Global birth prevalence of Robin sequence in live-born infants: a systematic review and meta-analysis

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Robin sequence occurs globally and affects 9.5 per 100 000 live-born infants. Prevalence variability is likely due to different study methodologies and case definitions. The impact of ethnicity is poorly described and should be a target of future research. https://bit.ly/46F763f

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Abstract

Robin sequence (RS), a congenital disorder of jaw maldevelopment and glossoptosis, poses a substantial healthcare burden and has long-term health implications if airway obstruction is suboptimally treated. This study describes the global birth prevalence of RS and investigates whether prevalence estimates differ by geographical location, ethnicity or study data source (registry *versus* non-registry data). The protocol was prospectively registered with PROSPERO.

Databases were searched using keywords and subject terms for "Robin sequence", "epidemiology", "incidence" and "birth prevalence". Meta-analysis was performed fitting random effects models with arcsine transformation.

From 34 eligible studies (n=2722 RS cases), pooled birth prevalence was 9.5 per 100 000 live births (95% CI 7.1–12.1) with statistical heterogeneity. One third of studies provided a case definition for RS and numerous definitions were used. A total of 22 countries were represented, predominantly from European populations (53% of studies). There was a trend towards higher birth prevalence in European populations and lower prevalence from registry-based studies. Only two studies reported ethnicity.

This study indicates that RS occurs globally. To investigate geographical differences in prevalence, additional studies from non-European populations and reporting of ethnicity are needed. Heterogeneity of estimates may be due to variable diagnostic criteria and ascertainment methods. Recently published consensus diagnostic criteria may reduce heterogeneity among future studies.

Introduction

Robin sequence (RS) is a congenital disorder characterised by micrognathia and glossoptosis, resulting in upper airway obstruction (UAO) [1]. Cleft palate is a common additional feature, present in 83–92% of cases [2–4]. These clinical features can occur in isolation or may be associated with additional congenital anomalies or an underlying genetic syndrome (non-isolated RS).

RS is a condition that carries a substantial healthcare burden. Affected infants commonly need interventions to support feeding and alleviate UAO, which often necessitate prolonged hospital admission. Management, particularly in cases of non-isolated RS, involves input from a large multidisciplinary team of medical specialists and allied health professionals. Accurate estimation of birth prevalence is needed to ensure that medical services are appropriately planned and resourced.

The aetiology of RS is not yet fully understood but is likely to include genetic and environmental factors. To progress our understanding of its aetiology it is important to understand whether the prevalence of RS varies across population subgroups, *e.g.* by ethnicity or geographical location.

A previous systematic review of the global birth prevalence of RS, which included data collected up to 2012, estimated a median birth prevalence of 1:14 500 births with a very wide range of 1:3900 to 1:122 400 births [4]. However, meta-analysis was not performed, and the review did not differentiate between birth prevalence among live-born infants and prevalence estimates that included stillbirths and terminations of pregnancy for a fetal anomaly (TOPFA). Furthermore, there was no exploration of the reasons for the variable birth prevalence estimates identified, *e.g.* whether prevalence differed between geographical areas or according to a study's method of case ascertainment. Since 2012, further relevant studies have been published, including a 20-year report from the European network of population-based registries of congenital anomalies (EUROCAT) [2]. In view of the limitations of the existing systematic review and publication of additional data over the past decade, an updated systematic review of RS birth prevalence, with meta-analysis, is warranted.

The primary aim of this systematic review and meta-analysis was to ascertain the global birth prevalence of RS among live-born infants. Secondary aims were to establish whether birth prevalence of RS varies according to geographical location or ethnicity, and whether birth prevalence estimates differed significantly depending on the data source used (*i.e.* congenital anomaly registry or non-registry-based data).

Methods

Protocol and registration

This review was carried out in accordance with the registered International Prospective Register of Systematic Reviews (PROSPERO) protocol (CRD42021230212) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [5] and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [6] guidelines.

Eligibility criteria

All types of population-based studies and published reports (*e.g.* congenital anomaly registry reports) describing the birth prevalence of live-born infants with RS, and using live birth rate as the population denominator, were eligible for inclusion. Studies that did not provide a population denominator were included if this information could be obtained separately from a credible source, *e.g.* a national statistics office.

Exclusions were not made based on a study's case definition of RS, given the reported variability in RS diagnostic criteria within published literature and clinical practice. However, the case definition applied in each study was recorded and was taken into consideration when interpreting the findings of the meta-analysis.

No date or language restrictions were placed on database searches, provided an English-language abstract was available.

Studies were excluded if participants were not representative of the wider population in which the study was conducted, *e.g.* hospital-based studies that included only private hospitals or tertiary referral centres were excluded.

Information sources

Eligible studies were identified through a search of the following databases from their inception to June 2021: Ovid MEDLINE, Embase, Scopus, CINAHL, ClinicalTrials.gov and the Cochrane Library. Reference lists of eligible studies were screened to identify additional relevant publications. Google Scholar and Open Grey were systematically searched to identify relevant grey literature for inclusion.

Search strategy

Database-specific searches were conducted using variations on keywords and subject terms for "Robin sequence", "epidemiology", "incidence" and "birth prevalence". Draft search strategies for each database are provided in supplementary appendix A. The development of database search strategies was assisted by a librarian.

Abstract screening

All citations were exported and de-duplicated in citation management software (EndNote 20; Clarivate, Philadelphia, PA, USA). The primary reviewer (MW) screened the titles and abstracts of the retrieved articles for relevance. A second reviewer (RK) screened a random 10% sample of all abstracts, and any inter-rater inconsistencies were resolved by discussion. Unweighted Cohen's κ was calculated to determine the strength of agreement between reviewers.

Full-text screening of relevant abstracts was carried out by the primary reviewer and articles were compared against predefined inclusion criteria that were co-developed by all study authors. Regular consensus meetings were held between the study authors at which decisions around study inclusion were discussed and equivocal cases were reviewed. Reasons for ineligibility were recorded at both stages of abstract screening. Full-text articles that were not publicly available were requested from the authors.

Data extraction

Data were extracted from each eligible study by the primary reviewer using a piloted survey co-designed by all study authors. Extracted data were reviewed and analysed by study authors during consensus meetings.

Data extraction domains included study methodology (study design, data sources, data collection period), study setting and population, case definition for RS, total number of RS cases, population denominator, summary of patient characteristics (*e.g.* sex, ethnicity, gestational age at birth, birth weight) and summary of RS-related clinical characteristics (*e.g.* presence of UAO and/or cleft palate, associated syndromes and genetic mutations). Studies with missing data items were included provided they included a birth prevalence estimate.

Data were stored electronically in a Research Electronic Data Capture (REDCap) [7] database hosted by University College London.

Duplicate data

Data were only included once in the systematic review and meta-analysis. In the event of multiple studies from the same population with overlapping data collection periods, the study containing the most recent data was included.

Quality assessment

A methodological quality assessment of included studies was carried out using the Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data, which incorporates measures of methodological quality and risk of bias [8]. Studies were scored a maximum of one point per criterion against nine quality criteria. Based on the total score, studies were appraised as being of high (score 8–9), moderate (5–7) or low (0–4) quality. All studies were included in the meta-analysis, but a sensitivity analysis was performed excluding low-quality studies.

Data analysis and synthesis of results

Pooled birth prevalence of RS with 95% CI was calculated using the double arcsine transformation of proportions to account for study size variability and the low birth prevalence of RS with potential for negative value lower CIs [9]. Random effects models were fitted owing to the relatively large number of studies included in the meta-analysis and because the included studies were heterogeneous in terms of the study population and design [10]. Prevalence estimates from each study and the pooled estimate were graphically summarised as a Forest plot. Statistical heterogeneity was evaluated using the I^2 statistic, with an I^2 of $\geqslant$75% indicating high heterogeneity [11]. Funnel plots and Egger's test were used to assess for publication bias [12].

Subgroup analyses were performed to explore whether birth prevalence differed according to the geographical location of the study (European *versus* non-European studies) or the source of case ascertainment (registry-based *versus* non-registry studies). The comparison between European and non-European studies was chosen in view of the small number of studies from any continent other than Europe. Birth prevalence estimates between groups were compared using binomial logistic regression. Generalised linear models with mixed effects were fitted to incorporate both within-study and between-study heterogeneity and in view of the use of random effects models in the meta-analysis.

Sensitivity analyses were performed to ascertain whether the application of different eligibility criteria would have affected the results of the meta-analysis. Analyses were performed excluding low-quality studies, studies with short data collection periods ($\leqslant$2 years) and studies reporting data that are now over 20 years old. Analysis was also performed including studies involving non-live-born infants (*e.g.* stillbirths or TOPFA) in either the population denominator or RS case numbers.

Meta-analysis was performed using the MetaXL software add-in for Microsoft Excel (v5.3; EpiGear International Pty Ltd) and the R language and environment for statistical computing and graphics (metafor, meta, dmetar and lme4 packages; www.r-project.org) [13–15].

Results

Selection of eligible studies

A total of 1315 records were retrieved from database searches, from which 335 duplicate records were removed. After initial screening, 57 abstracts were considered potentially relevant. Cohen's κ indicated high inter-observer agreement (κ=0.825, 95% CI 0.59–1.06). Following full-text review, 39 articles were excluded and 18 were considered eligible for inclusion in the systematic review. Reasons for exclusion are summarised in the PRISMA diagram in figure 1. An additional 16 eligible publications were identified through grey literature and bibliography searches. In total, 34 papers were included in the systematic review [3, 4, 16–47].

Quality assessment

Results of the quality assessment are presented in supplementary appendix B. The median quality score was 6 out of 9 (interquartile range (IQR) 4–7). Three studies (9%) were graded as being of high quality, 22 (65%) were of medium quality and nine (26%) were of low quality.

Studies scored highest for having an adequate sample size and a sample frame appropriate to address the target population and for sampling study participants in an appropriate way. Studies scored lowest for using valid methods for identification of RS cases, measuring RS in a standard and reliable way and performing appropriate statistical analysis.

Study characteristics

Characteristics of the included studies are summarised in table 1.

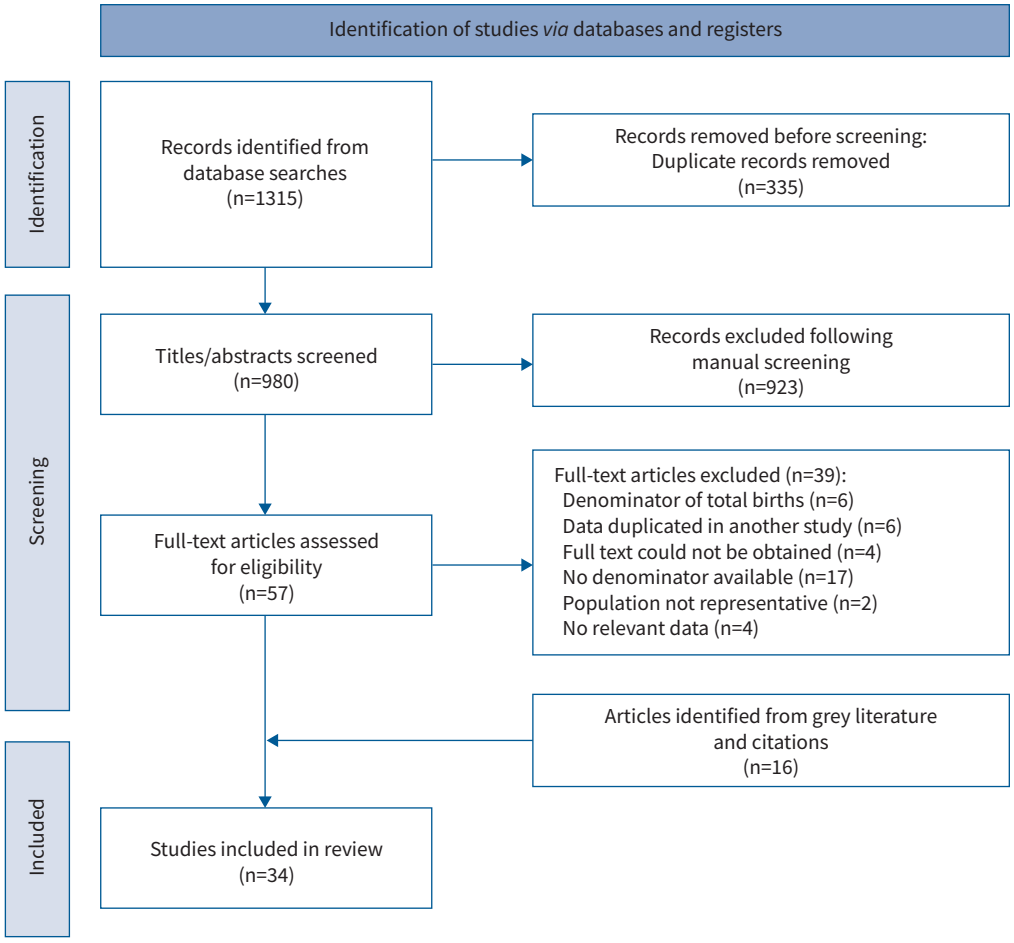

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

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TABLE 1 Characteristics of included studies

First author year [ref.]	Country	Setting	Study period	Study type	Data source	RS case definition	Population live births (n)	RS cases (n)	Births per one case of RS	RS cases per 100 000 live births (95% CI)
Alyami 2020 [16]	Saudi Arabia	H	2013–2016	RC	MR	(CP)	24 367	3	8122	12.3 (−1.6–26.2)
Bellis 1999 [17]	UK	R	1971–1990	RC, Reg	MR, HOS	N/A	356 733	53	6731	14.9 (10.9–18.9)
Bister 2011 [18]	UK	R	1993–1997	RC	CU, B/D, MR	N/A	22 765	1	22 765	4.4 (−4.2–13.0)
Bittar 1998 [19]	Lebanon	H	1991–1993	PC	NB	N/A	3736	1	3736	26.8 (−25.7–79.2)
Brogan 1978 [20]	Australia	R	1963–1975	RC	"Multiple" including PI	CP+MG+GP+UAO +FD	254 949	50	5099	19.6 (14.2–25.0)
Bush 1983 [21]	UK	R	1974–1982	PC	CU	CP+UAO/FD+Hosp	340 000	40	8500	11.8 (8.1–15.4)
Chi 1974 [22]	Australia	R	1964–1966	RC	MR	N/A	147 042	7	21 006	4.8 (1.2–8.3)
Cleary 2011 [23]	Ireland	H	2000–2007	RC	MR, B/D	N/A	61 030	12	5086	19.7 (8.5–30.8)
Cornel 1992 [24]	Netherlands	R	1981–1989	Reg	Reg	N/A	73 426	7	10 489	9.5 (2.5–16.6)
Czeizel 1997 [25]	Hungary	N	1980s	Reg	Reg, B/D	N/A	1 250 000	100	12 500	8 (6.4–9.6)
Dreise 2011 [26]	Uganda	R	2008–2009	SS	Surv, Exam	N/A	26 186	1	26 186	3.8 (−3.7–11.3)
Elahi 2004 [27]	Pakistan	R	1998–2001	CC, Reg	B/D, Reg	N/A	61 156	3	20 385	4.9 (−0.6–10.5)
Friedlander 2017 [28]	France	N	2008–2015	PC, Reg	Reg, MR	N/A	6 316 008[#]	883	7153	14 (13.1–14.9)
Greene 1964 [29]	USA	R	1956–1960	CC	B/D	CP+MG	3 578 438	49	73 029	1.4 (1.0–1.8)
Hagberg 1998 [30]	Sweden	R	1991–1995	PC	MR, PI, CU	CP+MG+UAO	122 148	10	12 215	8.2 (3.1–13.3)
Hewson 2000 [31]	Ireland	R	1980–1996	RC	Surv, Exam, PI	N/A	92 318	6	15 386	6.5 (1.3–11.7)
Higurashi 1990 [32]	Japan	H	1972–1985	PC	NB, GT	N/A	27 472	1	27 472	3.6 (−3.5–10.8)
Jensen 1988 [33]	Denmark	N	1976–1981	Reg	Reg, CU	(CP)	359 027	14	25 645	3.9 (1.9–5.9)
Kamal 2018 [34]	Iraq	R	2013–2016	RC	MR, Exam	N/A	178 954	11	16 269	6.1 (2.5–9.8)
Khrouf 1986 [35]	Tunisia	H	1983–1984	CC	Exam	N/A	9662	1	9662	10.3 (−9.9–30.6)
Kliškinjić 2019 [36]	Croatia	H	2000–2018	RC	MR	(CP)	88 813	7	12 688	7.9 (2.0–13.7)
Knox 1963 [37]	UK	R	1949–1960	RC	HOS, Surv	CP+MG	404 124	5	80 825	1.2 (0.2–2.3)
Koželj 1996 [38]	Slovenia	N	1973–1993	Reg	Reg	N/A	590 249	54	10 931	9.1 (6.7–11.6)
Kumar 2018 [39]	India	R	2011–2016	RC	MR	(CP)	77 667	3	25 889	3.9 (−0.5–8.2)
Lary 2001 [40]	USA	R	1968–1995	SS, Reg	MR, B/D, HOS, Gen	N/A	853 456	65	13 130	7.6 (5.8–9.5)
Maas 2014 [3]	Germany	N	2011–2013	SS, Reg	Surv, MR	MG+UAO/GP/FD/ CP+Hosp	1 336 229	151	8849	11.3 (9.5–13.1)
Nunes 2007 [41]	Brazil	R	1999–2004	PC	MR, B/D	(CP)	46 707	6	7785	12.8 (2.6–23.1)
Paes 2015 [4]	Netherlands	N	2000–2010	PC, Reg	Reg, MR, Gen, GT	CP+MG+UAO	2 113 858	246	8593	11.6 (10.2–13.1)
Printzlau 2004 [42]	Denmark	N	1990–1999	RC, Reg	Reg, CU	CP+MG+UAO	670 001	48	13 958	7.2 (5.1–9.2)
Scott 2014 [43]	USA	R	2006–2009	RC	HOS	CP+MG	1 654 805	529	3128	32 (29.2–34.7)
Tolarova 1998 [44]	USA	R	1983–1993	Reg	Reg, MR, Gen	(CP)	2 493 331	134	18 607	5.4 (4.5–6.3)
Vallino-Napoli 2006 [45]	Australia	R	1983–2000	Reg	Reg, B/D, HOS, GT	CP+MG	1 129 425[#]	112	10 084	9.9 (8.1–11.8)
Van Regemorter 1984 [46]	Belgium	H	1975: 10 000 births	PC	Surv, MR	N/A	9889	4	2472	40.4 (0.8–80.1)
Wright 2018 [47]	UK	R	2004–2013	RC	MR, HOS, CU	CP+MG+GP	281 885	105	2685	37.2 (30.1–44.4)

B/D: birth or death records/autopsy report; CC: case–control study; CP: cleft palate; (CP): no case definition given, but study only included children with cleft palate; CU: cleft unit records/assessment; Exam: clinical examination; FD: feeding difficulties; Gen: geneticist review; GP: glossoptosis; GT: genetic test results; H: hospital-based/single centre study; HOS: hospital coding/admission records/operation list; Hosp: admitted to hospital; MG: micrognathia; MR: medical records; N: national study; N/A: no case definition given; NB: newborn clinical examination in the first 24 h of life; PC: prospective case series/cohort; PI: parent interview; R: regional study; RC: retrospective case series/cohort; Reg: registry study; RS: Robin sequence; SS: surveillance study; Surv: survey; UAO: upper airway obstruction/respiratory distress. [#]: denominator obtained from separate source.

The years of data collection within the included studies spanned 1949 to 2018. The median duration of data collection was 8 years (IQR 4–13 years). Five studies had a data collection period of ⩽2 years.

All studies were observational. 13 studies (38%) included data from a registry, although in 11 cases at least one additional data source was used. The involved registries are listed in supplementary appendix C. Three studies used active surveillance as a method of case ascertainment.

A total of 22 countries across six continents were represented (figure 2). Over half the studies were from European countries (n=18, 53%). Six countries were represented by multiple studies (USA, n=4; UK, n=5; Australia, n=3; Denmark, Netherlands and Republic of Ireland, n=2), with each study describing either a distinct time period or study region.

Birth prevalence

In total, 2722 cases of RS were reported in the 34 included studies. Birth prevalence ranged between 1.2 and 40.4 per 100 000 live births (one case per 2472–80 825 live births). Pooled birth prevalence was 9.5 per 100 000 live births (95% CI 7.1–12.1) (figure 3). There was substantial heterogeneity of birth prevalence estimates between studies (I^2=98%). A low risk of publication bias was indicated by the absence of funnel plot asymmetry (Egger's test, p=0.96) (supplementary appendix D).

Subgroup analysis identified a higher pooled birth prevalence in European populations and lower birth prevalence from studies utilising registry data, although these findings did not meet statistical significance (table 2 and supplementary appendix E).

Patient characteristics

A summary of patient characteristics within the included studies is presented in supplementary appendix F.

Sex distribution was equal (n=689 out of 1374 female, 50%) among the 14 studies reporting this characteristic. In 12 studies (35%), the authors specified whether cases of RS with additional congenital anomalies ("non-isolated RS") were included or omitted. Of these, seven studies (n=893 cases) included both isolated and non-isolated cases and described their relative proportions: isolated RS represented 62% of cases (n=551 out of 893, range 57–75%), and Stickler syndrome was the most common RS-associated syndrome, constituting 7–12% of cases.

Ethnicity of RS infants was only described in two publications (n=663). With reference to maternal race, Tolarova and Cervenka [44] reported that, in California, USA, the highest birth prevalence was among infants of non-Hispanic white women (8 per 100 000 live births) and lowest was among infants of Asian women (1.7 per 100 000 live births). Scott and Mader [43] reported that, across multiple states of USA, the highest birth prevalence was among white infants (17–21 per 100 000 live births) and lowest was among infants from black ethnic groups (5–11 per 100 000 live births). Scott and Mader identified that isolated RS was more common than non-isolated RS in white ethnic groups and the opposite was true in black ethnic groups.

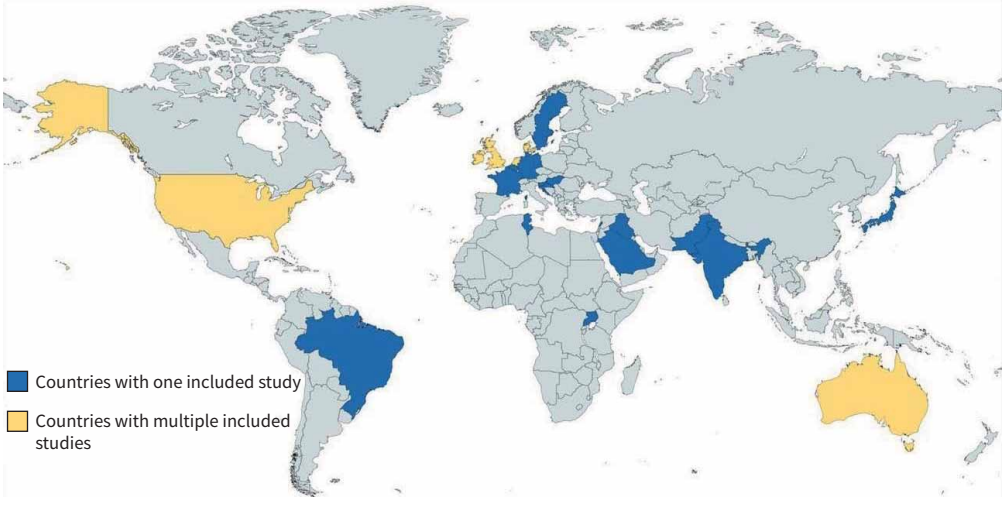

FIGURE 2 Geographical location of included studies.

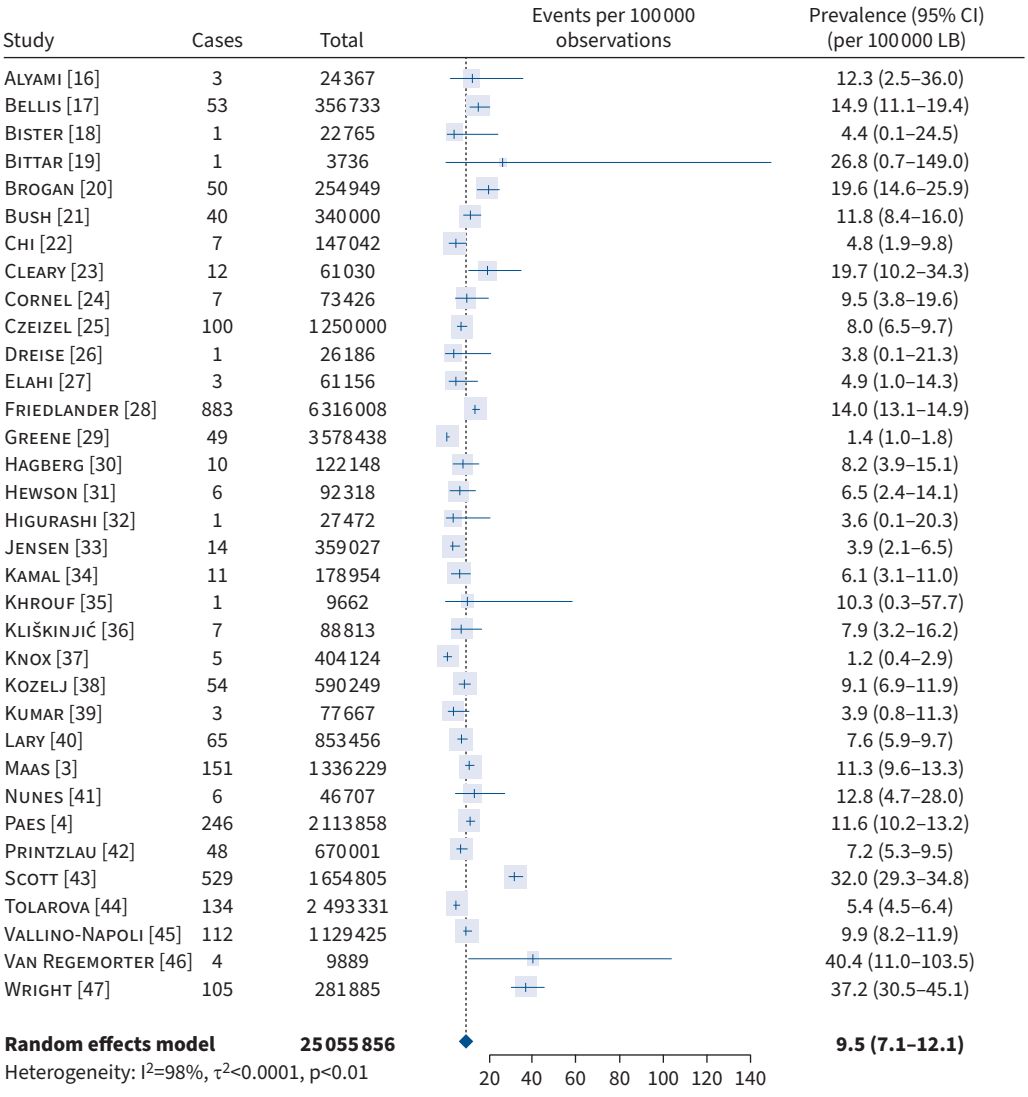

FIGURE 3 Pooled birth prevalence of Robin sequence. LB: live births.

RS case definition

A case definition was given for RS by 11 studies (n=1347 cases). The most common criteria were cleft palate and jaw abnormalities (micro/retrognathia), which were each included in the diagnostic criteria of 10 studies. Less common requirements were respiratory distress or UAO (five studies), feeding difficulties

TABLE 2 Summary of subgroup analyses

Subgroup	Studies (n)	Pooled birth prevalence (95% CI) per 100 000	I^2 (%)	Logistic regression	
				Estimate	p-value[#]
Geography				−0.288	0.299
European[¶]	18	10.4 (7.3–14.0)	94		
Non-European	16	8.3 (4.9–12.7)	98		
Data source				−0.079	0.776
Non-registry[¶]	21	10.4 (6.5–15.1)	98		
Registry	13	8.6 (6.9–10.5)	94		

[#]: groups compared with generalised linear regression mixed effect model; [¶]: reference category for comparison.

(three studies), glossoptosis (two studies) and hospital admission (two studies). A further 13 studies without a clear case definition included only children with cleft palate (*e.g.* data were obtained from a cleft database or registry); therefore, a total of 23 studies (68%) reported birth prevalence of RS with associated cleft palate.

Management of upper airway obstruction

Prevalence of UAO was reported in only two studies, as 87–93% [3, 47]. Across the three studies providing information about UAO management [3, 43, 47], management approaches differed substantially. Scott and Mader [43] reported that 77% of a cohort from the USA were managed surgically, most often with mandibular distraction osteogenesis. In contrast, the two European studies reported that nonsurgical interventions were the first-line approach; pre-epiglottic baton plate in the German cohort [3] and nasopharyngeal airway in Scotland [47] . In the Scottish cohort, only 7% of infants with RS were managed surgically. Tracheostomy was the most frequently used surgical intervention in both of the European studies.

Total births

An additional 84 prevalence estimates reporting total births (n=2785 RS cases) were extracted from 10 publications and one international registry network report (supplementary appendix G) [2, 48–57]. Birth prevalence ranged from 0 to 39.7 per 100 000 births. Sex distribution (52% female), the proportion of cases with additional congenital anomalies (68% isolated RS) and the proportion of studies that only included cases of RS with associated cleft palate (64%) were comparable to studies reporting live birth prevalence.

Sensitivity analysis

Sensitivity analyses excluded low-quality studies (n=6), studies in which data collection had ended over 20 years ago (n=21) and studies with a data collection period of ⩽2 years (n=5). Prevalence estimates from these analyses did not differ significantly from the meta-analysis pooled prevalence estimate, although there was a trend towards a higher pooled birth prevalence from studies that included more recent data (12.7 per 100 000 live births, 95% CI 8.1–18.3). A further analysis including studies in which the denominator was total births found that inclusion of these studies did not significantly alter the pooled birth prevalence estimate (9.2 per 100 000 births, 95% CI 7.7–10.7) (supplementary appendix H).

Discussion

This meta-analysis of the global birth prevalence of RS identified a pooled birth prevalence of 9.5 per 100 000 live births (95% CI 7.1–12.1) from 34 prevalence estimates spanning 22 countries. Sensitivity analyses did not identify any methodological factors that significantly affected the meta-analysis results, although slightly higher birth prevalence estimates were derived from more recent studies, which may reflect an increasing awareness of RS over time. This pooled birth prevalence may be underestimated because five studies (n=1141 RS cases) included only cases of isolated RS, which is reported to constitute only half of all RS cases [58].

A systematic review of RS birth prevalence has previously been published by Paes *et al.* [4], which reported a substantially lower birth prevalence of 6.5 per 100 000 births. This disparity may be attributable to differences in methodology between the studies, including systematic assessment for duplicate data within studies identified by our search strategy and inclusion of grey literature searches and a wider range of databases in our review.

Birth prevalence estimates varied significantly between the included studies. This heterogeneity was explored by subgroup analysis, which identified a trend towards lower birth prevalence among non-European countries and when registries were used for case ascertainment, although these findings were not statistically significant. Statistical heterogeneity might also be a result of variability in diagnostic criteria for RS or different diagnostic thresholds given its largely subjective clinical features. Fewer than one third of studies provided a case definition for RS, and among these six different case definitions were used.

A clinical consensus report published in 2016 defined RS as micrognathia, glossoptosis and airway obstruction, with cleft palate as a common additional feature [1]. This definition has since been commonly used within published research, and may help to reduce heterogeneity among future epidemiological studies of RS [1].

Notably, cleft palate was the most common diagnostic criterion within studies identified by this systematic review, which may reflect that all included studies were undertaken prior to the publication of the consensus criteria.

The systematic literature search applied in this study identified 84 prevalence estimates that reported RS birth prevalence for total births rather than live births. To avoid exclusion of this potentially useful and relevant dataset, it was included in the study by means of a sensitivity analysis, which confirmed that inclusion of these estimates did not significantly alter the meta-analysis results (9.2 per 100 000 births, 95% CI 7.7–10.7). This implies that birth prevalence estimates for RS based on live births and total births can be regarded as roughly equivalent and could be combined in future data syntheses.

In this systematic review, isolated RS comprised 62% of cases (reported in n=7 studies). A slightly higher proportion of isolated RS cases was reported from EUROCAT registries (68%) [2]. Although this may be due to the inclusion of stillbirths and TOPFA in the EUROCAT cohort, it is more likely related to misclassification or underreporting of congenital anomalies within registries [4, 59]. The proportion of RS cases that are isolated has previously been reported as 37% and 50% by two literature reviews describing the prevalence and spectrum of RS-associated genetic mutations [58, 60]. However, both reviews conveyed a high risk of publication bias which may have resulted in overestimation of non-isolated RS; neither was restricted to population-based studies, and the review by Varadarajan *et al.* [60] included case reports and series of specific RS-associated syndromes. Equally, this systematic review may potentially have underestimated the proportion of RS cases that were non-isolated, because genetic evaluation within the included studies was likely to have been incomplete and inconsistent. Consistent with the findings of both Gomez-Ospina and Bernstein [58] and Varadarajan *et al*. [60], Stickler syndrome was the most common RS-associated syndrome identified by this review.

This study has some notable strengths. The risk of inclusion bias was minimised by using a systematic search strategy that included multiple databases, unpublished literature and non-English-language publications. Prior to data analysis, the complete data set of eligible studies was scrutinised to identify studies that may contain duplicate data, and these overlapping studies were managed in a structured and consistent manner, precluding duplicate publication bias.

This systematic review also has some limitations. There was significant statistical heterogeneity between the included studies, which is likely due to the use of different case definitions for RS and different methods of case ascertainment. Consequently, the pooled birth prevalence and CI presented do not necessarily inform where prevalence estimates from future studies in different populations are likely to lie. Attempts to mitigate the effect of this statistical heterogeneity included the use of random effects modelling and sensitivity analyses.

Given that two thirds of the studies only included cases of RS associated with cleft palate, the pooled birth prevalence of RS identified by this meta-analysis may potentially underestimate the overall birth prevalence of RS by omitting the 8–17% of cases in which there is no cleft palate [2–4]. Birth prevalence could be further underestimated by the exclusion of cases of non-isolated RS, which are thought to constitute around half of all RS cases, within several studies.

Geographical differences in birth prevalence were evaluated by comparing European studies to non-European studies owing to the small number of studies from any continent other than Europe. However, combining geographical areas in this way could potentially miss a true geographical difference in birth prevalence. Furthermore, the relatively sparse non-European data limits the ability of this study to draw conclusions on geographic and ethnic variations in RS prevalence.

Finally, over a quarter of studies included in the systematic review were assessed as being of low methodological quality. However, sensitivity analysis indicates that inclusion of studies with low quality scores did not significantly affect the results of the meta-analysis. A common methodological weakness was that the approach to RS diagnosis was inconsistent or was poorly described within individual studies. This reduces the validity of the birth prevalence estimates derived from some included studies and means the prevalence estimates from each of the included studies may not be comparable. It is likely that publication of the international consensus diagnostic criteria for RS will result in a more consistent approach to diagnosis within future studies, which will increase the validity of subsequent meta-analyses on this subject.

Points for clinical practice

- Robin sequence affects 9.5 per 100 000 live-born infants according to meta-analysis of published research.
- There may be geographical variations in birth prevalence. This information can be used to plan clinical services for affected infants.

Questions for future research

- Are there true variations in prevalence by geographical location due to differences in environmental or genetic risk factors for disease development?
- Does ethnicity impact the birth prevalence of Robin sequence?

Conclusions

This study summarises the global birth prevalence of RS, indicating that this condition is present throughout the world and within different ethnic groups. It highlights the substantial heterogeneity in birth prevalence estimates among published epidemiological studies, which may be due to factors including variability in diagnostic criteria and thresholds, increasing awareness of RS over time and the use of different methods for case ascertainment. The recent consensus definition should help standardise future cohort studies that aim to establish RS birth prevalence. Future meta-analyses on this subject should compare birth prevalence estimates for studies conducted before and after publication of the 2016 consensus criteria to evaluate the impact that this change in approach to RS definition has had upon its reported birth prevalence.

To more clearly ascertain whether there are geographical differences in birth prevalence, a larger number of studies from non-European countries are required.

This study also highlighted the scarcity of data about how ethnicity affects the birth prevalence of RS, and this should also be another focus of future epidemiological studies. Additional studies in these areas may help to clarify the role of genetic susceptibility and environmental risk factors in the aetiology of RS.

Finally, the finding that RS birth prevalence for live births and total births was similar is important because it indicates that the two groups could be combined in future meta-analyses to increase the study size and precision of the derived birth prevalence estimate.

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References

1 Breugem CC, Evans KN, Poets CF, *et al.* Best practices for the diagnosis and evaluation of infants with Robin sequence: a clinical consensus report. *JAMA Pediatr* 2016; 170: 894–902.
2 Santoro M, Coi A, Barisic I, *et al.* Epidemiology of Pierre–Robin sequence in Europe: a population-based EUROCAT study. *Paediatr Perinat Epidemiol* 2021; 35: 530–539.
3 Maas C, Poets CF. Initial treatment and early weight gain of children with Robin sequence in Germany: a prospective epidemiological study. *Arch Dis Child Fetal Neonatal Ed* 2014; 99: F491–F494.
4 Paes EC, van Nunen DPF, Basart H, *et al.* Birth prevalence of Robin sequence in the Netherlands from 2000–2010: a retrospective population-based study in a large Dutch cohort and review of the literature. *Am J Med Genet A* 2015; 167A: 1972–1982.
5 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
6 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000; 283: 2008–2012.

7 Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377–381.
8 Munn Z, Moola S, Lisy K, *et al.* Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc* 2015; 13: 147–153.
9 Barendregt JJ, Doi SA, Lee YY, *et al.* Meta-analysis of prevalence. *J Epidemiol Community Health* 2013; 67: 974–978.
10 Tufanaru C, Munn Z, Stephenson M, *et al.* Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc* 2015; 13: 196–207.
11 Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–560.
12 Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; 54: 1046–1055.
13 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019; 22: 153–160.
14 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Soft* 2010; 36: 1–48.
15 Bates D, Mächler M, Bolker B, *et al.* Fitting linear mixed-effects models using lme4. *J Stat Soft* 2015; 67: 1–48.
16 Alyami B, Ali-Hassan M, Braimah R, *et al.* Prevalence and clinical case series of syndromic and nonsyndromic cleft lip and palate in a Saudi Arabian neonatal population. *Cleft Palate Craniofac J* 2020; 57: 1259–1265.
17 Bellis TH, Wohlgemuth B. The incidence of cleft lip and palate deformities in the south-east of Scotland (1971–1990). *Br J Orthod* 1999; 26: 121–125.
18 Bister D, Set P, Cash C, *et al.* Incidence of facial clefts in Cambridge, United Kingdom. *Eur J Orthod* 2011; 33: 372–376.
19 Bittar Z. Major congenital malformations presenting in the first 24 h of life in 3865 consecutive births in south of Beirut. Incidence and pattern. *J Med Liban* 1998; 46: 256–260.
20 Brogan WF, Murphy BP. The effects of zero population growth on the incidence of cleft lip and palate in Western Australia. *Med J Aust* 1978; 1: 126–131.
21 Bush PG, Williams AJ. Incidence of the Robin Anomalad (Pierre Robin syndrome). *Br J Plast Surg* 1983; 36: 434–437.
22 Chi SC. Cleft lip and cleft palate in New South Wales. *Aust Dent J* 1974; 19: 111–117.
23 Cleary BJ, Donnelly JM, Strawbridge JD, *et al.* Methadone and perinatal outcomes: a retrospective cohort study. *Am J Obstet Gynecol* 2011; 204: 139–139.
24 Cornel MC, Spreen JA, Meijer I, *et al.* Some epidemiological data on oral clefts in the northern Netherlands, 1981–1988. *J Craniomaxillofac Surg* 1992; 20: 147–152.
25 Czeizel A, Hirschberg J. Orofacial clefts in Hungary: epidemiological and genetic data, primary prevention. *Folia Phoniatr Logop* 1997; 49: 111–116.
26 Dreise M, Galiwango G, Hodges A. Incidence of cleft lip and palate in Uganda. *Cleft Palate Craniofac J* 2011; 48: 156–160.
27 Elahi MM, Jackson IT, Elahi O, *et al.* Epidemiology of cleft lip and cleft palate in Pakistan. *Plast Reconstr Surg* 2004; 113: 1548–1555.
28 Friedlander L, Choquet R, Galliani E, *et al.* Management of rare diseases of the head, neck and teeth: results of a French population-based prospective 8-year study. *Orphanet J Rare Dis* 2017; 12: 94.
29 Greene JC, Vermillion JR, Hay S, *et al.* Epidemiologic study of cleft lip and cleft palate in four states. *J Am Dent Assoc* 1964; 68: 386–404.
30 Hagberg C, Larson O, Milerad J. Incidence of cleft lip and palate and risks of additional malformations. *Cleft Palate Craniofac J* 1998; 35: 40–45.
31 Hewson AR, McNamara CM. Cleft lip and/or palate in the west of Ireland, 1980–1996. *Spec Care Dentist* 2000; 20: 143–146.
32 Higurashi M, Oda M, Iijima K, *et al.* Livebirth prevalence and follow-up of malformation syndromes in 27,472 newborns. *Brain Dev* 1990; 12: 770–773.
33 Jensen BL, Kreiborg S, Dahl E, *et al.* Cleft lip and palate in Denmark, 1976–1981: epidemiology, variability, and early somatic development. *Cleft Palate J* 1988; 25: 258–269.
34 Kamal NM, Othman N. Incidence and types of congenital anomalies in newborns in Sulaimaniyah city in Iraq. *Acta Med Iran* 2018; 56: 769–776.
35 Khrouf N, Spang R, Podgorna T, *et al.* Malformations in 10,000 consecutive births in Tunis. *Acta Paediatr Scand* 1986; 75: 534–539.
36 Kliškinjić A. The incidence of orofacial rifts in children born in the Clinical Hospital Center Split from 2000 to 2018 (Thesis). Split, University of Split, 2019.
37 Knox G, Braithwaite F. Cleft lips and palates in Northumberland and Durham. *Arch Dis Child* 1963; 38: 66–70.

38 Koželj V. Epidemiology of orofacial clefts in Slovenia, 1973–1993: comparison of the incidence in six European countries. *J Craniomaxillofac Surg* 1996; 24: 378–382.
39 Kumar PS, Dhull KS, Lakshmikantha G, *et al.* Incidence and demographic patterns of orofacial clefts in Mysuru, Karnataka, India: a hospital-based study. *Int J Clin Pediatr Dent* 2018; 11: 371–374.
40 Lary JM, Paulozzi LJ. Sex differences in the prevalence of human birth defects: a population-based study. *Teratology* 2001; 64: 237–251.
41 Nunes LMN, Queluz DDP, Pereira AC. Prevalence of oral cleft in Campos dos Goytacazes-RJ, 1999–2004. *Rev Bras Epidemiol* 2007; 10: 109–116.
42 Printzlau A, Andersen M. Pierre Robin sequence in Denmark: a retrospective population-based epidemiological study. *Cleft Palate Craniofac J* 2004; 41: 47–52.
43 Scott AR, Mader NS. Regional variations in the presentation and surgical management of Pierre Robin sequence. *Laryngoscope* 2014; 124: 2818–2825.
44 Tolarova MM, Cervenka J. Classification and birth prevalence of orofacial clefts. *Am J Med Genet* 1998; 75: 126–137.
45 Vallino-Napoli LD, Riley MM, Halliday JL. An epidemiologic study of orofacial clefts with other birth defects in Victoria, Australia. *Cleft Palate Craniofac J* 2006; 43: 571–576.
46 Van Regemorter N, Dodion J, Druart C, *et al.* Congenital malformations in 10,000 consecutive births in a university hospital: need for genetic counseling and prenatal diagnosis. *J Pediatr* 1984; 104: 386–390.
47 Wright M, Mehendale F, Urquhart DS. Epidemiology of Robin sequence with cleft palate in the East of Scotland between 2004 and 2013. *Pediatr Pulmonol* 2018; 53: 1040–1045.
48 Cherian AG, Jamkhandi D, George K, *et al.* Prevalence of congenital anomalies in a secondary care hospital in South India: a cross-sectional study. *J Trop Pediatr* 2016; 62: 361–367.
49 FitzPatrick DR, Raine PA, Boorman JG. Facial clefts in the west of Scotland in the period 1980–1984: epidemiology and genetic diagnoses. *J Med Genet* 1994; 31: 126–129.
50 Forrester MB, Merz RD. Structural birth defects associated with oral clefts in Hawaii, 1986 to 2001. *Cleft Palate Craniofac J* 2006; 43: 356–362.
51 Genisca AE, Frias JL, Broussard CS, *et al.* Orofacial clefts in the national birth defects prevention study, 1997–2004. *Am J Med Genet A* 2009; 149: 1149–1158.
52 Groisman B, Liascovich R, Bidondo MP, *et al.* Birth defects surveillance: experiences in Argentina and Colombia. *J Community Genet* 2019; 10: 385–393.
53 Milan M, Astolfi G, Volpato S, *et al.* 766 cases of oral cleft in Italy. Data from Emilia Romagna (IMER) and Northeast Italy (NEI) registers. *Eur J Epidemiol* 1994; 10: 317–324.
54 Nazer J, Hubner ME, Catalan J, *et al.* Incidencia de labio leporino y paladar hendido en la Maternidad del Hospital Clínico de la Universidad de Chile y en las maternidades chilenas participantes en el estudio colaborativo Latino Americano de malformaciones congénitas (ECLAMC) período 1991-1999 [Incidence of cleft lip and palate in the University of Chile Maternity Hospital and in Chilean maternity patients participating in the Latin American Collaborative Study of Congenital Malformations (ECLAMC)]. *Rev Med Chil* 2001; 129: 285–293.
55 Robert E, Kallen B, Harris J. The epidemiology of orofacial clefts. 1. Some general epidemiological characteristics. *J Craniofac Genet Dev Biol* 1996; 16: 234–241.
56 Sawardekar KP. Profile of major congenital malformations at Nizwa Hospital, Oman: 10–year review. *J Paediatr Child Health* 2005; 41: 323–330.
57 World Health Organization. Typical Orofacial Clefts - Cumulative Data By Register 2007. https://web.archive.org/web/20150928043736/www.who.int/genomics/anomalies/cumulative_data/en/#
58 Gomez-Ospina N, Bernstein JA. Clinical, cytogenetic, and molecular outcomes in a series of 66 patients with Pierre Robin sequence and literature review: 22q11.2 deletion is less common than other chromosomal anomalies. *Am J Med Genet A* 2016; 170A: 870–880.
59 Rozendaal AM, Luijsterburg AJ, Ongkosuwito EM, *et al.* Delayed diagnosis and underreporting of congenital anomalies associated with oral clefts in the Netherlands: a national validation study. *J Plast Reconstr Aesthet Surg* 2012; 65: 780–790.
60 Varadarajan S, Balaji TM, Raj AT, *et al.* Genetic mutations associated with Pierre Robin syndrome/sequence: a systematic review. *Mol Syndromol* 2021; 12: 69–86.