Review

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Gestational Age-Specific Prevalence of Retinopathy of Prematurity in Very Preterm Infants: An Exploratory Meta-Analysis

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Review

Gestational Age-Specific Prevalence of Retinopathy of Prematurity in Very Preterm Infants: An Exploratory Meta-Analysis

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Impact

- Research studies on retinopathy of prematurity are frequently performed using study cohorts defined by regional screening guidelines as below a certain gestational age and/or a certain birthweight.
- This article provides data in support of the notion that populations for research on retinopathy of prematurity should be defined by gestational age threshold only, not gestational age and/or birthweight.

Abstract

Background: The prevalence of retinopathy of prematurity (ROP) is studied in populations defined by gestational age (GA) only, GA or birthweight (BW), and GA and BW. Aggregate differences in gestational age week-specific prevalence estimates are unknown. Methods: Literature search of publications between 1971 and 2024 and data extraction using predefined search terms and inclusion criteria. Results: ROP prevalence changes notably at around 28wks GA, decreasing appreciably at older gestational ages. Including BW alongside GA (as is done in some ROP screening guidelines) affects the variability of ROP prevalence data and may obscure the true population-level association between GA and ROP severity. Conclusion: Clinical study populations for ROP research should be defined by GA thresholds only without additional BW inclusion criteria.

Keywords: retinopathy of prematurity; ROP

Introduction

Retinopathy of prematurity (ROP) is a neonatal disorder of retinal vascularization that may lead to retinal detachment and blindness. First identified in the early 1940s, ROP emerged due to supplemental oxygen used in closed incubators, introduced to improve preterm infant survival at the cost of visual morbidity and blindness. The clinical course of ROP after birth is separated in two phases, the first being characterized by a retinal vessel development cessation or delay shortly after birth and the second by a reinitiation of vessel growth with outgrowth of vessels into the vitreous in severe cases [1]. In severe cases, laser treatment and/or ocular injections of vascular growth factor inhibitors are needed. Despite treatment, some infants will develop adverse visual outcomes, which are more common in preterm infants who had ROP than in their peers who were discharged without ROP [2].

Research reports and national guidelines frequently state that the prevalence of ROP is linked to the gestational age (GA) and birth weight (BW) of preterm infants. Since BW and GA are strongly associated, research studies often do not define their study population by GA only when reporting the prevalence of ROP but also include various cutoff points for BW. While this is plausible for ROP screening purposes, it might introduce bias when defining ROP study populations by GA and/or BW. For example, the American Academies of Ophthalmology and Pediatrics recommend screening for all infants born ≤ 30 weeks of GA or with a BW ≤ 1,500 grams [3]. While such "mixed definitions" might make sense for screening purposes, using the same criteria for research purposes might lead to biased estimates in analyses of risk factors for ROP that are closely related to gestational age and/or birthweight. For example, in study populations defined by a birthweight below 1500g (union of sections B and C in Figure 1) gestationally older infants with intrauterine growth restriction (IUGR) will be over-represented (section C in Figure 1), potentially making IUGR infants look "protected" while this effect is due to higher gestational age, not IUGR [4]. Consequently, the ROP prevalence estimates in the literature vary appreciably.

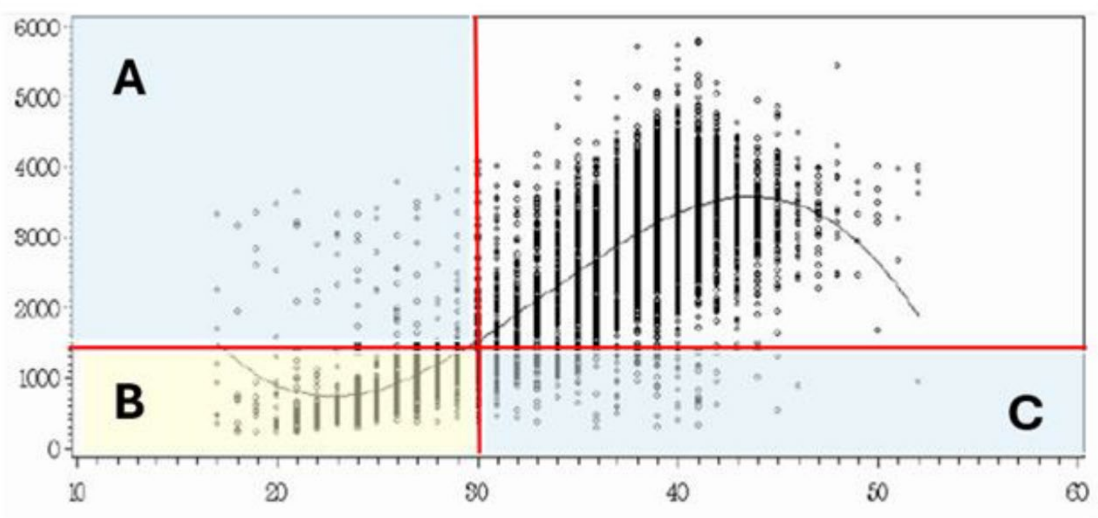

Figure 1. Scatter plot of gestational age against birthweight. Data are from the 1988 U.S. National Maternal and Infant Health Survey, 1988. Plot is modified from [52]. The vertical red line indicates a threshold at 30 weeks gestational age; the horizontal red line indicates a cut-off at 1,500g birthweight. A study sample definition that is the same as screening criteria (<30 weeks ***or*** <1,500g) is indicated by the sum of fields A, C (blue) and B (yellow). A definition as <30weeks ***and*** <1,500g is indicated by field B (yellow).

Since data are often reported across several gestational weeks, important week-to-week variations in ROP prevalence might be masked. In risk analyses, variables that code GA by gestational week have the disadvantage of estimating the risk increase for every single GA week, which assumes linearity of ROP risk across GA weeks which is unlikely. Aggregation into broader and mutually exclusive gestational age categories (e.g., <24 weeks, 24–26 weeks, and ≥27 weeks) might be more informative and even achieve statistical significance (a criterion of dubitable importance) albeit at the expense of precision [5]. Moreover, the overall inconsistency in inclusion criteria across studies limits comparisons of results between them and poses significant challenges for literature synthesis and drawing reliable conclusions.

We wanted to determine the range of ROP prevalence by week gestation based on published data from studies that report ROP prevalence in weekly GA intervals. Our report is not intended to be exhaustive, but merely a beginning for further research into the intricacies of ROP research performed in populations defined by GA and/or BW or only one of the two.

Methods

In the next subsections we offer information about literature search, selection and eligibility criteria, as well as data extraction. We have refrained from using formal PRISMA rules and flowcharts simply because this is an exploratory meta-analysis, not a systematic review.

Search Keyword and Selection Criteria

A literature search was conducted in PubMed, utilizing the search term:

("Retinopathy of Prematurity"[MeSH Terms] OR "Retinopathy of Prematurity"[Title/Abstract] OR "ROP"[Title/Abstract]) AND ("Gestational Age"[MeSH Terms] OR "Gestational Age"[Title/Abstract] OR "GA"[Title/Abstract]) AND ("Cohort Studies"[MeSH Terms] OR "Cohort"[Title/Abstract])

This comprehensive search term was chosen to capture studies that explicitly address ROP, factor in the variable of gestational age, and are designed as cohort studies. The use of both MeSH Terms and keywords in the title/abstract ensures that the search includes both indexed and recently published articles that may not yet have MeSH Terms assigned. The search term resulted in a total of 2,225 search results on PubMed. All studies reporting ROP prevalence for GAs up to 32 weeks were included for analysis per the WHO definition of "very preterm infant" [6].

Eligibility Criteria

To be eligible for inclusion, studies needed to meet the following criteria:

(1) Research articles providing hospital- or population-based data on the prevalence of ROP;

(2) Studies reporting the prevalence of ROP as a percentage within single GA weeks;

(3) Studies with a sample size greater than 300 infants (arbitrary threshold to ensure inclusion of reasonably sized cohorts).

Exclusion criteria encompassed articles that were not peer-reviewed, not published in English, or papers that reported prevalence in GA week ranges that could not be disaggregated into individual weeks. If multiple articles were reported on the same population, the article with the most comprehensive and inclusive data was included.

Data Extraction

Following the initial literature search, we assessed each of the 2,225 results individually to confirm that the studies we identified met the pre-defined eligibility criteria. The extracted studies and data were organized based on whether study samples were defined by GA (Tables 1 and 2), GA or BW (Tables 3 and 4), or both GA and BW (Tables 5 and 6). In each set of tables, the first displays the prevalence of ROP stages 1-5, and the second the prevalence of more severe stages 3-5. We also plotted the data and applied exponential trendlines to illustrate the correlations and trends within each set of criteria and ROP stages (Figures 2-4).

Table 1. Prevalence of ROP stage 1-5 (%) in studies using only gestational age (GA) as cohort definition.

Ref.	Cohort Definition	Birth Years	Inclusion Criteria	N	Gestational Age (weeks)										
					22	23	24	25	26	27	28	29	30	31	32
Seasely et al. [9]	All surviving infants born at the University of Alabama at Birmingham	2013 - 2019	21 < GA < 26	302	91	82	80	60	.	.	.	.	.	.	.
Chan, et al. [10]	All live-born infants admitted to 17 Canadian NICUs	1996 - 1997	GA < 26	754	100	87	84	71	.	.	.	.	.	.	.
Austeng, et al. [11]	Swedish national database	2004 - 2007	GA < 27	506	100	91	86	77	56	.	.	.	.	.	.
Glaser et al.[12]	68 tertiary level neonatal intensive care units in Germany	2009 - 2021	21 < GA < 29	12565	87	86	74	62	47	35	28	.	.	.	.
Shin, et al.[13]	Infants admitted to the Samsung Medical Center neonatal intensive care unit	2005 – 2011	GA < 31	566	100	100	97	90	73	58	20	13	23	.	.
Holmström, et al. [14]	All Swedish infants recorded by the Swedish national register for ROP (SWEDROP)	2008 - 2009	GA < 32	1784	100	89	71	77	49	37	22	10	6	2	.
Dai et al.[15]	All infants dis-charged from NICUs with ROP screening in 68 hospitals from 31 provinces in China.	2010 – 2019	22 < GA < 28	3756	.	91	81	75	69	55	.	.	.	.	.
Holmström et al.[16]	Infants born and screened in are registered in the Swedish register, SWEDROP.	2008–2017	GA < 31	7162	.	90	83	74	55	32	20	13	5	.	.
Klevebro, et al.[17]	Boston cohort from Brigham and Womens' Hospital.	2005 – 2008	22< GA < 31	2521	.	92	95	83	66	60	38	27	11	.	.
	North American cohort from USA and Canada.	2006 – 2009													
	EXPRESS study in Sweden.	2004 – 2007													
	The Gothenburg cohort	2011 - 2012													
	Unpublished Stockholm study	2008 - 2011													
Kiechl-Kohlendorfer et al. [18]	Infants born in Austria.	2011 - 2016	22 < GA < 32	5197	.	37	56	57	37	30	16	10	6	2	.

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Larsson, et al.[19]	Infants born in Stockholm County, Sweden.	1998 - 2000	GA < 32	392	.	100	100	88	86	53	34	14	11	5	5
Holmström, et al.[20]	Infants recorded in the Extremely Preterm Infants in Sweden Study (EXPRESS).	2004 - 2007	GA < 27	411	.	.	87	79	57	.	.	.	.	.	.
Barjol et al.[21]	All premature infants who had a complete screening record at six neonatal centers in France.	2011- 2018	23 < GA < 32	2246	.	.	87	76	54	40	34	21	14	5	.
Ying et al.[22]	Infants undergoing ROP examinations in Postnatal Growth and ROP (G-ROP) Study at 29 North American hospitals.	2006 –2012	24< GA < 30	4163	.	.	.	83	72	52	37	27	.	.	.
Zhou, et al.[23]	Infants admitted to the NICU of BaYi Children's Hospital, China.	2010 - 2011	GA < 32	668	.	.	.	.	.	.	38	17	6	9	.
				Median	100	90	84	76	56	46	28	14	11	3	5
				Min	87	37	56	57	37	30	16	10	5	2	5
				Max	100	100	100	90	86	60	38	27	23	9	5

Table 2. Prevalence of ROP stage 3-5 (%) in studies using only gestational age (GA) as cohort definition.

Ref.	Cohort Definition	Birth Years	Inclusion Criteria	N	Gestational Age (weeks)										
					22	23	24	25	26	27	28	29	30	31	32
Chan, et al.[10]	All live-born infants admitted to 17 Canadian NICUs	1996 - 1997	GA < 26	754	33	55	37	27	.	.	.	.	.	.	.
Diguisto et al.[24]	All liveborn infants in 25 regions in France	2011	21 < GA < 27	783	0	0	8	5	1	.	.	.	.	.	.
Express Group, et al.[25]	All liveborn extremely preterm infants in Sweden who survived 365 days	2004 - 2007	GA < 27	493	80	62	48	32	19	.	.	.	.	.	.
Grottenberg, et al.[26]	Infants discharged alive recorded in the Norwegian Neonatal Network of registry NICUs	2009 – 2017	GA < 28	1100	20	35	30	16	9	4	.	.	.	.	.
Goldstein et al.[27]	All infants with data available from the California Perinatal Quality Care Collaborative (CPQCC)	2007 - 2011	21 < GA < 30	14444	65	47	42	31	15	6	2	1	.	.	.

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Holmström, et al.[14]	All Swedish infants recorded by the Swedish national register for ROP (SWEDROP)	2008 - 2009	GA < 32	1784	82	67	32	31	15	7	6	1	2	0	.
Agarwal, et al.[29]	Infants born carried out in a tertiary perinatal hospital in Singapore	1990 - 2007	GA < 27	570	.	47	50	39	13	.	.	.	.	.	.
Boland, et al. [30]*	All livebirths in Victoria, Australia's 70 hospitals with Level 1 or Level 2 obstetric and special care nursery (SCN) and three NICUs	2010 - 2011	22 < GA < 27	360	.	20	5	4	6	1	.	.	.	.	.
Dai et al. [15]	All infants discharged from NICUs with ROP screening in 68 hospitals from 31 provinces in China.	2010 - 2019	22 < GA < 28	3756	.	16	48	30	20	11	.	.	.	.	.
Klevebro, et al. [17]	Boston cohort from Brigham and Womens' Hospital.	2005 – 2008	22< GA < 31	2521	.	58	53	29	17	9	4	1	1	.	.
	North American cohort from USA and Cansplitada.	2006 – 2009													
	EXPRESS study in Sweden.	2004 – 2007													
	The Gothenburg cohort	2011 – 2012													
	Unpublished Stockholm study	2008 - 2011													
Jensen et al.[31]	Clinical data from the Optum Corporation database of liveborn infants admitted to NICUs	2010 to 2016	GA < 32	6264	.	28	21	12	9	3	2	1	1	0	.
Kiechl-Kohlendorfer et al. [18]	Infants born in Austria.	2011 - 2016	22 < GA < 32	5197	.	19	21	9	6	2	2	1	0	0	.
Ancel, et al.[32]	98% of all infants born in France who survived to discharge	2011	22 < GA < 34	3477	.	0	17	9	2	1	0	0	0	0	0
Larsson, et al.[19]	Infants born in Stockholm County, Sweden	1998 - 2000	GA < 32	392	.	100	78	77	45	20	9	4	2	2	0
Travers, et al.[33]**	Infants from 300 participating NICUs in the United States for the database of the Pediatrix Clinical Data Warehouse	2009 - 2013	22 < GA < 38	54225	.	33	27	16	9	3	2	1	0	0	0

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Kong, et al.[34]	Liveborn infants in nine general hospitals and six maternal and children's hospitals from major cities of 11 provinces in China.	2013 - 2014	23 < GA < 27	1760	.	.	.	29	18	15	10	7	4	2	.
Parappil, et al.[35]	All infants born in the Women's Hospital's NICU in Doha that accounts for 99% of birth in Qatar	2002–2006	GA < 32	597	.	.	.	.	.	.	.	18	7	5	3
				Median	49	40	31	27	12	5	2	1	1	0	0
				Min	0	0	5	4	1	1	0	0	0	0	0
				Max	82	100	78	77	45	20	10	18	7	5	3

*Require laser treatment, ** ROP stage ≥3 or treated with ablation/antivascular endothelial growth factor

Table 3. Prevalence of ROP stage 1-5 (%) in studies using gestational age (GA) OR birthweight (BW) as cohort definition.

Ref.	Cohort Definition	Birth Years	Inclusion Criteria	N	Gestational Age (weeks)										
					22	23	24	25	26	27	28	29	30	31	32
Bell et al.[36]	Infants born and recorded at 19 Neonatal Research Network's centers in US	2013 - 2018	22 £ GA £ 28 or 401 < BW < 1000	9966	93	88	86	71	58	42	30	.	.	.	.
Gunn, et al.[37]	All infants admitted to the NICU of the Royal Brisbane and Women's Hospital in Queensland Australia	1992 - 2009	GA<26 or BW<1500 g	373	.	91	90	76	.	.	.	.	.	.	.
Markestad, et al.[38]	All survivor in Norway recorded by all obstetric and pediatric departments in Norway.	1999 - 2000	22 < GA < 28, or 500 < BW < 1000	376	.	56	60	38	27	24	.	.	.	.	.
Gerull et al.[39]	Infants registered at the national registry of very preterm infants in Switzerland	2006 - 2015	22 < GA < 32, or BW < 1501g	6719	.	37	44	38	23	14	8	4	2	1	.
Quinn et al.[40]	Infants born at 29 hospitals in the United States and Canada	2006 - 2011	GA ≤ 30 or BW < 1501 g	7483	.	97	94	83	72	52	37	27	15	9	.
Almeida et al.[41]	All infants admitted to two neonatal intensive care units from two institutions in Portugal	2012 - 2020	GA ≤ 32, or BW ≤ 1500, or BW ≤ 2000 with prolonged O_2 exposure	475	.	100	85	75	74	58	38	18	16	4	2
Yau, et al.[34]	All live-born infants at Caritas Medical Centre's 2 NICUs in HongKong, China	2007 – 2012	GA < 33 or BW < 1501g	513	.	.	95	83	74	38	19	13	3	4	2
Braimah, et al.[42]	Infants admitted to the NICU of Korle-Bu Teaching Hospital, Ghana	2018 - 2019	GA < 37 or BW < 2kg	400	.	.	.	.	.	88	55	36	22	21	9
				Median	93	89	86	75	65	42	34	18	15	4	2
				Min	93	37	44	38	23	14	8	4	2	1	2
				Max	93	100	95	83	74	88	55	36	22	21	9

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Table 4. Prevalence of ROP stage 3-5 (%) in studies using gestational age (GA) OR birthweight (BW) as cohort definition.

Ref.	Cohort Definition	Birth Years	Inclusion Criteria	N	Gestational Age (weeks)										
					22	23	24	25	26	27	28	29	30	31	32
Bell et al.[36]	Infants born at 19 Neonatal Research Network's centers in US.	2013 – 2018	22 £ GA £ 28 or 401 < BW < 1000	9966	31	38	32	19	10	4	2	.	.	.	.
Muether, et al.[43] *	All inborn preterm infants who received complete in-house primary care at the Department of Neonatology, University Hospital of Cologne, Germany	2001 – 2009	GA < 32 or BW <1501 g	767	62	25	27	15	3	4	1	1	1	0	0
Wang et al. [44] **	Any White, Black, and Asian infants in the study site of 29 hospitals, born between 2006-2011, and 41 hospitals who underwent ROP screening.	2015 – 2017	GA < 30 or BW < 1501g	9185	45	56	47	33	17	9	3	2	1	1	1
				White: 5580	48	59	49	40	19	12	4	2	1	1	1
				Black: 3252	29	53	43	24	13	4	2	1	1	1	0
				Asian: 353	100	33	65	36	31	7	3	0	0	4	2
Yu, et al. [45] ***	Infants underwent ROP screening in the G-ROP-1 and G-ROP-2 studies at 29 and 41 hospitals in US and Canada	2006 – 2011	GA < 32 or BW < 1501g	11463	38	28	22	17	8	4	2	1	0	0	0
Gunn, et al.[37]	All infants admitted to the NICU of the Royal Brisbane and Women's Hospital in Australia.	1992 – 2009	GA<26 or BW<1500 g	373	.	29	18	12	.	.	.	.	.	.	.
Gerull et al.[39]	Infants who were registered at the national registry of very preterm infants in Switzerland	2006 – 2015	22 < GA < 32 or BW<1501g	6719	.	6	21	9	5	1	1	1	0	0	.
Cao et al.[45]	All liveborn infants admitted the Chinese Neonatal Network (CHNN) NICUs.	2019	GA < 32 or BW <1500g	8171	.	50	39	26	16	8	6	3	2	2	.
Darlow, et al.[46]	Infants admitted to a NICU in Australia or New Zealand	1998 – 1999	GA<32 or BW<1500 g	2105	.	.	.	16	11	3	3	.	.	.	.
				Median	45	36	36	19	12	4	3	1	1	1	0
				Min	29	6	18	9	3	1	1	0	0	0	0
				Max	100	59	65	40	31	12	6	3	2	4	2

* ROP treated according to German guidelines **Type I, Type II, or stage 3 in zone 3 with or without Plus disease ***Type I ROP

Table 5. Prevalence of ROP stage 1-5 (%) in studies using gestational age (GA) AND birthweight (BW) as cohort definition.

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Ref.	Cohort Definition	Birth Years	Inclusion Criteria	N	Gestational Age (weeks)										
					22	23	24	25	26	27	28	29	30	31	32
Shemesh et al.[47]	Twin infants born in Israel with ROP screening.	1995 - 2020	22 ≤ GA ≤ 25 and BW ≤ 1500g	4092	.	.	69	55	40	26	14	6	.	.	.
Fernández, et al.[48]	Infants recorded in Neonatal Network's 26 NICUs from: Argentina, Brazil, Chile, Paraguay, Peru and Uruguay		23 < GA < 32 and 500g< BW < 1500g	8234	.	.	79	71	57	43	29	22	18	18	.
Hutchinson, et al.[49] *	Infants underwent screening examinations for ROP in Phoenix, US metropolitan area	1993 - 1999	GA < 33 and BW > 1250g	973	.	.	.	.	.	.	40	34	22	15	11
				Median	.	.	74	63	48	35	29	22	20	17	11
				Min	.	.	69	55	40	26	14	6	18	15	11
				Max	.	.	79	71	57	43	40	34	22	18	11

*ROP Stage 1-4

Table 6. Prevalence of ROP stage 3-5 (%) in studies using gestational age (GA) AND birthweight (BW) as cohort definition.

Ref.	Cohort Definition	Birth Years	Inclusion Criteria	N	Gestational Age (weeks)										
					22	23	24	25	26	27	28	29	30	31	32
Costeloe, et al.[50]	All infants liveborn in all 182 maternity hospitals in England.	2006	22 < GA < 26, and BW > 500g	1041	33	42	35	21	11	.	.	.	.	.	.
Miyazawa et al.[51]*	All survived infants including deceased as described in the Committee Report in Japan.	2015	BW < 1000g and GA < 29	2508	64	60	50	38	31	20	12	.	.	.	.
Hutchinson, et al.[49]	Infants underwent screening examinations for ROP in Phoenix, US metropolitan area	1993 - 1999	GA < 33 and BW > 1250	973	.	.	.	.	.	.	11	8	3	2	1
				Median	45	45	44	35	30	20	11	8	3	2	1
				Min	33	42	35	21	11	20	11	8	3	2	1
				Max	64	60	50	38	31	20	12	8	3	2	1

* ROP requiring treatment such as photocoagulation, anti-vascular endothelial growth factor or vitrectomy

Results

The data extraction process resulted in the identification of 47 articles that met the criteria and were included in the analysis. The studies included data collected ranging from 1971 - 2024 and encompass a diverse range of neonatal intensive care levels, variations in race, ethnicity, socioeconomic backgrounds, and healthcare systems.

Among study populations defined by GA only, the median prevalence of ROP stages 1-5 decreased from 100% at 22 wks to 5% at 32 wks (Table 1). The median prevalence of ROP stage 3-5 ranged from 49% at 22 wks and bottomed out at 0-1% at 29-32wks (Table 2).

Among studies that included infants below a certain GA or BW threshold, e.g., below 26 wks or <1,500g, the median prevalence of ROP stage 1-5 ranged from 93% at 22 weeks (data from one study) to 2% at 32 wks (Table 3). The median prevalence of ROP stage 3-5 ranged from a 45% at 22 wks to 0% at 32 wks. Again, the bottoming out started at 29 wks (Table 4).

Only three studies defined their study population by GA *and* BW threshold (Table 5). The median prevalence of ROP stage 1-5 ranged from 74% at 24 wks to 11% at 32 wks while the median prevalence of ROP stage 3-5 ranged from 45% at 22 wks to 1% at 32 wks (Table 6). In these studies, the prevalence of severe ROP did not bottom out, but started to decline below 10% at 29 wks.

We observed some prominent changes in ROP prevalence at certain gestational ages. For example, in study samples defined by GA *only*, ROP stage 1-5 drops by >50% between 28 and 29 wks from 28% to 14% (Table 1) and ROP stage 3-5 between 25 and 26 wks from 27% to 12% (Table 2). For studies reporting GA or BW, similar drops are noted between 28 and 29 wks from 34% to 18% for ROP 1-5 (Table 3), and between 26 and 27 wks from 12% to 4% for ROP 3-5 (Table 4). Among studies using GA and BW as inclusion criteria, the decline of ROP prevalence stage 1-5 is more steady and less prominent (Table 5) while the prevalence of severe ROP drops from 20% to 11% between 27 and 28 weeks (Table 6).

The data on ROP prevalence confirm the well-established association between decreasing GA and increasing ROP risk (Figures 2-4). Not surprisingly, this pattern persists across various study population definitions, whether they employ gestational age alone or in conjunction with birth weight as cohort definition.

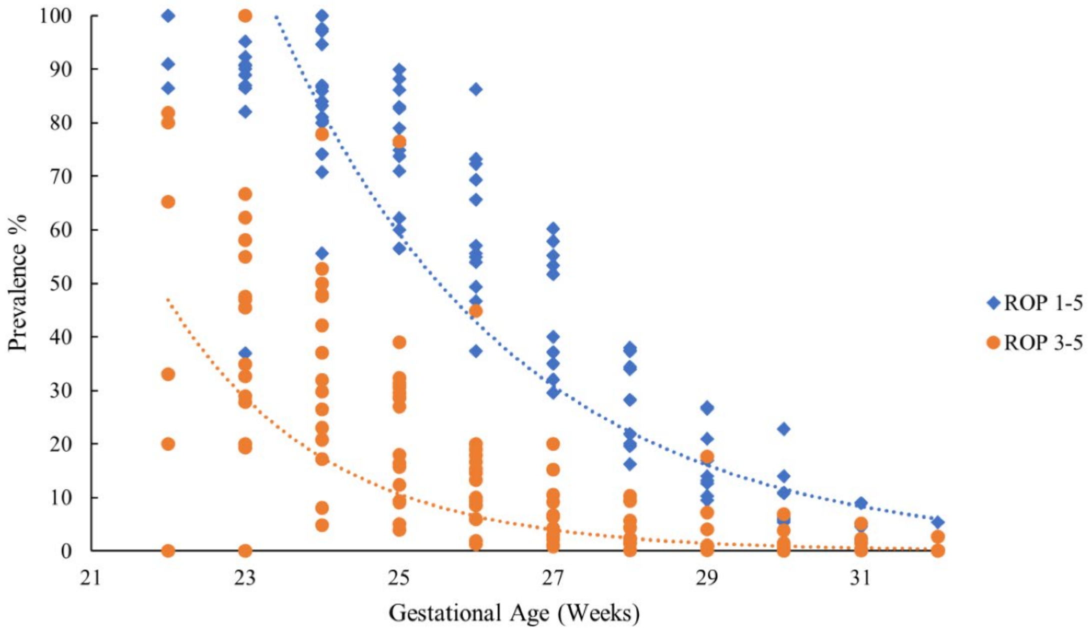

Figure 2. Scatter plot based on data from 30 published studies showing the reported prevalence of retinopathy of prematurity (ROP) for stages 1-5 (blue dots) and stages 3-5 (orange dots) in studies with gestational age (GA) as the sole entry threshold. The ROP stage 1-5 data points are more tightly grouped, indicating lower variability, in contrast to the stage 3-5 data. Both data groups exhibit a downward trend in prevalence with increasing gestational age.

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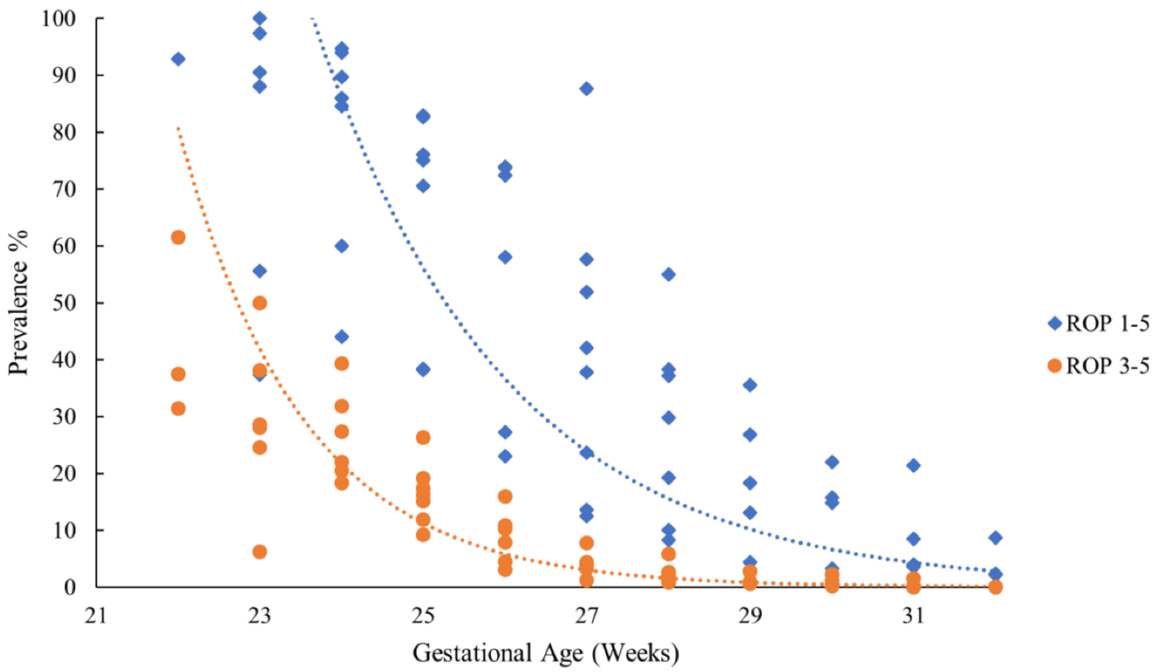

Figure 3. Scatter plot based on data from 13 published studies showing the reported prevalence of retinopathy of prematurity (ROP) for stages 1-5 (blue dots) and stages 3-5 (orange dots), with GA or BW thresholds as the entry criteria. Both stage 1-5 and stages 3-5 data display a higher variance compared to studies that use only a GA-based entry criterion (see Figure 1). Both data groups exhibit a downward trend in prevalence with increasing gestational age.

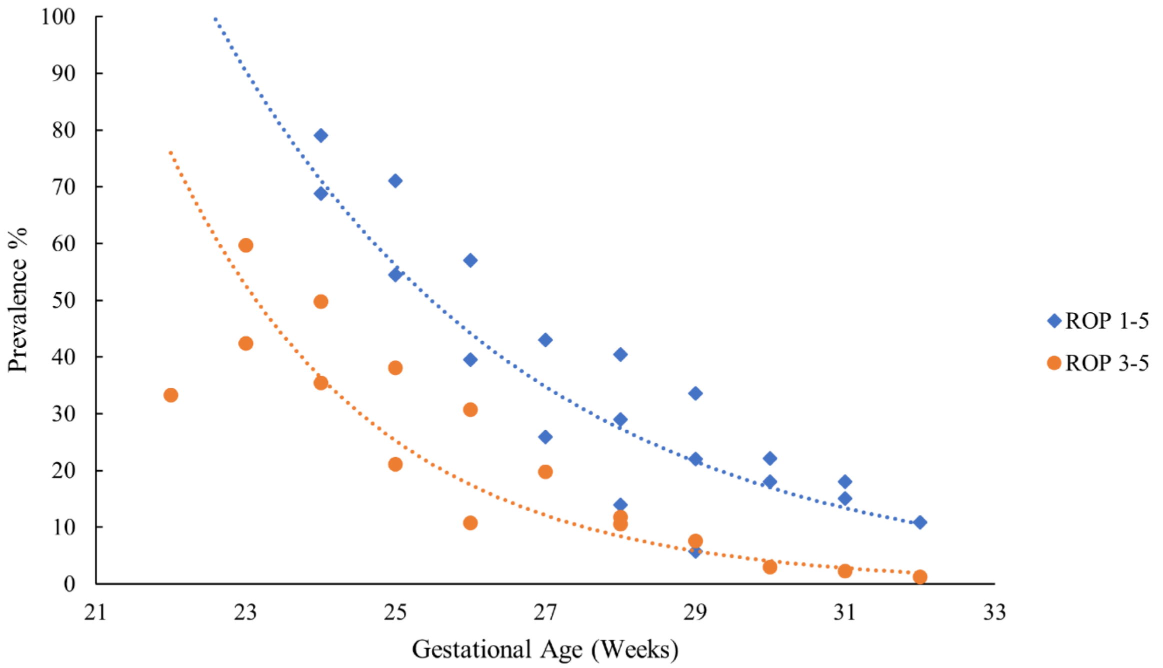

Figure 4. Scatter plot based on data from 5 published studies showing the reported prevalence of retinopathy of prematurity (ROP) for stages 1-5 (blue dots) and stages 3-5 (orange dots), with GA and BW thresholds as the entry criteria. Although both data groups exhibit a low variance similar to GA-only prevalence (see Figure 1), the small number of studies included in this figure certainly limits the interpretation of the observed lower variance.

Discussion

In this study of published data, we systematically examined the prevalence of ROP across studies that used different definitions of study populations. Our findings contribute to the existing body of research on ROP by providing a detailed analysis of ROP prevalence by each gestational week, a perspective that has not been previously explored in meta-analyses of published data.

First, we looked at the prevalence of any (stage 1-5) and severe (stage 3-5) ROP in studies that included infants with a gestational age below a pre-defined threshold (Tables 1 and 2, resp.). This would be the type of study in which we assume the GA-specific ROP prevalence estimate to be closest to the true value in the population. Second, we looked at studies that included infants with a gestational age below a certain threshold or a birthweight below a predefined weight cut-off (Tables 3 and 4, see Figure 1, areas A, B, and C). These studies might include infants whose gestational age might be above the gestational age threshold simply because their birthweight is untypically low (i.e., infants with IUGR that are small for gestational age (SGA) at birth). In these studies one might underestimate the association between ROP and GA, because although SGA newborns are at increased risk for ROP [7], SGA infants *of higher GA* might carry a lower risk for ROP due to their comparatively advanced maturity. Third, we were interested in the ROP prevalence in studies defined by both GA *and* BW (Tables 5 and 6; see Figure 1, area B). In these studies, infants might be excluded because their birthweight is above a predefined birthweight threshold while their gestational age is below the gestational age threshold. For example, a male infant with 1550g birthweight born at 29 wks is roughly at the 91st centile for gestational age. He might be included in a study that defines its population by GA < 30wks *or* BW <1500g (because he is <30 wks) but would be excluded from a study that uses both a GA <30 wks *and* a BW < 1500 g as the inclusion thresholds, because he meets one (GA) but not the other entry criterion (BW).

Our analysis of data from 47 articles demonstrated a clear correlation, with lower GA associated with an increased risk of ROP, with and without including BW as an inclusion criterion. This finding aligns with previous studies that have established a strong negative association between GA and ROP prevalence [8].

Our analysis suggests certain GA cutoff points at which ROP prevalence drops appreciably. Such cutoff points may be interesting to those who study risk factors for ROP that are closely related to GA.

Building on these findings, the data also illustrate a difference in detecting critical cutoff points for ROP prevalence among the three methods of cohort inclusion criteria. In studies defining solely by GA (Tables 1 and 2), the cutoff points are more spread apart [25–28], indicating a two-week gap between significant drops in ROP prevalence. Conversely, for studies that define cohort by GA *or* BW (Tables 3 and 4), the cutoff points are the same, with just a two-week difference [26–29]. However, all cut-off points are shifted one week later compared to GA-only studies. This gap significantly narrows in cohort definition by GA *and* BW (Tables 5 and 6) with the cutoff points aligning exactly for ROP stage 1-5 and ROP stage 3-5 groups.

Our results suggests that the gestational age-specific data variability for any ROP (stages 1-5) is smaller than that of severe ROP (stage 3-5) in studies defined only by GA (Figure 2), while being comparatively greater in studies that use GA *or* BW as an entry criterion (Figure 3). In study populations defined by both GA *and* BW, the data variability is relatively tight for both ROP stage 1-5 and ROP stage 3-5 (Figure 4). It remains to be studied whether this difference might be related to the prevalence of ROP stage 1-5 reflecting ROP *occurrence*, while the prevalence of ROP stage 3-5 reflect *progression* to severe disease. Factors related to the former are more likely to explain the etiology of ROP, while factors related to the latter might be correlates of the clinical course leading to disease progression. Of course, such differences could also occur due to chance. We found 30 studies that were defined by GA only and 13 studies defined by GA *and* BW, so the data variability is expected to be higher in the latter group due to lower number. Another difference is that the GA and BW group of studies includes at least two studies that defined ROP by Type I/II and Plus disease, which implies

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that they have more solid data on ROP than those that defined ROP by stage. This might lead to a more reliable classification of severe disease and, thus, less variability.

Our study comes with inherent limitations on the interpretability of the findings. Many factors may have contributed to the appreciable data variability across studies beyond study sample definition. For example, samples drawn from hospital populations are probably more biased than samples that are truly population-based. Moreover, the methods of GA-estimation is surely different across studies and over the years. As indicated in all tables, the infants included in the studies we analyzed were born across a wide range of calendar years. Obstetric, perinatal, neonatal, and ophthalmological care has changed appreciably over the past decades. However, the vast majority of infants included in the studies we analyzed was born after the year 2000 and of those born in the 1990s most were born in the second half of the decade. Finally, reporting data on ROP by stage only may be considered a weakness. Additional information about zone and Plus disease would be more specific information about the need for treatment.

However, despite these methodological limitations, this study provides valuable insights into the complex relationships between GA, BW, and ROP prevalence, highlighting the need for uniform reporting standards to enhance the robustness and applicability of future meta-analyses in this field.

In conclusion, we found that the variability of gestational week-specific ROP prevalence data across published studies might differ by study cohort definition. As researchers interested in explaining ROP etiology, we advocate for the definition of cohort studies by GA only. We also encourage students of ROP occurrence to report their data by individual gestational weeks.

Authors' contributions: Shiyu Zhang performed the literature search and created the first version of tables, figures, and the manuscript text. Paige Scudder oversaw the literature search and assisted with the design and creation of the tables and edited subsequent versions of the paper. Tora Sund Morken contributed to the work process from the ophthalmological perspective and offered manuscript edits. Christiane E.L. Dammann lent her neonatological expertise and participated in the writing and editing of the paper. Olaf Dammann had the initial idea for the project, oversaw the literature review and creation of tables and figures, and contributed to the writing and editing of the manuscript at all stages.

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