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Prevalence and risk factors for congenital diaphragmatic hernia: A global view

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ABSTRACT

Purpose: To determine the global prevalence for congenital diaphragmatic hernia (CDH) and identify CDH-related risk factors.
Methods: Using a defined strategy, a systematic review of the literature was conducted according to PRISMA guidelines, searching for population-based epidemiological studies to evaluate the prevalence of CDH globally and per country. Studies containing overlapping populations or timeframes were excluded. CDH-related risk factors were calculated by meta-analysis using RevMan5.3 and expressed as risk ratio and 95% confidence interval.
Results: *Prevalence:* Of 8230 abstracts screened, 30 full-text articles published between 1980 and 2019 were included. The overall prevalence of CDH was 2.3 in 10,000 births (16,710 CDH babies in 73,663,758 livebirths). *Risk factors:* From 9 studies we found that male sex [RR 1.38 (1.05–1.80), p = 0.02] and maternal age >35 years [RR 1.69 (1.26–2.25), p = 0.0004] were associated with CDH. Conversely, maternal black ethnicity resulted as a protective factor [RR 0.82 (0.77–0.89, p<0.00001].
Conclusion: This study reveals that there is a worldwide paucity of population-based studies, and those studies that report on prevalence and risk factors come from a small number of countries. The prevalence of CDH varies within and across geographical world regions. The main risk factors for CDH identified are male sex and older maternal age. More epidemiological studies, involving more world regions, are needed to identify possible strategies to help strengthen our understanding of the risk factors, provide clinicians with the tools necessary for prenatal and postnatal counseling, and inform policy makers on how to strategize CDH care in different parts of the world.
Type of study: Systematic review and meta-analysis.
Level of evidence: Level III.

Contents

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Table 1
Inclusion criteria of the systematic review.

Publication	
Language	English
Time period	1990–2019
Subject	Human studies
Study type	Retrospective
	Prospective
	Case–control
	Cohort
Excluded	Case-report
	Editorials
	Letters
	Grey literature
Keywords	Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) is a severe malformation characterized by a defect in the diaphragm that results in the herniation of the intraabdominal organs into the thoracic cavity during development. CDH is typically associated with pulmonary hypoplasia and vascular remodeling that leads to pulmonary hypertension, and in some cases with other congenital defects, such as congenital heart defects [1]. As a result, the mortality of babies born with CDH remains high and survivors may suffer from long-term morbidities, including persistent pulmonary hypertension, gastroesophageal reflux, and neurodevelopmental impairment [2,3]. The economic burden of CDH is also high, with an estimated upwards cost for CDH repair in the United States of America at $156,500 per patient, and in Canada at $244,734 per patient [4,5]. The projected economic burden for all USA CDH patients was reported to exceed $250 million/year [4].

The epidemiology of CDH remains partly unknown. The prevalence of this condition has been reported to range between 0.7 and 15.9 in 10,000 births, depending on the geographical area and the period examined [6,7]. However, despite the vast literature that has been produced on CDH over the last five decades, there are few population-based studies that have investigated the different aspects of CDH epidemiology. Epidemiological studies such as these are important for the field, as they will aid in family counseling and treatment of patients with CDH. Similarly, the etiology of CDH remains unknown. Although there is evidence that supports a genetic contribution to the etiology of CDH, only a small proportion of patients with CDH usually has a genetic or chromosomal abnormality.

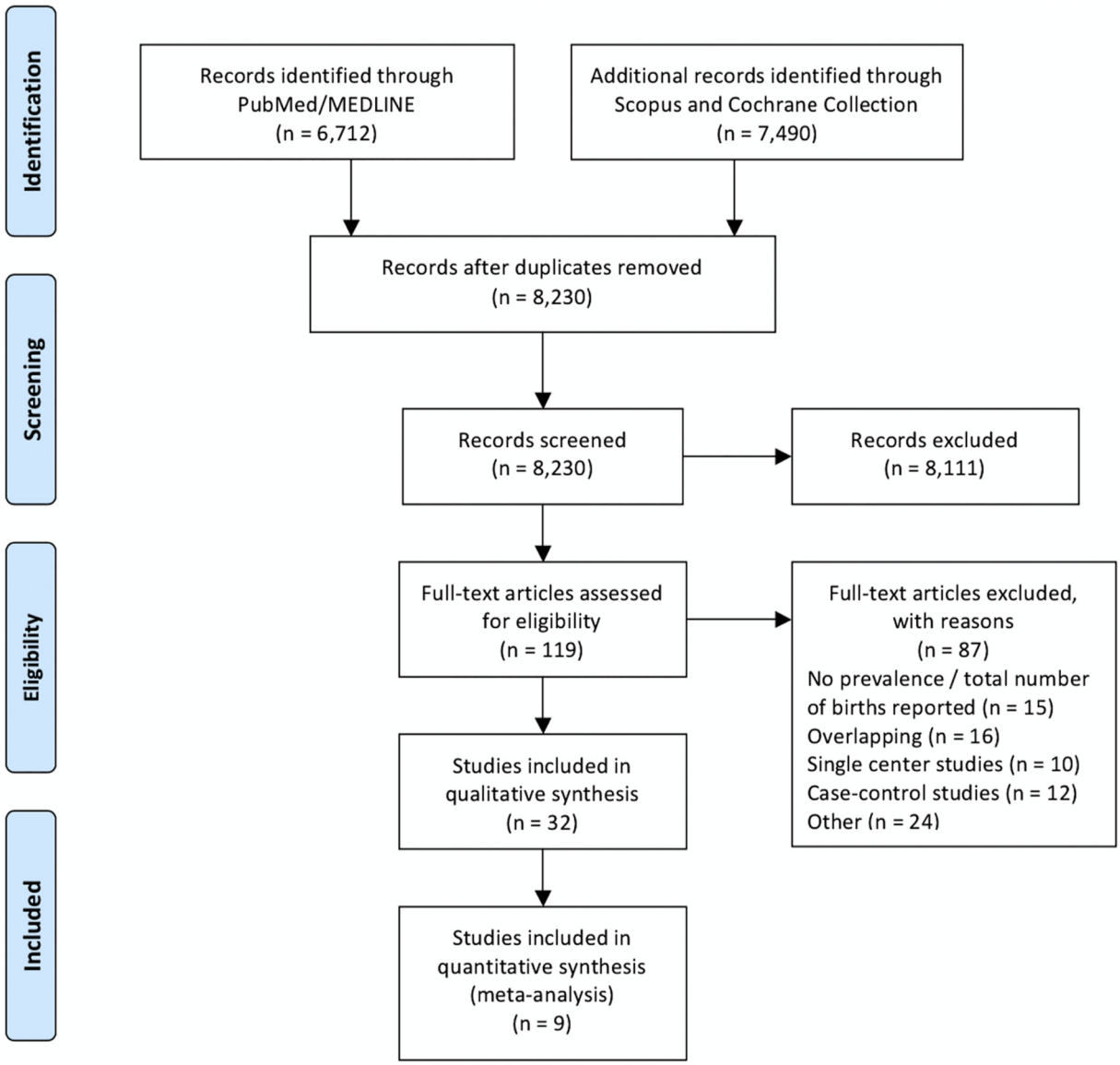

Fig. 1. PRISMA flowchart of searched results.

On the one hand, more than 60 loci have been associated to CDH in animal and human studies, and gene network and pathway modeling have generated a large number of candidate genes and pathways [8–10]. On the other hand, some environmental factors have been associated with the development of CDH, such as a specific season of the year, a geographical region of birth, maternal socioeconomics characteristics, maternal use of medication or smoking/alcohol, or maternal chronic disease [11–19]. However, some studies have contradicting results and the real risk factors remain unknown. To the best of our knowledge, a worldwide epidemiological study that combines information about disease prevalence and risk factors has not been done so far although it is very important.

The aim of the present study was to investigate the prevalence of CDH across the world and to identify the risk factors for CDH by examining the population-based epidemiological studies that have been published in the literature.

1. Methods

The present systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [20] and were registered on the international prospective register of systematic reviews, called PROSPERO (registration number: CRD42019130519) [21]. The systematic review was conducted, using a defined search strategy, by two investigators (MP and GR) using three electronic databases (PubMed/MEDLINE, Scopus, and Cochrane Collaboration) (Table 1). The only keyword used was "congenital diaphragmatic hernia" (Supplementary file 1). We included only population-based epidemiological studies that reported the prevalence of CDH and/or risk factors for the development of CDH. We focused only on data regarding posterolateral CDH and we did not include cases of other diaphragmatic malformations, i.e. eventration or Morgagni hernia. We excluded case-reports, editorials, letters, and all gray literature publications (i.e., reports, theses, conference proceedings, bibliographies, commercial documentations, and official documents not published commercially) (Table 1). After the selection of the potential eligible papers using the title and the abstract, three reviewers (MP, GR, and SL) independently retrieved the full-text articles to assess the final eligibility. When we identified more than one study from the same population or region over the same period, we only included the study with the larger cohort. Any disagreement over the eligibility of a specific study was resolved through the discussion with a fourth author (AZ).

1.1. Prevalence of CDH

The overall prevalence of CDH was calculated as the total number of CDH cases (including stillbirths and termination of pregnancy) over the total number of livebirths population, as described by Mason et al [22]. In some cases, the study accurately reported an overall population including livebirths, stillbirths, termination of pregnancy, and fetal losses, and we used this as the denominator to calculate the prevalence. When a study reported the prevalence and the number of CDH cases, we calculated the overall population. Furthermore, when reported, we analyzed the proportion of livebirths, stillbirths, and terminations of pregnancy.

1.2. Risk factors

Only studies that reported the prevalence of a risk factor in the CDH population and in the general population were included, and case–

Table 2
Prevalence of CDH in population-based studies.

Year	Study	Country (region)	Years	Births (*n*)	CDH (*n*)	Prevalence (in 10,000)
1990	Scott and Renwick [27]	UK (Northern England)	1987	40,603	9	2.2
1991	Philip et al [28]	France (Southern France)	1982–1988	136,161	56	4.1
1991	Wenstrom et al [29]	USA (Iowa)	1983–1988	241,473	60	2.5
1994	Yang et al [30]	USA (Maryland, Washington DC, Virginia)	1980–1987	554,761	95	1.7
1994	Steinhorn et al [31]	USA (Minnesota)	1988–1990	133,162	46	3.5
1997	Robert et al [32]	USA (California)	1983–1992	2,221,735	631	2.8
2002	Garne et al [33]	Denmark (Funen)	1980–1993	71,213	19	2.7
2003	Stege et al [34]	UK (Northern England)	1991–2001	377,551	185	4.9
2004	Tonks et al [35]	UK (West Midlands)	1995–2000	396,577	145	3.7
2004	Castilla and Orioli [36]	Central and South America (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, Paraguay, Peru, Uruguay, Venezuela)	1982–2001	3,574,609	853	2.4
2004	Bétrémieux et al [37]	France (Brittany)	1999–2003	37,500	30	8.0
2005	Rankin et al [38]	UK (Greater Glasgow, North Thames Valley, Oxford)	1991–1999	394,592	104	2.6
2005	Thong et al [39]	Malaysia (Kinta)	2000–2005	17,720	4	2.3
2006	Levison et al [40]	Australia (New South Wales, Australian Capital Territory)	1992–2001	919,182	242	2.6
2007	Gallot et al [41]	France (Central–Eastern)	1986–2003	1,835,022	501	2.7
2009	Materna-Kiryluk et al [42]	Poland (Dolnoslaskie, Kujawsko-Pomorskie, Lubuskie, Opolskie, Pomorskie, Warminsko-Mazurskie, Wielkopolskie, Zachodniopomorskie, Slaskie, Lubelskie and Podkarpackie)	1998–2002	902,452	98	1.1
2014	Balayla and Abenhaim [43]	USA	1995–2002	30,878,893	5958	1.9
2015	McGivern et al [44]	Europe (regions from Belgium, Spain, Ireland, UK, Germany, Italy, Switzerland, France, Austria, Hungary, Malta, Portugal, Denmark, Czech Republic, Ukraine, Netherlands)	1980–2009	10,686,202	2437	2.3
2016	Garcia et al [45]	Colombia (Bogota, Capital District)	2001–2013	386,419	81	2.1
2016	Grizelj et al [46]	Croatia	2001–2013	543,757	145	2.7
2017	Groisman et al [47]	Argentina	2009–2013	703,325	225	3.2
2017	Burgos and Frenckner [48]	Sweden	1987–2013	2,867,772	1000	3,5
2017	Dehdashtian et al [49]	Iran (Khuzestan)	2011–2016	548,052	60	1.1
2017	Singh and Kumar [50]	Barbados	1993–2012	63,176	9	1.4
2018	Lee et al [51]	Australia (Western)	1996–2010	576,600	215	3.7
2018	Bent et al [52]	California	2007–2012	3,213,822	705	2.2
2018	Hautala et al [53]	Finland	2002–2011	587,961	145	2,5
2019	Ebbing et al [54]	Norway	1999–2015	918,933	231	2.5
2019	Wang et al [55]	UK (England)	2003–2016	9,516,000	2379	2.5
2019	Wittekindt et al [56]	Germany (Hesse)	2010–2015	318,533	42	1.3
Total				**73,486,994**	**16,710**	**2.3**

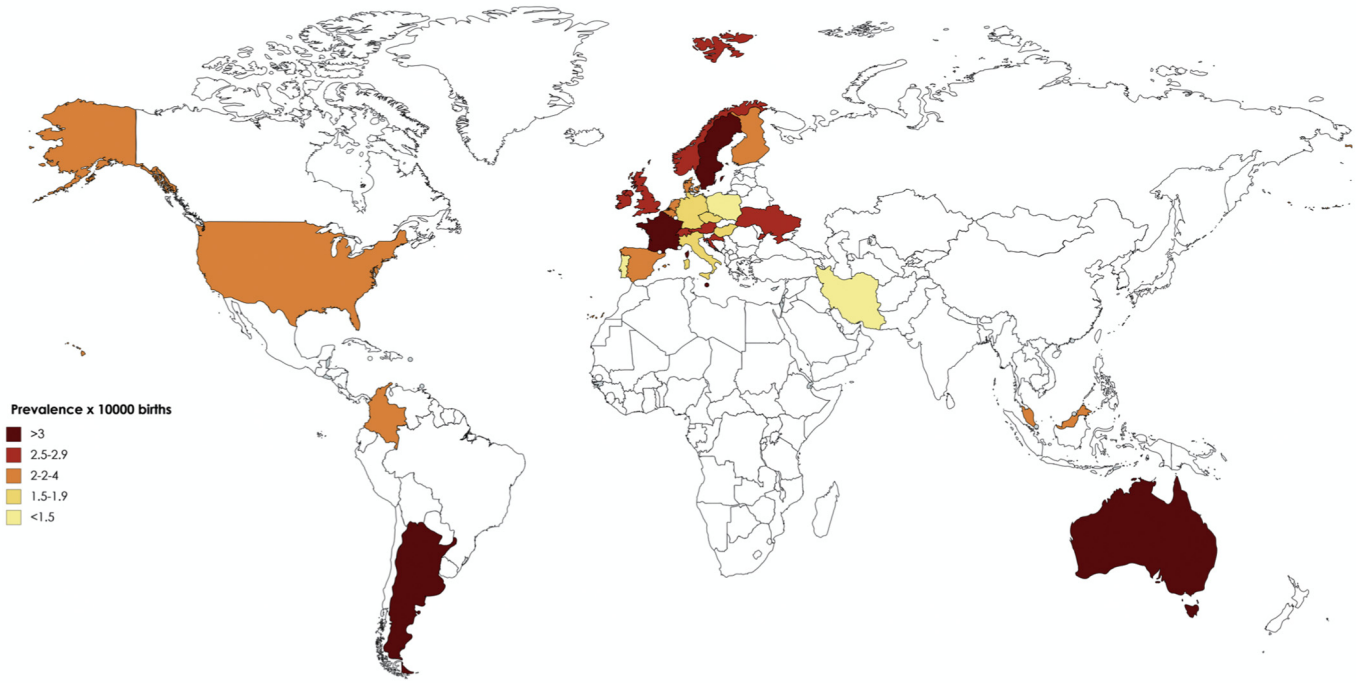

Fig. 2. Prevalence of CDH across the world.

control studies were excluded. We analyzed risk factors directly related to the CDH patient and/or their mothers.

2. Statistical analysis

The meta-analysis of comparative studies was conducted with RevMan 5.3. Data are presented as risk ratio (RR) for categorical variables, along with 95% confidence intervals (CIs), with p values shown for Z test for overall significance and I^2 statistic for heterogeneity. A p-value <0.05 was considered statistically significant.

3. Quality assessment

The risk of bias for each study was evaluated in duplicate (GR and GL) using the methodological index for nonrandomized studies (MINORS) [23]. Differences between the two reviewers (GR and GL) were resolved through consensus and discussion with a third author (AZ). The total score for this 12-item instrument ranges from 0 to 24 points with a validated "gold standard" cutoff of 19.8. Moreover, we assessed the methodological quality for each outcome by grading the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [24]. Quality of evidence was rated as high, moderate, low, and very low for each outcome. Observational studies start with a low quality of evidence. The quality of evidence was rated down in the presence of risk of bias, inconsistency, indirectness, imprecision, and publication bias. For assessment of risk of bias in observational studies, we used the MINORS instrument. Inconsistency was determined according to heterogeneity. We produced I^2 values to assess heterogeneity. As established by the GRADE guidelines, I^2 values of 0–40, 30–60, 50–90, and 75–100% were considered as low, moderate, substantial, and considerable heterogeneity, respectively [25]. In case of an I^2 score that overlapped two groups (e.g. 35), the study would be classified as having mixed heterogeneity in the GRADE table (e.g. low/moderate).

Imprecision was assessed using optimal information size (OIS), which was based on 25% relative risk reduction, 0.05 of α error and 0.20 of β error [26].

Table 3
Proportion of CDH livebirths, stillbirths, and terminations of pregnancy.

Year	Study	CDH (*n*)	Livebirths, % (*n*)	Stillbirths, % (*n*)	Terminations, % (*n*)	Country (Region)
1997	Robert et al [32]	631	95 (602)	5 (29)	–	USA (California)
2002	Garne et al [33]	19	90 (17)	5 (1)	5 (1)	Denmark (Funen)
2003	Stege et al [34]	185	70 (129)	6 (12)	24 (44)	UK (Northern England)
2004	Bétrémieux et al [37]	27	67 (18)	–	33 (9)	France (Brittany)
2006	Levison et al [40]	242	83 (200)	9 (23)	8 (19)	Australia (New South Wales, Australian Capital Territory)
2007	Gallot et al [41]	501	77 (387)	4 (18)	19 (96)	France (Central–Eastern)
2014	Balayla and Abenhaim [43]	5958	91 (5411)	9 (547)	–	USA
2016	Garcia et al [45]	81	96 (78)	4 (3)	–	Colombia (Bogota, Capital District)
2016	Grizelj et al [46]	145	97 (141)	2 (3)	1 (1)	Croatia
2017	Burgos and Frenckner [48]	1000	86 (861)	2 (17)	12 (122)	Sweden
2018	Lee et al [51]	215	63 (135)	6 (14)	31 (66)	Australia (Western)
2018	Hautala et al [53]	145	55 (80)	5 (7)	40 (58)	Finland
2019	Wang et al [55]	2379	98 (2336)	2 (43)	–	UK (England)
Total		**11,528**	**90 (10,395)**	**6 (711)**	**4 (416)**	

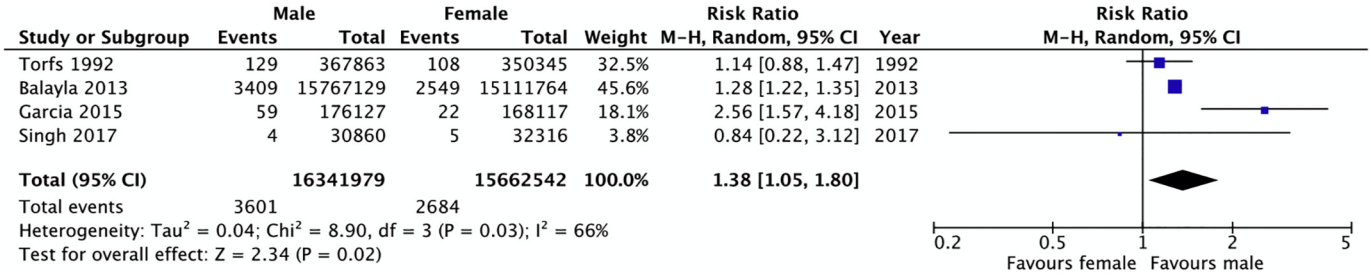

Fig. 3. Forest plot comparison of the patient sex.

4. Results

4.1. Data selection and characteristics of the studies

Of the 8230 titles and abstracts selected after the exclusion of duplicates, 119 full-text articles were examined (Fig. 1). Of these, we included 32 studies in the systematic review and used 9 comparative studies in the meta-analysis. The selected papers were published between 1990 and 2019 and evaluated a period of 36 years (1980–2016). Most studies were from Europe ($n = 16$) and USA ($n = 6$), whereas none was from Africa. Most studies were observational with retrospective analysis, and registry-based.

4.2. Prevalence

The overall prevalence of CDH was found to be 2.3 in 10,000 births (16,710 CDH cases over a total number of 73,663,758 births), as calculated from 30 population-based studies [27–56] (Table 2). The distribution of CDH studies with the relative prevalence per country is shown in Fig. 2. The breakdown of CDH cases calculated from 13 studies was 90% for livebirths, 6% for stillbirths and 4% for terminations of pregnancy (Table 3) [32–34,37,40,41,43,45,46,48,51,53,55].

4.3. Risk factors

From the 4 studies that reported the sex of babies with and without CDH [43,45,50,57], we found that CDH was more prevalent in male than female patients ($p = 0.02$, RR 1.38 [95% CI 1.05–1.80]; Fig. 3). Nine population-based studies reported that 600 patients with CDH had a proven genetic abnormality out of an overall population of 5927 CDH cases (prevalence of genetic cases of 10%) [12,29,31,32,35,44,58–60]. Within this cohort of patients, 73% were affected by a chromosomal anomaly and 27% by a genetic syndrome (Fig. 4). The analysis of studies that reported the ethnicity of mothers of babies with CDH showed that black ethnical background was less likely associated with CDH, whereas there were no differences between the other backgrounds (Fig. 5A–C) [32,43,60]. We found that young maternal age, defined as an age <20 years at the time of delivery, was not a risk factor for CDH (Fig. 6A) [42–45,50]. Conversely, a maternal age >35 years at the time of delivery was found to be significantly associated with CDH ($p = 0.0004$, RR 1.69 [95% CI 1.26–2.25]; Fig. 6B). The analysis of data from 3 studies on maternal parity showed that CDH has similar prevalence in nulliparous and multiparous women (Fig. 6C) [12,45,57]. Other risk factors for CDH that have been investigated by several authors are maternal education [12,43,61], maternal smoking [19,43,45,61–63], alcohol use during pregnancy [43,45,62,64], maternal obesity [19,45,61,65], multiple pregnancies [12,17,32,43,57,61], maternal medical conditions, such as diabetes and hypertension [19,66], and paternal factors, such as age and occupation (Table 4) [42,67,68]. Although we were unable to perform a meta-analysis for these factors as some studies had overlapping populations, some were case–control studies, and some were based on responses to questionnaires, we report this list of risk factors as it could serve as a road map for future epidemiological studies.

4.4. Quality assessment

All studies included in the meta-analysis were retrospective observational studies or analysis of databases and therefore none of them reached the gold standard cutoff on MINORS of 19.8 out of 24 (Table 5). None of the papers provided sample size calculations, none of the studies reported a blinded evaluation of objective endpoints, and follow-up period, when mentioned, was no longer that 1 year. As there were a maximum of five included studies, we did not perform funnel plot analysis. According to the GRADE methodology, the quality of evidence was low with regards some of the possible risk factors (gender, parity, maternal age >35 and >20 years, Black ethnicity) and very low in others (Caucasian, Hispanic, and Asian ethnicity) (Table 6). No study had overlapping I^2 scores. However, when independently assessed by two authors (GL and AZ) using A Measurement Tool to Assess Systematic Reviews (AMSTAR) version 2 [69], the present systematic review and meta-analysis received a "moderate" score (Supplementary file 2). The PRISMA checklist was then completed (Supplementary file 3).

5. Discussion

Epidemiological studies are crucial for the understanding of disease distribution and risk factors, which are then critical for disease prevention and treatment [70]. The present study shows that despite decades of research on CDH, there are only few population-based studies that allow a limited picture of the actual epidemiology of CDH around the

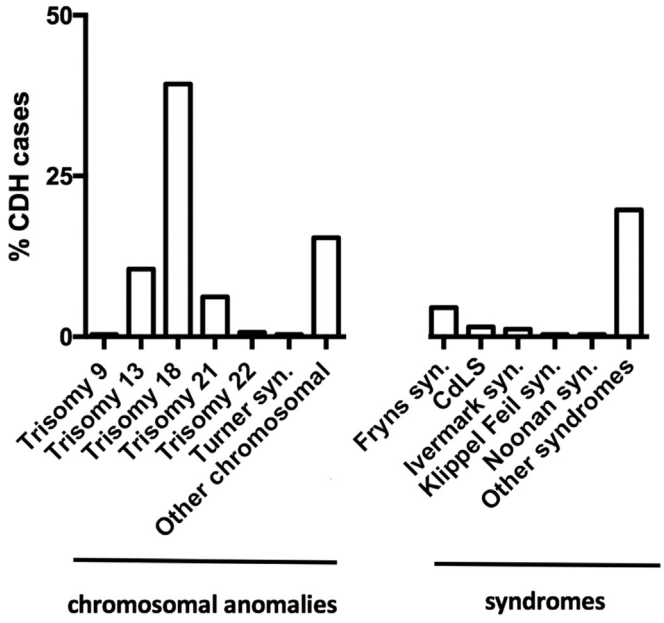

Fig. 4. Distribution of chromosomal anomalies and syndromes in CDH cases reported in population-based studies.

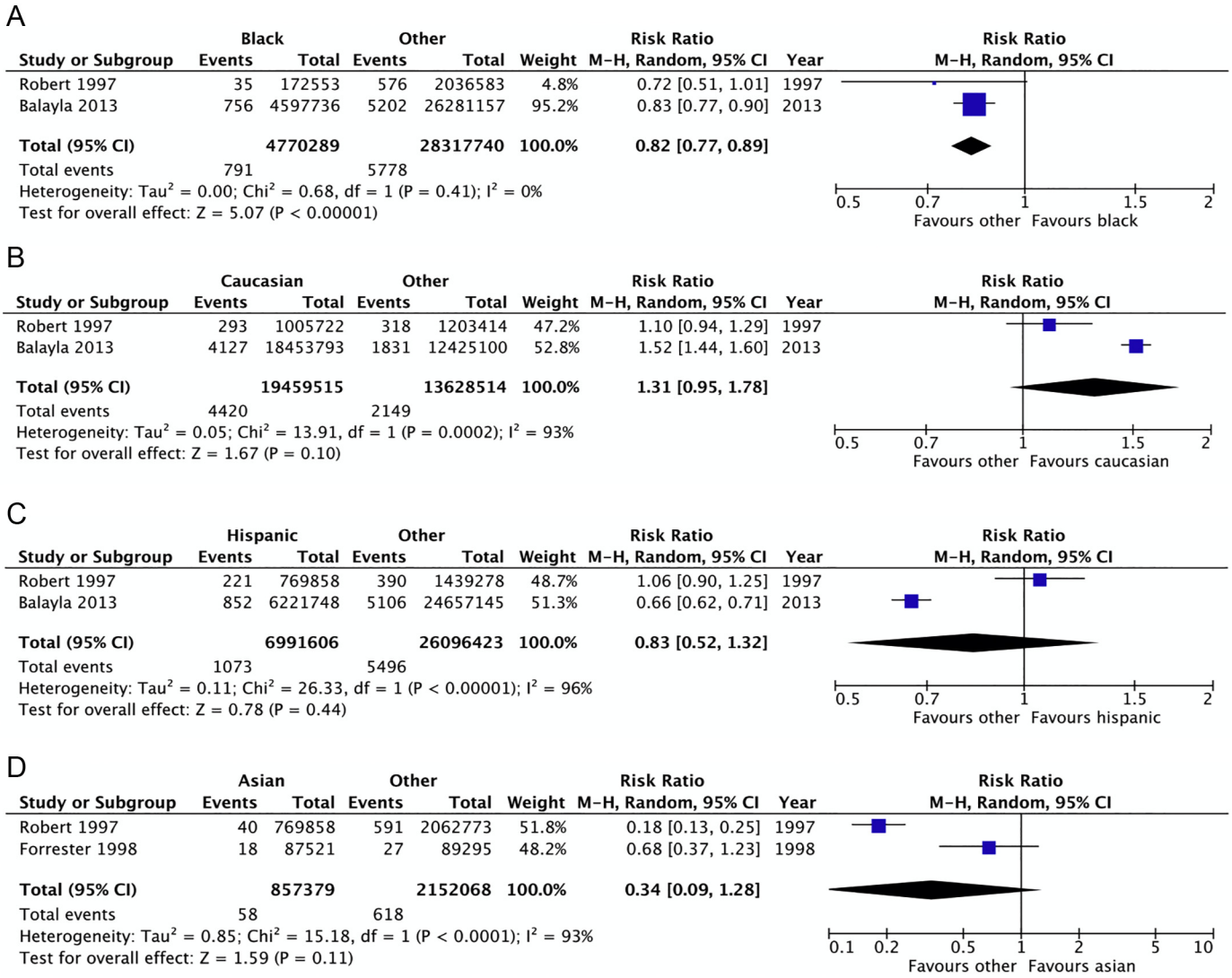

Fig. 5. Forest plot comparison on ethnical background for CDH patients: (A) Black; (B) Caucasian; (C) Hispanic; (D) Asian.

world. In fact, only a few countries have contributed to the study of CDH prevalence and risk factors, with large geographical areas, such as the entire African continent, not having yet participated in such an endeavor. To the best of our knowledge, only one study has previously attempted to collate all population-based studies on CDH [71]. In 2000, Skari et al conducted a systematic review of the English literature, but given the paucity of data, the authors only included studies from six countries, that is, USA, England, Ireland, France, Norway, and Sweden [71]. In the last two decades, we have witnessed an increase in CDH epidemiological studies, some of which are part of continent-wide initiatives that involved regions of central and south America, as well as Europe [36,44]. Moreover, an increased representation has been noticed in large countries, like the USA, where currently more states compared to the past have population-based data for CDH. These improvements are partially because of the establishment of nation/region-wide registries that have increasingly allowed the collection and analysis of birth data, and in some instances of fetal statistics.

The prevalence herein calculated is 2.3 cases of CDH in 10,000 livebirths. This figure comes from a large population of CDH cases (16,710) over a very large population of livebirths (>73 million). This prevalence is in line with the one previously reported by Skari et al that was 2.5 in 10,000 livebirths [71]. Interestingly, the global prevalence of CDH varies within and across geographical world regions. To calculate CDH prevalence, we have followed the criteria highlighted by Mason et al in a seminal paper where they explained why prevalence is the preferred measure to express the frequency of birth defects: for congenital defects, the population at risk is defined as all conceptions that reach the gestational age for the development of a given malformation [22]. For this reason, in our population of CDH cases we have included livebirths as well as stillbirths, and terminations of pregnancy. In our systematic review, we adopted a stringent approach for study selection. Indeed, we acknowledge that in the literature there are far more population-based studies than those 30 reported in Table 1, which we used to calculate the overall CDH prevalence. However, some studies were excluded from the analysis as they reported all congenital diaphragmatic defects together, including eventrations [72,73]. Some epidemiology studies were based on the administration of a questionnaire to physician and families rather than on a registry database, and were excluded to avoid potential selection bias [17,18,74,75]. Other studies were representative of single centers, rather than of a "region" [7,76–84]. We elected to include only studies that covered regions ranging from a metropolitan area to a nation [38,45]. We also excluded studies where the prevalence of CDH cases was difficult to determine with regards to the overall population [85]. For countries with multiple epidemiological studies conducted during similar timeframes, such as the USA, UK, and Australia, we opted to exclude those with smaller

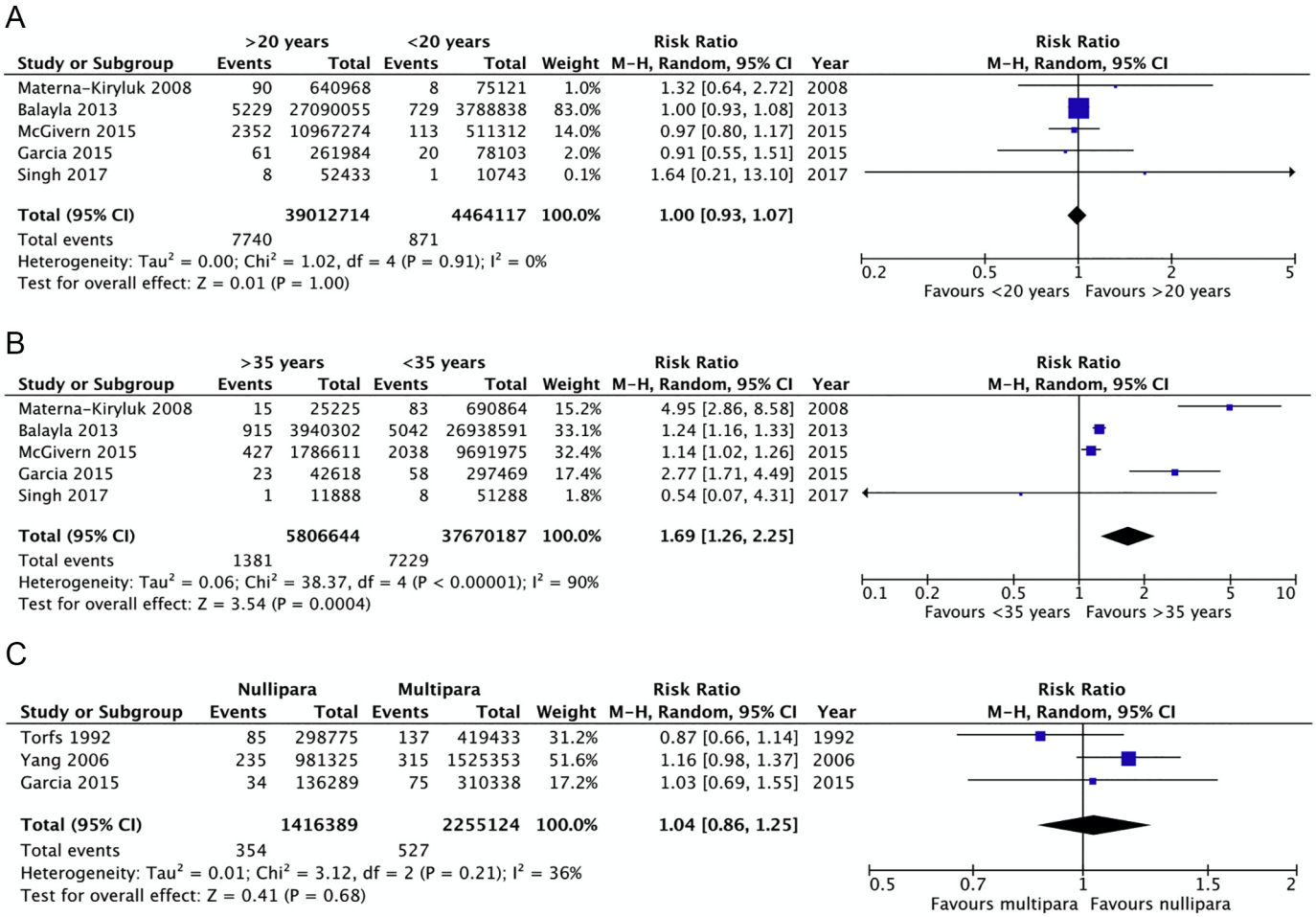

Fig. 6. Forest plot comparison on maternal age (A, B) and parity (C).

Table 4
Risk factors identified in studies that were excluded.

Factor	Study	Country (region)	Years
Maternal education	Yang et al [12]	USA (California)	1989–1997
	Balayla and Abenhaim [43]	USA	1995–2002
	Ramakrishnan et al [61]	USA (Florida)	1998–2012
Maternal smoking	Mesas Burgos et al [19]	Sweden	1987–2013
	Balayla and Abenhaim [43]	USA	1995–2002
	García et al [45]	Colombia (Bogota)	2001–2013
	Ramakrishnan et al [61]	USA (Florida)	1998–2012
	Purisch et al [62]	USA	1989–1997
	Perry et al [63]	USA (Ohio)	2006–2015
Alcohol use during pregnancy	Balayla and Abenhaim [43]	USA	1995–2002
	García et al [45]	Colombia (Bogota)	2001–2013
	Purisch et al [62]	USA	1989–1997
	Felix et al [64]	Netherlands	2000–2004
Maternal obesity	Mesas Burgos et al [19]	Sweden	1987–2013
	García et al [45]	Colombia (Bogota)	2001–2013
	Ramakrishnan et al [61]	USA (Florida)	1998–2012
	Waller et al [65]	Canada (Toronto) and USA (Boston, Philadelphia)	1993–1997
Multiple pregnancies	Yang et al [12]	USA (California)	1989–1997
	Dawson et al [17]	USA	1997–2009
	Robert et al [32]	Sweden	1973–1992
	Balayla and Abenhaim [43]	USA	1995–2002
	Torfs et al [57]	USA (California)	1983–1987
	Ramakrishnan et al [61]	USA (Florida)	1998–2012
Maternal medical conditions (e.g., diabetes, hypertension)	Mesas Burgos et al [19]	Sweden	1987–2013
	McAteer et al [66]	USA (Washington)	1987–2009
Paternal factors (e.g., age, occupation)	Materna-Kiryluk et al [42]	Poland	1998–2002
	David and Illingworth [67]	United Kingdom	1943–1974
	Green et al [68]	USA	1997–2004

Table 5
Risk of bias assessment for individual studies using methodological index for nonrandomized studies (MINORS) [23].

Item	Balayla 2013 [43]	Forrester 1998 [60]	Garcia 2015 [45]	Materna-Kiryluk 2008 [42]	McGivern 2015 [44]	Ramakrishnan 2018 [61]	Robert 1997 [32]	Singh 2017 [50]	Torfs 1992 [57]	Yang 2006 [12]
1. A clearly stated aim	2	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2	2	2	2	2
3. Prospective collection of data	0	0	0	0	0	0	0	0	0	0
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	1	1	1	0	0	0	1	1	1	1
7. Loss to follow-up less than 5%	0	0	0	0	0	0	1	0	0	2
8. Prospective calculation of the study size	0	0	0	0	0	0	0	0	0	0
9. An adequate control group	2	2	2	2	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	2	2	2	2	2	2	2
12. Adequate statistical analyses	2	0	2	2	2	2	2	2	2	2
Total score	15	13	15	14	14	14	16	15	15	17

0 = not reported; 1 = reported but inadequate; 2 = reported and adequate.
Validated "gold standard" cutoff: 19.8.

populations [11,12,15,38,57–62,68,86–95]. Lastly, we excluded studies that did not report all births, as it was not possible to calculate the prevalence for CDH [93,96–110].

In the present study, we also focused on risk factors for CDH development. In this regard, there is a vast body of CDH literature that reports on patient or maternal/paternal related factors that might contribute to

Table 6
GRADE evidence profile [24] for risk factors in congenital diaphragmatic hernia.

Quality assessment							No. of patients		Effect		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cases	Controls	Relative (95% CI)	Absolute (95% CI)	Quality
Gender in CDH							**Male**	**Female**			
4	OS	Moderate[a]	Substantial	Not serious	Serious[b]	None	3.601/ 16,341,979 (0.022%)	2684/ 15,662,542 (0.017%)	RR 1.38 (1.05, 1.80)	5 more per 100,000 (from 1 more to 10 more)	⊗⊗OO Low
Parity in CDH							**Nullipara**	**Multipara**			
3	OS	Moderate[a]	Not serious	Serious[b]	None	354/ 1,416,389 (0.025%)	527/ 2,255,124 (0.023%)	RR 1.04 (0.86, 1.25)	2 more per 100,000 (from 7 fewer to 12 more)	⊗⊗OO Low	
Maternal age in CDH (cutoff 35 years)							**>35 years**	**<35 years**			
5	OS	Moderate[a]	Considerable	Not serious	Serious[b]	None	1381/ 5,806,644 (0.024%)	7229/ 37,670,187 (0.019%)	RR 1.69 (1.26, 2.25)	5 more per 100,000 (from 2 more to 9 more)	⊗⊗OO Low
Maternal age in CDH (cutoff 20 years)							**>20 years**	**<20 years**			
5	OS	Moderate[a]	Low	Not serious	Serious[b]	None	7740/ 39,012,714 (0.019%)	871/ 4,464,117 (0.019%)	RR 1.00 (0.93, 1.07)	Equal number per 100,000	⊗⊗OO Low
Caucasian ethnicity in CDH							**Caucasian**	**Other**			
2	OS	Moderate[a]	Considerable	Not serious	Serious[b]	None	4420/ 19,459,515 (0.023%)	2149/ 13,628,514 (0.016%)	RR 1.31 (0.95, 1.78)	7 more per 100,000 (from 1 fewer to 18 more)	⊗OOO Very low
Black ethnicity in CDH							**Black**	**Other**			
2	OS	Moderate[a]	Low	Not serious	Serious[b]	None	791/ 4,770,289 (0.016%)	5778/ 28,317,740 (0.020%)	RR 0.82 (0.77, 0.89)	4 fewer per 100,000 (from 5 fewer to 2 fewer)	⊗⊗OO Low
Hispanic ethnicity in CDH							**Hispanic**	**Other**			
2	OS	Moderate[a]	Considerable	Not serious	Serious[b]	None	1073/ 6,991,606 (0.015%)	5496/ 26,096,423 (0.021%)	RR 0.83 (0.52, 1.32)	6 fewer per 100,000 (from 17 fewer to 11 more)	⊗OOO Very low
Asian ethnicity in CDH							**Asian**	**Other**			
2	OS	Moderate[a]	Considerable	Not serious	Serious[b]	None	58/ 857,379 (0.007%)	618/ 2,152,068 (0.029%)	RR 0.34 (0.09, 1.28)	22 fewer per 100,000 (from 30 fewer to 9 more)	⊗OOO Very low

CDH: congenital diaphragmatic hernia; OS: observational study; CI: confidence interval; RR: risk relative.
GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[a] Bias owing to possible confounding.
[b] OIS not met.

the development of this condition. In our analysis, we elected to include only population-based studies that would report on potential CDH risk factors and exclude those that were based on single-center cohorts. With this stringent strategy, we identified that male sex and a maternal age >35 years at the time of delivery were associated with CDH, whereas having black ethnicity was a protective factor. It is difficult to speculate on the causality of these factors, partly owing to the fact that these analyses stem from a small number of studies. Moreover, it is possible that the rate of CDH in the black ethnic community could be underestimated, owing to less testing and access to prenatal care as dictated by disparities in socioeconomic status and regional healthcare [15]. Furthermore, an additional factor that might reflect the increase of CDH with advanced maternal age is that this population is more likely to receive prenatal care that would lead to a CDH diagnosis.

Our meta-analyses also showed that a maternal age <20 years and parity were not associated with CDH. Moreover, as it is known, genetic factors such as chromosomal anomalies and some recognized syndromes are associated only to a small proportion of babies with CDH, and cannot be considered as causative factors for the development of the diaphragmatic defect. Similar to our analysis on CDH prevalence, we indeed recognize that we have excluded from our meta-analysis a large number of studies that reported on CDH risk factors, as these did not meet our study criteria.

5.1. Limitations

We acknowledge that the present study has some limitations. Many of the papers selected for our analysis were retrospective observational studies, had very different size populations, and included different timeframes. Nonetheless, we made an effort to adopt strict criteria for study selection and the findings of the present study are based on a large population of patients over three decades. Another limitation encountered is the variability in the CDH populations, whereby some studies reported only livebirths and others included also stillbirth and terminations of pregnancy. According to the literature, this is a known phenomenon related to the specific nature of epidemiological studies on congenital anomalies, and it is considered acceptable to calculate their prevalence including fetal losses in the numerator [22]. Similarly, because the number of congenital anomalies is relatively small compared to all births, the absence of fetal deaths in the denominator has a negligible impact on the prevalence estimate [22]. Moreover, most studies included cases without specifically defining the type of CDH. This is possibly because of coding issues, whereby different types of diaphragmatic defect may be recorded using the same code. Nonetheless, we excluded all studies that included eventrations or Morgagni hernias without specifying the exact number of patients. Lastly, our evaluation on risk factors for CDH mainly stem from the analysis of studies conducted in few parts of the world, as shown by the predominance of studies from the USA. Some of these risk factors might not be applicable and translatable to other parts of the world. Nonetheless, the strength of the present study depends on the huge number of CDH cases and total number of births that, to the best of our knowledge, is the largest ever reported.

In conclusion, this study revealed that there is a paucity of population based epidemiological studies that report on CDH prevalence and risk factors from a small number of countries. Further epidemiological studies, involving more world regions, are needed to identify possible strategies to prevent CDH. These epidemiological studies will help strengthen our understanding of the risk factors for this devastating disease, provide clinicians with the tools necessary for prenatal and postnatal counseling, and inform policy makers on how to best allocate resources and strategize CDH care in different parts of the world.

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