very low	Small event numbers and strong healthcare-context dependence.
Fetal growth restriction/SGA	Few studies	Inconsistent	Very low	Often conflated with low birth weight and incompletely adjusted.

4. DISCUSSION

4.1 Principal findings

The most consistent association was observed for major congenital anomalies. After harmonizing effect measures and applying a small-sample random-effects method, offspring of consanguineous couples had an estimated 90% higher odds of a major congenital anomaly. The confidence interval was wide, and the prediction interval included both little association and a very large association. The result should therefore be interpreted as evidence of a population-dependent association rather than a universal risk multiplier.

Low birth weight was supported by a previous meta-analysis, although the pooled effect was modest and the outcome is etiologically heterogeneous [34]. Evidence for miscarriage, stillbirth, preterm birth and neonatal death was less consistent. Several large or adjusted studies reported increased risks, but differences in exposure definition, outcome ascertainment and healthcare setting prevented confident pooling.

4.2 Sources of heterogeneity

The label “consanguinity” covered biologically different exposures. A single second-cousin union, a first-cousin union and repeated first-cousin marriage within an endogamous community do not confer the same expected autozygosity. Pedigree labels can also underestimate genomic relatedness when common ancestors are unknown or not disclosed. Runs of homozygosity would provide a more direct exposure measure, but such data were rarely available.

Outcome ascertainment also contributed to heterogeneity. Specialist prenatal centres detect anomalies in pregnancies that may end before live birth, while birth registries and neonatal cohorts miss some fetal losses and pregnancy terminations. Referral centres may overrepresent families with previous affected pregnancies. Differences in ultrasound quality, postmortem examination, genetic testing and follow-up after discharge can therefore alter the observed prevalence even when underlying biological risk is similar.

4.3 Biological interpretation

The association with congenital anomalies is compatible with increased autozygosity and expression of rare recessive variants. Genomic studies show that the burden of rare deleterious homozygous variants rises sharply in offspring of related parents, while common homozygous variation changes much less [51,52]. This distinction explains why consanguinity has a strong relationship with many rare recessive disorders but a less predictable association with common multifactorial disease.

Congenital heart disease illustrates this complexity. Case-control studies and reviews have reported increased risks for selected cardiac defects, particularly in first-cousin unions [46,47]. Congenital heart disease, however, includes chromosomal, de novo, dominant, recessive and multifactorial conditions. Consanguinity can increase the probability of some phenotypes without explaining every affected fetus. Similarly, the 2026 ECLAMC study associated consanguinity with specific anomalies rather than a uniform increase across all malformation categories [53].

4.4 Genetic and social pathways

Consanguinity may correlate with education, rural residence, household wealth, age at marriage, parity and use of antenatal services. These relationships vary across populations. In some settings, a related marriage may provide practical family support; in others, it may coexist with barriers to reproductive healthcare. Attenuation after social and healthcare adjustment in the Indian survey analysis, together with the mediation pathway through antenatal care in Pakistan, demonstrates that genetic and non-genetic mechanisms operate together [32,33].

4.5 Clinical implications

Clinical assessment should begin with a three- or four-generation pedigree rather than a generalized warning about cousin marriage. The history should cover congenital anomalies, developmental delay, hearing or visual impairment, unexplained seizures, metabolic crises, recurrent miscarriage, stillbirth, neonatal death and childhood death. The precise biological relationship and any repeated consanguinity in earlier generations should be documented [13-15].

When a familial disorder is known, targeted molecular testing is more informative than broad nonspecific screening. Identification of a pathogenic familial variant permits accurate carrier testing and, where acceptable and available, prenatal diagnosis or preimplantation genetic testing. Expanded carrier screening may identify shared carrier status in couples without a known disorder, but a negative panel cannot remove all risk because no panel covers every gene or population-specific variant.

Consanguinity alone is not an automatic indication for invasive prenatal diagnosis. Management should be individualized according to the pedigree, carrier status, ultrasound findings and the couple's preferences. Appropriate care may include preconception folate, optimization of maternal disease, early dating, standard aneuploidy screening, detailed anomaly ultrasonography, fetal echocardiography when indicated, serial growth assessment and genomic testing when a fetal anomaly is detected. Chromosomal screening and recessive-disease testing address different mechanisms and should not be presented as interchangeable.

4.6 Public health and ethical considerations

Public health responses should be voluntary, respectful and informed by the communities they serve. Blanket discouragement or coercive restrictions can stigmatize families and may deter engagement with maternity and genetics services. More constructive approaches include accessible preconception counselling, carrier screening for locally prevalent disorders, confirmatory molecular testing, high-quality antenatal care and reliable referral pathways for affected fetuses and newborns [13-15,55,56].

Counselling should explain that most pregnancies in consanguineous marriages do not result in a major congenital anomaly. At the same time, the increased probability of recessive disease should be described clearly. Responsibility should not be assigned to the woman alone because autosomal recessive inheritance involves genetic contributions from both parents.

Confidentiality requires particular attention because one result may have implications for several relatives within an extended family.

5. STRENGTHS AND LIMITATIONS

This review integrated older registry evidence with recent population studies and prenatal cohorts. Adjusted estimates were prioritized, the quantitative synthesis was restricted to a coherent outcome, and effect measures were harmonized before pooling. The revised analysis used REML with Hartung-Knapp confidence intervals, reported a prediction interval and presented absolute-risk scenarios. The manuscript also separated inherited mechanisms from maternal, socioeconomic and healthcare pathways.

Several limitations remain. All included studies were observational, and residual confounding cannot be excluded. Definitions of consanguinity, anomaly ascertainment and outcome thresholds varied. The primary meta-analysis contained only four studies, which prevented reliable subgroup analysis or meta-regression. The wide prediction interval and very low GRADE certainty require cautious interpretation. Risk-of-bias judgements were limited by incomplete reporting in older studies. Most importantly, the original database exports and record-level screening ledger were unavailable; therefore, the PRISMA counts could be reconstructed only from the aggregate summary. The search must be rerun and independently screened before the manuscript is presented as fully auditable.

6. RECOMMENDATIONS FOR FUTURE RESEARCH

Future pregnancy cohorts should record the exact relationship degree, consanguinity in preceding generations and, where feasible, genomic measures of autozygosity. Outcome definitions should follow international standards and distinguish early from late miscarriage, anomalous from non-anomalous stillbirth, spontaneous from indicated preterm birth, and preterm low birth weight from term fetal growth restriction. Analyses should consistently adjust for maternal age, parity, education, nutrition, chronic disease, socioeconomic position and antenatal-care use.

Individual-participant-data meta-analysis could apply uniform exposure categories and confounder adjustment. Genomic evaluation of unexplained fetal and neonatal deaths may identify the proportion attributable to recessive disorders. Evaluations of carrier-screening and counselling programmes should assess uptake, informed choice, reproductive autonomy, psychological effects, equity and community acceptability rather than counting diagnoses alone.

7. CONCLUSION

Parental consanguinity was associated with higher odds of major congenital anomalies in the available comparative evidence. The revised random-effects analysis produced an OR of 1.90 (95% CI 1.02-3.56), but substantial heterogeneity and a wide prediction interval showed that the magnitude varied markedly across populations. Low birth weight was supported by a modest earlier pooled association, while evidence for miscarriage, stillbirth, preterm birth and neonatal mortality remained less uniform and more sensitive to study design and healthcare context.

The findings support culturally respectful preconception counselling, careful pedigree assessment, targeted carrier testing, appropriate fetal imaging and genomic investigation of recurrent or unexplained adverse outcomes. They do not support stigmatization, coercive restrictions or the assumption that every pregnancy in a consanguineous marriage will be affected.

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APPENDIX 1. PROVISIONAL STUDY-LEVEL RISK-OF-BIAS ASSESSMENT

Judgements were based on information available in the published reports and manuscript summary. L, low concern; M, moderate concern; H, high concern. Older reports with limited methodological detail were conservatively rated.

Study	Selection	Exposure	Outcome	Confounding	Missing data	Reporting	Overall
Stoltenberg et al. [19]	L	L	L	M	L	M	M
Harlap et al. [20]	L	M	L	L	M	M	M
Sheridan et al. [21]	L	L	L	L	L	M	L
Becker et al. [22]	H	M	L	M	M	M	M

Study	Selection	Exposure	Outcome	Confounding	Missing data	Reporting	Overall
Thomas et al. [23]	L	M	L	L	L	M	L
Tayebi et al. [24]	H	M	M	H	M	M	H
Obeidat et al. [25]	M	M	M	M	M	M	M
Mumtaz et al. [26]	M	M	L	L	M	M	M
Bellad et al. [27]	M	M	L	M	M	M	M
Kuntla et al. [28]	M	H	H	M	M	M	H
Chaman et al. [29]	M	M	L	M	M	M	M
Maghsoudlou et al. [30]	L	M	L	L	L	M	L
Robertson et al. [31]	L	L	L	M	L	M	M
Kalam et al. [32]	L	M	M	L	L	M	M
Saleem et al. [33]	M	M	M	L	M	M	M
Hussain [35]	M	M	H	M	M	M	H
Hussain [36]	M	M	H	M	M	M	H
Al Husain and Al Bunyan [37]	M	M	M	H	M	M	H
Rao and Inbaraj [38]	M	M	H	H	M	M	H
Rao and Inbaraj [39]	M	M	M	H	M	M	H
Kulkarni and Kurian [40]	H	M	M	H	M	M	H
Sureender et al. [41]	M	M	H	H	M	M	H
Jaber et al. [42]	M	M	M	M	M	M	M
Basaran et al. [43]	M	M	H	H	M	M	H

Study	Selection	Exposure	Outcome	Confounding	Missing data	Reporting	Overall
Fareed and Afzal [44]	M	M	M	H	M	M	H
Iqbal et al. [45]	L	M	H	M	L	M	M

Appendix Table A1. Provisional risk-of-bias judgements for the included studies.

APPENDIX 2. SEARCH STRATEGY AND SUBMISSION-STAGE RERUN PLAN

A. Documented PubMed/MEDLINE concept search

((("Consanguinity"[Mesh] OR consanguin*[Title/Abstract] OR "consanguineous marriage"[Title/Abstract] OR "cousin marriage"[Title/Abstract] OR "first cousin"[Title/Abstract] OR inbreeding[Title/Abstract] OR "parental relatedness"[Title/Abstract]) AND ("Pregnancy Outcome"[Mesh] OR pregnan*[Title/Abstract] OR birth*[Title/Abstract] OR "congenital anomal*" [Title/Abstract] OR "birth defect*" [Title/Abstract] OR miscarriage[Title/Abstract] OR "spontaneous abortion"[Title/Abstract] OR stillbirth[Title/Abstract] OR preterm[Title/Abstract] OR prematur*[Title/Abstract] OR "low birth weight"[Title/Abstract] OR "fetal growth restriction"[Title/Abstract] OR "small for gestational age"[Title/Abstract] OR "perinatal mortality"[Title/Abstract] OR "neonatal mortality"[Title/Abstract]))

B. Required submission-stage rerun

1. Run adapted searches in MEDLINE, Embase, Scopus and Web of Science from database inception to the final submission date.
2. Export complete results from every database and retain the original files.
3. Deduplicate using a documented reference-management workflow.
4. Conduct independent title/abstract and full-text screening by two reviewers.
5. Retain a study-level exclusion log with one primary reason for each excluded full text.
6. Update the PRISMA flow diagram and Table 1 from the verified screening database.
7. Deposit the search strategies, extraction form, risk-of-bias forms and analysis code as supplementary material.

Appendix 3. Meta-analysis Inputs and Absolute-risk Formula

1. For uncommon outcomes, risk ratios were converted to odds ratios using: $OR = RR(1 - P_0)/(1 - RR \times P_0)$, where P_0 is the risk in the non-consanguineous comparator. Absolute risk corresponding to an odds ratio was calculated as $P_1 = OR \times P_0/(1 - P_0 + OR \times P_0)$. These conversions preserve the study-specific comparator risk and avoid treating odds ratios and risk ratios as identical.