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Postanesthesia Apnea in Former Preterm and Term Infants: A Qualitative Systematic Review and Meta-analysis

Priti G. Dalal, M.D., Shobha Malviya, M.D., Charles J. Coté, M.D., Manon Haché, M.D., Amy Knehans, M.L.I.S., Laura D. Donohue, M.D., Jennifer L. Chiem, M.D., Tatiana Kubacki, M.D., James Fehr, M.D., Joseph P. Cravero, M.D., Vernon M. Chinchilli, Ph.D., Eugenie Heitmiller, M.D.

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ABSTRACT

Former preterm and term infants are at risk for postanesthesia apnea, but the lack of uniform standards for monitoring and discharge criteria leads to inconsistent practice. The primary aim of this study was to identify major risk factors for postanesthesia apnea. This systematic review and meta-regression analysis used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Agency for Healthcare Research and Quality guidelines. The literature search included English language case reports, case series, clinical studies, and clinical trials. Major databases were queried from inception to October 2025. A total of 6,191 articles underwent title and abstract screening, 491 underwent full-text screening, and 173 underwent detailed reviews. Data were extracted from 115 of 173 articles (98 studies, 17 case reports or series). Across studies (preterm or full term infants), the median incidence of apnea was 7.6% (range, 0 to 85%). Univariable meta-regression analysis (96 eligible articles) identified five significant predictors of apnea: gestational age, postmenstrual age at time of procedure, birth weight, procedure duration, and year of publication. Odds for apnea incidence decreased with later publication year, older gestational age at birth, older postmenstrual age at time of surgery, higher birth weight, and shorter procedure duration. A multivariable "best fitting model" (64 eligible articles) including publication year (1986 to 2025) and postmenstrual age (32 to 63 weeks) found a decrease in odds of apnea incidence with later publication year (odds ratio [OR], 0.936; CI, 0.91 to 0.964; $P < 0.001$) and higher postmenstrual age (OR, 0.889; CI, 0.828 to 0.954; $P = 0.001$). Recommended postanesthesia monitoring duration ranged from 6 to 24 h based on postmenstrual age. Meta-regression showed significantly lower apnea odds with neuraxial *versus* general anesthesia (OR, 0.236; CI, 0.094 to 0.592; $P = 0.003$). Postmenstrual age appears to be the strongest and most consistent risk factor for postanesthesia apnea; neuraxial anesthesia may reduce this risk. An individual participant data meta-analysis in a follow-up article will shed further light on the at-risk postmenstrual age threshold for increased risk and help refine monitoring recommendations for these vulnerable infants.

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Former preterm and term infants are at increased risk for apnea after sedation or anesthesia.[1] This vulnerability is attributed to immature central respiratory mechanisms, underdeveloped respiratory musculature, and sensitivity to anesthetic and sedative agents.[2] Their higher oxygen consumption further increases the risk for oxygen desaturation and associated bradycardia during apnea events.[3,4] Furthermore, cardio-respiratory insults may affect neurocognitive development, underscoring the need for optimal management.[5] Studies suggest that the "at-risk" period for postanesthesia apnea and bradycardia extends up to 60 weeks

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Priti G. Dalal, M.D.: Department of Anesthesiology and Peri-operative Medicine, Penn State College of Medicine, Penn State Health Children's Hospital, Hershey, Pennsylvania.

Shobha Malviya, M.D.: Professor Emeritus, Department of Anesthesiology, University of Michigan, Ann Arbor, Michigan.

Charles J. Coté, M.D.: Division of Pediatric Anesthesia, Department of Anesthesia, Critical Care and Pain Management, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts.

Manon Haché, M.D.: Department of Anesthesiology, Columbia University Medical Center, New York, New York.

Amy Knehans, M.L.I.S.: Penn State College of Medicine, Hershey, Pennsylvania.

Laura D. Donohue, M.D.: Department of Anesthesiology, Mary Bridge Children's Hospital, Tacoma, Washington.

Jennifer L. Chiem, M.D.: Department of Anesthesiology and Pain Medicine, University of Washington, Seattle Children's Hospital, Seattle, Washington.

Abbreviations: AAP, American Academy of Pediatrics; **CASP**, Critical Appraisal Skills Program; **MeSH**, Medical Subject Heading; **OR**, odds ratio; **PACU**, postanesthesia care unit; **PRISMA**, Preferred Reporting Items for Systematic Reviews postconceptual age for former preterm infants and up to 45 weeks in full-term infants.[1,6] Multiple case reports, clinical studies, and systematic reviews[7–10] have described numerous risk factors contributing to postanesthesia apnea.[1,7,8,11–13] However, no consistent criteria exist across institutions for admission age cutoff, monitoring modalities, and monitoring duration. This practice variability increases the risk of adverse events for infants and liability for clinicians; one author (C.J.C.) is aware of such a malpractice case.

Recommendations put forth by the American College of Surgeons' (Chicago, Illinois) optimal resource document for level 1 verification of children's surgical centers[14] and the American Academy of Pediatrics (AAP; Itasca, Illinois)[15] are based on previously available data. The American College of Surgeons recommends admitting former preterm infants younger than 50 weeks postmenstrual age and term infants up to 4 weeks of age after general anesthesia.[14] The AAP recommends at least 12 h of monitoring after anesthesia and surgery for former preterm infants younger than 50 to 60 weeks postconceptual age and term infants under 4 weeks[15] of age. These recommendations differ in terminology (the use of postmenstrual age rather than postconceptual age is recommended by the AAP[16]; these position statements were reaffirmed in 2008 and 2021), leaving no clear consensus regarding thresholds for an at-risk cutoff age for postanesthesia admission or duration of monitoring.

The goal of our study was to evaluate the available literature to help establish evidence-based recommendations. Our primary objectives were to (1) perform a systematic review and meta-analysis of the available English language literature; (2) describe the extensive literature review we used to unify the available data; (3) identify risks factors for postanesthesia apnea; and (4) clarify with greater specificity infants at risk for postanesthesia apnea.

Materials and Methods

Data Sources and Searches

A systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17,18] and methods recommended in the Agency for Healthcare Research and Quality Methods Guide for Effectiveness and Comparative Effectiveness Reviews using a predefined protocol.[19] The planned workflow is shown in appendix 1. We used a combination of keywords and Medical Subject Headings (MeSH) with the major search terms: apnea, bradycardia, premature infants, anesthesia, and postoperative care (appendix 1). Two research librarians (A.K. and B.H.) executed systematic comprehensive searches of Medline (1966 to 2025), Embase (1947 to 2025), the Cochrane Library (1992 to 2025), the Cochrane Neonatal Review Group (1993 to 2025), Web of Science (1900 to 2025), and the Cumulative Index to Nursing and Allied Health Literature (1981 to 2025). We also examined published and unpublished research from the following sources: Clinical Trials.gov, the World Health Organization International Clinical Trials Registry Platform, the Agency for Healthcare Research and Quality, the International Standard Randomized Controlled Trial Number Registry, the Health Services Research Projects in Progress, the European Union Clinical Trials Register, the Society for Pediatric Sedation, the Pediatric Regional Anesthesia Network, the Pediatric Sedation Consortium, and the Wake-up Safe Patient Safety Organization. We reviewed all articles included in our final analysis for possible additional references. Citations were stored and managed in EndNote (Clarivate Analytics, USA); and duplicate records were removed (fig. 1).

Study Selection

The inclusion criteria were articles with infants younger than 12 months of age who underwent diagnostic or therapeutic procedures under general anesthesia (with or without regional analgesia), neuraxial (spinal or caudal) anesthesia, or sedation, with a specific focus on reports of apnea and/or bradycardia and/or oxygen desaturation within the first 24 h postanesthesia. Case reports, case series, clinical studies, and clinical trials published in English were reviewed; if they described infants of mixed ages, we only included data from infants aged less than 12 months that met our inclusion criteria. Infants from the pediatric intensive care unit who were not intubated or on continuous positive airway pressure pre- or postprocedure were included if they met inclusion criteria. The definition of apnea based on duration varied among the articles, ranging from 15 to 30 s; in some cases, apnea duration was not defined. Only articles where "apnea" was clearly described as an adverse event were included. Articles where no monitoring was reported were included if apnea, bradycardia, or desaturation were documented based on clinical assessments (*e.g.*, nursing observation).

Exclusion criteria were studies of infants 12 months of age or older, procedures using only local anesthesia, infants who remained intubated after the procedure, review articles (defined as articles summarizing existing literature), animal studies, and non–English literature.

Data Extraction and Quality Assessment

The reviewer team consisted of 10 investigators (C.J.C., J.L.C., J.P.C., L.D.D., P.G.D., J.F., M.H., E.H., T.K., and S.M.) using a four-phase process (appendix 2). Phase 1

Tatiana Kubacki, M.D.: Department of Anesthesiology, Columbia University Medical Center, New York, New York.

James Fehr, M.D.: Department of Anesthesiology, Stanford University, Stanford, California.

Joseph P. Cravero, M.D.: Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts; and Department of Anesthesiology, Boston Children's Hospital, Boston, Massachusetts.

Vernon M. Chinchilli, Ph.D.: Penn State College of Medicine, Hershey, Pennsylvania.

Eugenie Heitmiller, M.D.: Department of Anesthesiology and Pediatrics, Children's National Hospital, George Washington School of Medicine and Health Sciences, Washington, D.C.

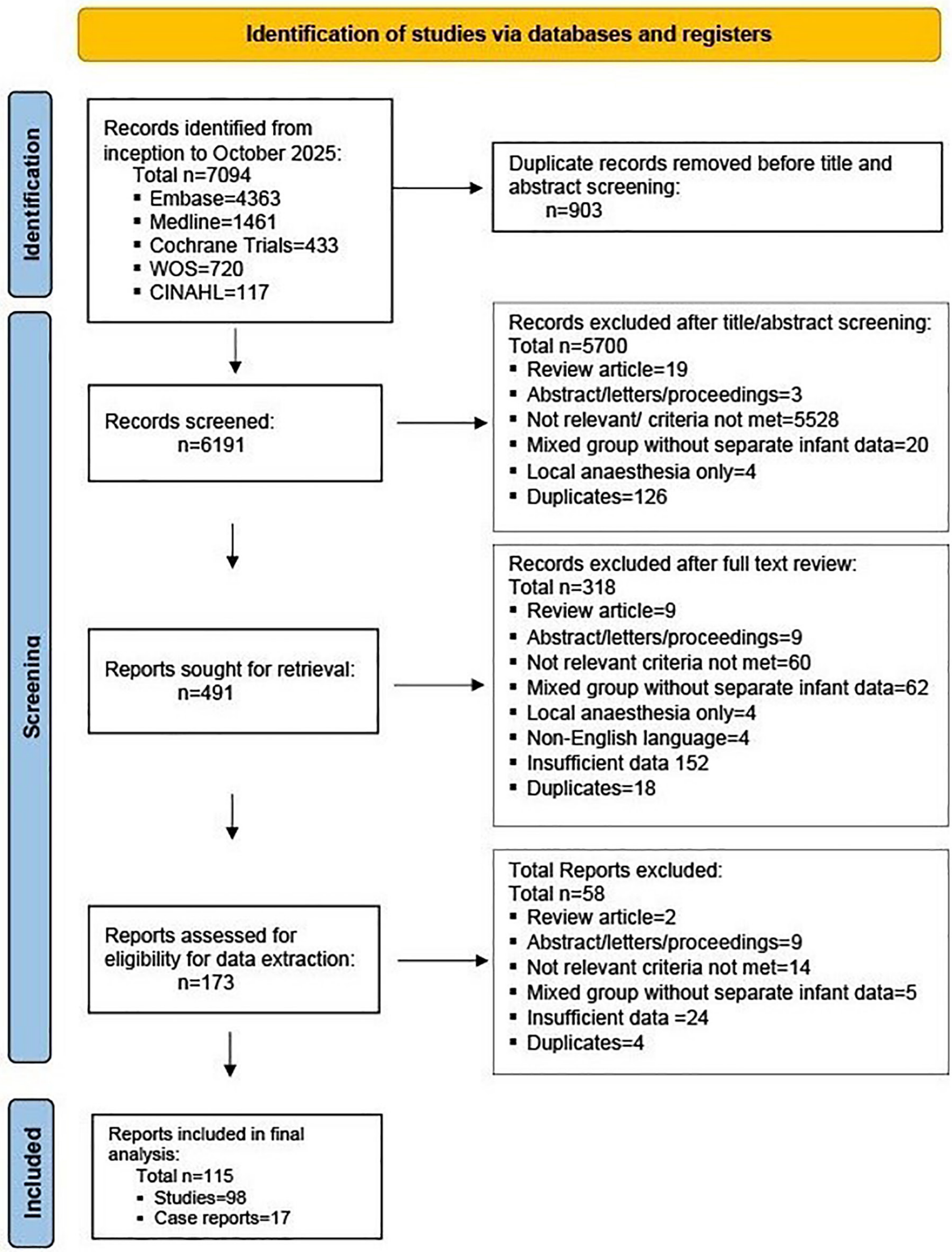

Fig. 1. PRISMA[18] 2020 flow diagram. The figure shows a summary of the articles searched. CINAHL, Cumulative Index to Nursing and Allied Health Literature; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WOS, Web of Science.

identified articles through title and abstract screening, phase 2 was a full methodologic text review, phase 3 was full data extraction, and phase 4 was data summary for statistical analysis.[20] To reduce the risk of selection bias, two authors independently reviewed abstracts and full-text articles at each review phase. A senior tiebreaker resolved disagreements. Reasons for exclusion were documented at every phase.

Phase 1: Article Identification and Inclusion. Phase 1 consisted of a complete literature search to identify articles related to the research question. Two investigators independently screened titles and abstracts for inclusion; disagreements were resolved by a third investigator (tiebreaker). Articles were included only if they met all four screening questions: (1) article in English; (2) postanesthesia apnea reported as a primary or secondary outcome variable; (3) age less than 12 months; and (4) general or neuraxial anesthesia or sedation was administered.

Each abstract was independently screened by two reviewers. Citations were excluded if both reviewers answered "No" to any question above and advanced to phase 2 if both reviewers answered "Yes" to all four questions. Disagreements between reviewers were resolved by two tiebreakers (P.G.D. and M.H.). When the two tiebreakers were unable to resolve the disagreement, an additional independent reviewer made the final decision. Duplicate abstracts and titles were deleted. Articles that passed phase 1 review then entered phase 2 review.

Phase 2: Full-text and "Gray Literature" Screening. Phase 2 included all articles that passed phase 1 screening (fig. 1). Full-text articles were reviewed for methodology, with inclusion or exclusion criteria again applied; articles finally selected were then rated for quality. Inclusion and exclusion criteria and disagreements between screeners were handled in the same manner as phase 1; the number of full-text articles excluded and the reasons for exclusion were documented. This phase also screened "gray literature," which consisted of reports apart from the traditional databases that identified apnea events and met our inclusion and exclusion criteria.

Phase 3: Data Extraction. The data extracted from the phase 2 articles that fulfilled our criteria were entered into a master database using Excel (Microsoft, USA). One author (P.G.D.) entered data into a data extraction form and then one of five authors (J.L.C., L.D.D., T.K., M.H., and S.M.) acted as the "checker." If any question arose regarding inclusion of a article, the article was referred to two senior authors (C.J.C. and E.H.) for independent review and tiebreaking. This process extracted raw data (supplemental table S1, https://links.lww.com/ALN/E444) available within the articles and, where possible, used numerators and denominators to calculate the incidence of apnea. Postconceptual age values across studies were converted to postmenstrual age values to conform with AAP recommendations which defines gestational age (weeks) as time from the first day of the last menstrual period and the day of delivery; postmenstrual age at time of procedure was calculated as the sum of gestational age and time elapsed (weeks) from birth to day of procedure; postmenstrual age is 2 weeks longer than postconceptual age.[16]

Phase 4: Article Grading and Data Summary. Articles that passed phase 3 inclusion criteria were graded according to recommendations of the AAP[21]: "A" indicates well designed, randomized controlled trials or diagnostic studies on the relevant population; "B" indicates randomized control trials or diagnostic studies with minor limitations, overwhelmingly consistent with evidence from observational studies; "C" indicates observational studies (case control and cohort design); "D" indicates expert opinion, case reports, reasoning from first principles; and "X" indicates exceptional situations in which validating studies cannot be performed and there is clear preponderance of benefit or harm.

We assessed the risk of bias for selected studies using the Critical Appraisal Skills Program (CASP) checklists, available at https://casp-uk.net/casp-tools-checklists/ (accessed December 13, 2025); detailed in supplemental figures S1, S2, and S3 traffic light plots (https://links.lww.com/ALN/E444). The study was registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY2025100100), available at www.inplasy.com (https://inplasy.com/wp-content/uploads/2025/10/INPLASY-Protocol-8426.pdf; accessed October 25, 2025).

Statistical Analysis

A random-effects meta-regression analysis was conducted using a generalized linear mixed-effects model with a binomial outcome (the proportion of children with a postanesthesia apnea event in each study) to clarify potential meta-regressors.[22] Each potential regressor was assessed in a univariable analysis, and those that were statistically significant were then entered into a multivariable stepwise selection regression model. Heterogeneity was tested using the I^2 statistic. The meta-regressors used in a univariable and multivariable manner were as follows: (1) year of study publication; (2) mean gestational age at birth; (3) mean postmenstrual age at the time of anesthesia; (4) mean body weight at birth; and (5) mean procedure duration. The "year of publication" was used as a meta-regressor, based on the assumption that advances in pharmacology and technology over time may improve anesthetic care, which, in turn, may affect the occurrence and detection of apnea. SAS version 9.4 (SAS Institute, USA) was used for all statistical analyses.

Results

We identified a total of 7,094 articles through October 2025, of which 6,191 were subjected to title and abstract screening and 491 met criteria for full-text review. From these, 173 articles were identified for detailed data extraction (fig. 1). After further review, 58 were excluded; the reasons for exclusion are as shown in figure 1. Thus, data extracted from 98 studies[5–8,10,12,23–114] and 17 case reports and case series (supplemental tables S1 and S2, https://links.lww.com/ALN/E444)[13,115–130] were used for the final analysis. Of the 98 studies, 47 had only former preterm infants,[6,8,12,24,25,27,30–32,34–37,40,42–46,49,50,55,56,62,64,65,70,73,74,76,79–84,86,88,90,-94,96,97,99,100,102,107,114] 3 had only full-term,[51,67,77] and 48 had mixed populations[5,7,10,23,26,28,29,33,38,39,41,47,52–54,57–61,63,66,68,69,71,72,75,78,85,87,89,91–93,95,98,101,103–106,108–113] (one study did not detail the infant population[48]). Seven articles[51,58,72,77,93,105,108] included only infants presenting for pyloromyotomy, and of these, two[51,77] had only full-term infants, while the remaining five had a mixed former preterm and full-term population. The reported range for apnea incidence for all infants across 98 studies was 0 to 85% (median, 7.6; interquartile range, 2.5 to 20). Of the 47 studies that had only former preterm infants,[6,8,12,24,25,27,30–32,34–37,40,42–46,49,50,55,56,62,64,65,70,73,74,76,79–84,86,88,90,-94,96,97,99,100,102,107,114] the reported median incidence of apnea was 14.6% (interquartile range, 4.76 to 31); no occurrence of apnea was reported in three of these studies[42,44,74] in which neuraxial (spinal or caudal) anesthesia was used as the anesthetic technique. The distribution of articles based on study design and grading of level of evidence are presented in table 1. The "gray literature" review screened 29 articles that were deemed not relevant.

For the data from case reports or case series, of the 17 case reports, 10 were individual cases[116–121,123,127,128,130] and 7 were case series.[13,115,122,124–126,129] Twelve reported data for former preterm infants,[115,117,119–122,124,126–130] four for full-term infants,[13,116,118,123] and one case series included both preterm and full-term infants.[125] No apnea was reported in seven of the case reports or series.[115,120,122,126,128–130] Two case reports or series reported severe postanesthesia apnea requiring chest compressions.[13,117] A descriptive summary of these data is shown in supplemental table S3 (https://links.lww.com/ALN/E444).

Meta-regression Analysis

For the meta-regression analysis using apnea incidence as the outcome variable, we excluded the 17 case reports or case series due to small sample sizes. Of the 98 studies, 96 were used in the meta-regression for the incidence of apnea,[5–8,10,12,23–50,52–77,79–114] but two[51,78] were excluded because they lacked clarity on apnea incidence; however, those two were included in the descriptive analysis. There was moderate heterogeneity across studies; I^2 value = 0.35. Five meta-regressors were identified and used for further clarification using univariable and multivariable analyses: gestational age at birth, postmenstrual age at the time of anesthesia, body weight at birth, duration of procedure, and year of publication. Univariable analysis showed that more recent year of publication, older gestational age at birth, older postmenstrual age at the time of surgery, and greater birth weight were associated with a lower incidence of apnea, whereas a longer mean duration of anesthesia was associated with a higher incidence of apnea (fig. 2, Forest plot).

For further clarification, we investigated various combinations of meta-regressors to develop a multivariable meta-regression model. Only 24 of the 96 studies reported complete data for the five meta-regressors[10,28,30,43,45,50,52,53,64,73,79,80,83,84,86,96,102–104,107,109,110,113,114]; a formal regression model-building procedure was possible, but not considered representative. We therefore used a trial-and-error approach to identify an appropriate multivariable model. A multivariable "best fitting model" analysis based on 64[6,8,10,12,23,25–32,34–38,41–46,49,50,52–57,62,64,66,73–76,79,80,82–86,89,91,92,94,96,97,99,100,102–104,107,109–114] of 96 studies identified year of publication and postmenstrual age as significant meta-regressors. This "best fitting model," which included

Table 1. Distribution of Studies Based on Study Design and Level of Evidence Grading

Study Characteristics	Number of Studies (n = 115)
Study design	
Prospective randomized	21[12,35–37,41,52,58,59,62,64,69,71,74,77,94,95,97,100,102,103,114]
Prospective nonrandomized	37[6–8,23,25,26,28,31,32,34,38,42–45,47–51,54,61,63,65–68,70,72,76,81,86,87,89,98,109,113]
Retrospective	40[5,10,24,27,29,30,33,39,40,46,53,55–57,60,73,75,78–80,82–85,88,90–93,96,99,101,104–108,110–112]
Case series	7[13,115,122,124–126,129]
Case reports	10[49,116–120,123,127,128,130]
Level of evidence grade	
A	14[12,35–37,62,64,69,76,95,97,100,102,103,114]
B	9[23,41,52,58,59,71,74,94,113]
C	75[5–8,10,23–34,38–40,42–51,53–57,60,61,63,65–68,70,72,73,75,78–93,96,98,99,101,104–112]
D	17[13,115–130]
X	0

A, randomized controlled trial; B, randomized controlled trial with minor limitations or consistent evidence from observational studies; C, cohort or case control; D, case reports or case series; X, exceptional situations.

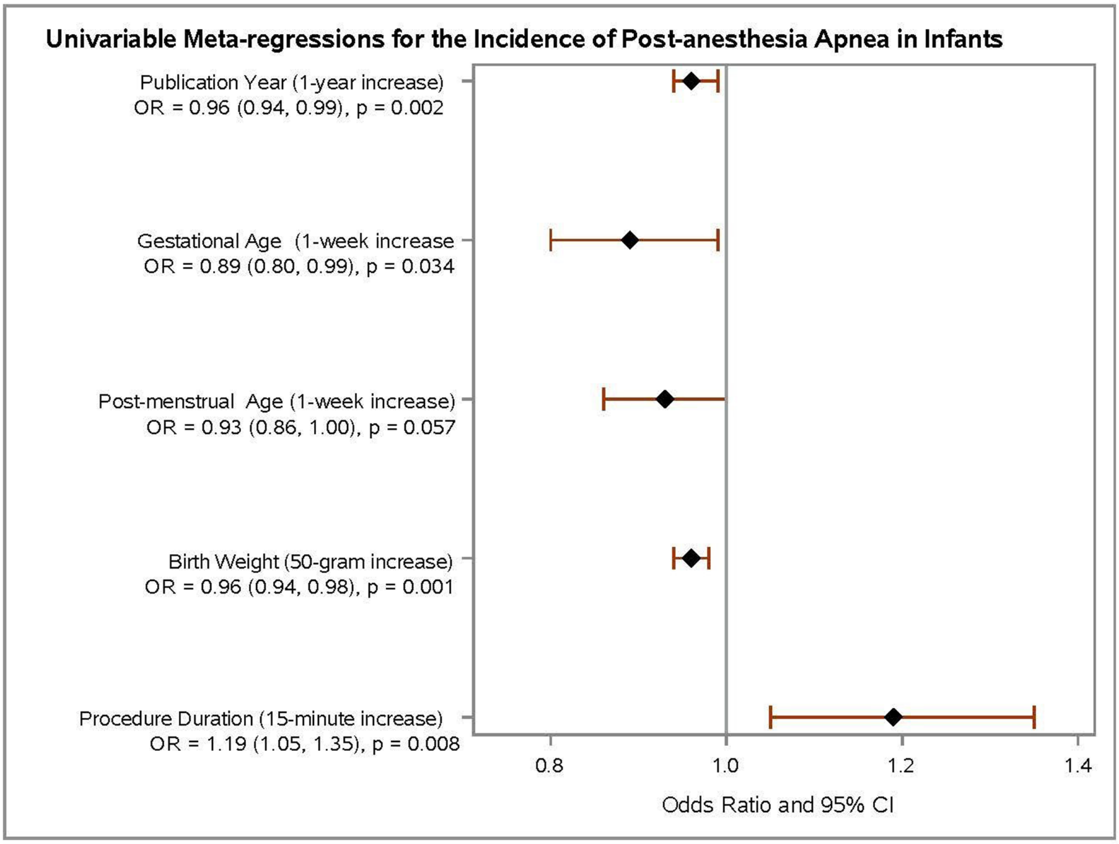

Fig. 2. Forest plot for the odds ratio for univariable meta-regression analysis. The *horizontal lines* are the odds ratios with CI and respective point estimates. An odds ratio less than 1.00 indicates that an increase in the meta-regressor is associated with a decrease in apnea incidence, whereas an odds ratio greater than 1.00 indicates that the meta-regressor is associated with an increased incidence of apnea. OR, odds ratio.

publication year (1986 to 2025) and postmenstrual age (32 to 63 weeks), showed a decrease in the odds of apnea with later publication year (OR, 0.936; CI, 0.91 to 0.964; $P <$ 0.001) and increase in postmenstrual age (OR, 0.889; CI, 0.828 to 0.954; $P = 0.001$). Figure 3 illustrates the distribution of postanesthesia apnea incidence across these 64 studies.

Of the 96 articles, a subset of 61 studies had sufficient data on anesthesia technique and apnea incidence.[5–8,23–25,27,29–32,34–39,42–46,48–50,53–58,61,65–68,70–72,74,75,77,79–83,85–87,90–92,94,96–100,102] The odds of apnea were significantly lower with neuraxial anesthesia as the sole anesthetic *versus* general anesthesia (with or without a regional block; OR, 0.23; CI, 0.094 to 0.592; $P = 0.003$). Meta-regression analysis of six studies[7,23,29,38,75,85] that reported data regarding apnea incidence in both preterm and full term infants showed that former preterm infants had 18.54 times higher odds for postanesthesia apnea *versus* full term infants (CI, 7.591 to 45.289; $P < 0.001$).

Because the data on caffeine use were sparse (two studies[36,37]), it was not subjected to meta-regression analysis. Six studies investigated anemia as a risk factor, of which three[31,80,97] reported an association between anemia and postanesthesia apnea, and three[79,95,98] found no association.

Timing of Apnea Events

Of the articles (studies or case reports and series) that reported the timing of apnea events, the first apnea event occurred as early as postanesthesia care unit (PACU) arrival[79,119,121] and as late as 14 h postanesthesia.[79,127] The last reported apnea event, including those with multiple events, occurred 4 to 56 h postanesthesia.[6,88,95,117]

Studies Recommending Minimum Age for Admission and Monitoring

Fourteen studies[7,8,10,12,23,29,36,38,55,78,80,82,83,96] recommended cutoff ages for prolonged postanesthesia monitoring ranging from less than 48 weeks up to 62 weeks postmenstrual age; two of these studies were categorized as level A evidence,[12,36] and 12 were categorized as level C evidence (table 2). Fifteen studies[5–8,12,28,32,38,51,55,78,80,83,88,101] made recommendations regarding the duration of postanesthesia monitoring, which varied from 6 to 24 h (table 3). One

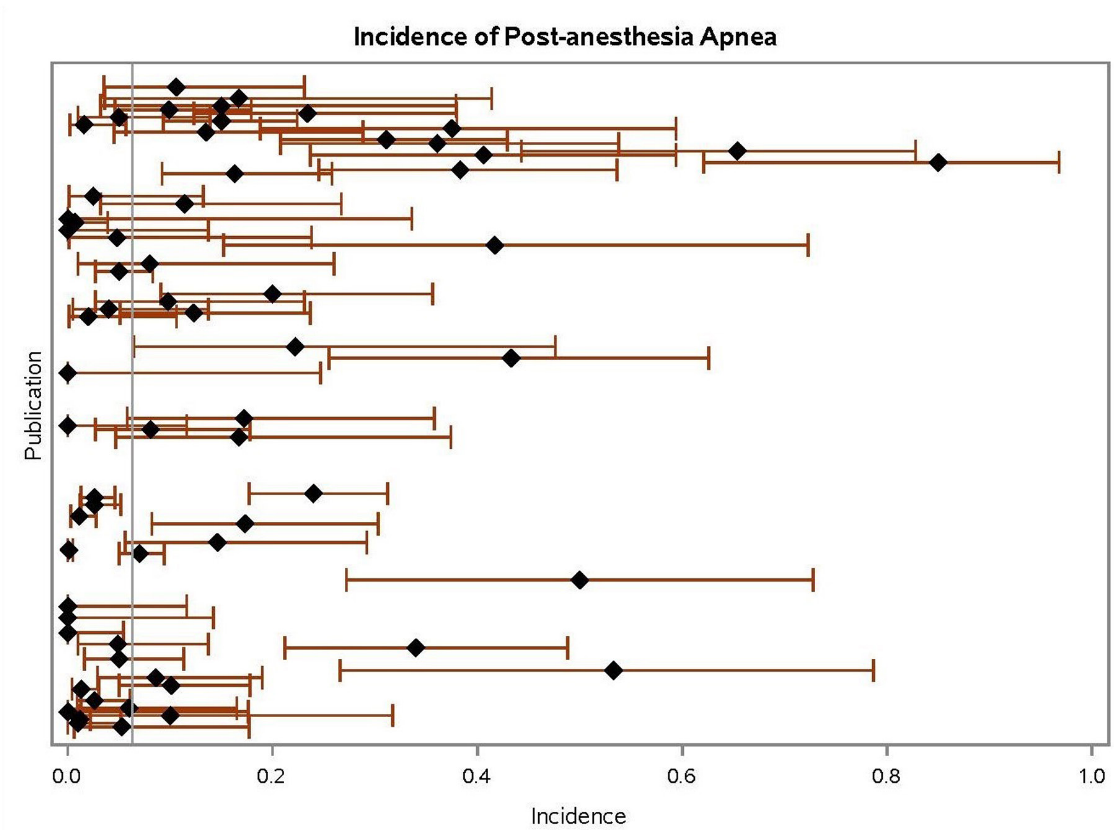

Fig. 3. Forest plot for the incidence of postanesthesia apnea with point estimates and CIs in the 64 studies that underwent multivariable meta-regression analysis.[6,8,10,12,23,25–32,34–38,41–46,49,50,52–57,62,64,66,73–76,79,80,82–86,89,91,92,94,96,97,99,100,102–104,107,109–114]

study was categorized as grade A evidence,[12] and 14 were categorized as grade C evidence.[5–8,28,32,38,51,55,78,80,83,88,101]

Data Regarding Interventions Reported and Outcomes

A total of 98 studies reported adverse events that required six types of rescue interventions: stimulation or oxygen supplementation, bag–valve–mask ventilation, tracheal intubation, mechanical ventilation, upgrade to intensive care level and chest compressions. However, we could not determine the number of patients receiving these interventions because many studies reported only summary outcomes precluding a quantitative analysis. The studies that reported types of rescue interventions for apnea were as follows: (1) stimulation or supplemental oxygen, 25 studies[5–8,23–25,27–30,32–35,46,49,52,54,55,59,62,64,69,73]; (2) tracheal intubation, 27 studies[7,8,23,24,27–29,35,39,45,46,55,56,60,73,78–80,82–84,93,95,102,103,106,107,114]; (3) bag–valve–mask ventilation, 29 studies[5,7,23,24,27–29,35,45–47,52,55,56,60,69,73,78,80,82–84,88,90,95,99,103,104,112]; (4) postprocedure mechanical ventilation, 28 studies[7,8,23,24,28,29,35,39,45,46,55,56,60,73,78–80,82–84,93,95,100,102,103,106,107,114]; (5) upgrade to intensive care, 32 studies,[7,8,23,24,28,29,32,33,35,39,40,45,49,56,61,73,78–80,83,88,93,95,101–104,106–110]; and (6) cardiac arrest or chest compressions, two studies.[95,104]

Discussion

Postanesthesia apnea has been reported in up to 75% of former preterm infants after general anesthesia dating back to the 1970s and 1980s.[5,37,40] These observations, mainly attributed to the immaturity of the respiratory center and/or pharmacologic effects of anesthetics,[7] led to recommendations for hospital admission and postanesthesia monitoring. Coté *et al.*[1] were the first to perform a pooled microanalysis using original data obtained from eight prospective studies examining the incidence of apnea in former preterm infants undergoing inguinal hernia repair exclusively under general anesthesia. They found a strong association between apnea and both lower gestational age and postmenstrual age at the time of surgery; anemia (hemoglobin less than 10 g/dl) was an independent risk factor. The relatively small cohort point analysis suggested that for nonanemic patients who did not develop apnea in the PACU, this apnea risk did not fall less than 1% until approximately 54 weeks postconceptual age (56 weeks postmenstrual age) with gestational age 35 weeks or 55 weeks postconceptual age (57 weeks postmenstrual age) with gestational age 32 weeks. The major limitations of the study by Coté *et al.*[1] study included small

Table 2. Overall Summary of Number of Studies with Recommendations for Cutoff Postmenstrual Age for Postanesthesia Admission for Observation

Postmenstrual Age Cutoff Range	Number of Studies Recommending Cutoff Ages for Former Preterm Infants	Number of Studies Recommending Cutoff Ages for Full-term Infants
< 48 weeks	9[7,12,29,36,38,55,80,83,96]	1[51]
≥ 48 to ≤ 52 weeks	1[82]	2[29,78]
> 52 weeks	3[8,10,78]	1[23]

Table 3. Summary of Studies with Recommendations for the Duration of Monitoring

Duration of Monitoring	Number of Studies
24 h	4[5,7,32,78]
18 h	1[51]
Overnight	4[28,80,88,101]
Up to 12 h	6[6,8,12,38,55,83]

sample size, the use of only general anesthesia with legacy inhalational agents (halothane and isoflurane), the lack of extended monitoring outcomes, and needed rescue interventions. These limitations were the reason for our more extensive up-to-date review.

Over the years, while prematurity was consistently identified as a specific risk factor, subsequent studies[80,82,88,101] identified additional risk factors that increased the propensity for apnea.[1,30,79,80,95,101] However, recommendations for the duration of monitoring, as well as optimal monitoring devices, were influenced largely by individual experience and concerns about cost and family burden of prolonged PACU stays or overnight admission, with relatively limited support from clinical data. As a result, institutional practices varied widely regarding postanesthesia admission, monitoring modalities, and duration of monitoring. These confounding issues provided the impetus for our current updated systematic review and meta-analysis, which revealed that the major meta-regressors were gestational age at birth, postmenstrual age at the time of anesthesia, body weight at birth, duration of procedure, and year of publication. Our findings support previous studies showing that older postmenstrual age infants at the time of anesthesia experienced a significantly lower risk of apnea. Additionally, we found that longer procedure duration was associated with higher apnea rates, a relationship not previously reported.

Another notable finding was a lower incidence of apnea with more recent years of publication. Including year of publication as a meta-regressor was a surrogate for the modernization of drugs, equipment, and techniques over time, all of which could affect postanesthesia apnea. We also found that the odds of apnea were significantly lower with neuraxial anesthesia when used as the sole anesthetic compared with general anesthesia. This may be clinically significant because it suggests that increasing adoption of neuraxial techniques over time may have contributed to our findings.

Our review indicates that former preterm infants have a median postoperative apnea risk of approximately 14.6%, which is lower than that reported in early studies from greater than 30 years ago.[36,40] The lower incidence likely reflects greater use of neuraxial anesthesia techniques (spinal or caudal) instead of general anesthesia, improved postanesthesia monitoring, and introduction of modern anesthetics that are shorter acting and with a rapid offset (*e.g.*, sevoflurane, remifentanil).

Above all, prematurity remains the strongest risk factor for postanesthesia apnea, and former preterm infants still require careful postanesthesia observation regardless of their anesthetic management. Although the risk of apnea is lower in full-term infants than for former preterm infants, the exact risk is unknown, and our data were unable to further clarify the at-risk period for this cohort. It is for these reasons that most institutions will likely continue to consider full term infants younger than 4 weeks of age to be at risk and therefore admit them for postanesthesia monitoring as recommended by the AAP.[16]

Limitations

As with any systematic review and meta-analysis, we faced several challenges including variations in study design, population characteristics, and data quality. Inconsistent definitions of apnea, differences in anesthetic techniques, and heterogenous monitoring strategies further increased complexity. We addressed these issues by using random effects modeling. Publication bias may have also influenced our results, as studies with positive findings are more likely to be published. We attempted to mitigate this bias by including gray literature and expert consensus in our search. We also assessed quality of studies using the CASP checklists (supplemental figures S1, S2, and S3, https://links.lww.com/ALN/E444). Another potential source of bias is reviewer subjectivity in interpreting the screening questions, which may lead to exclusion of relevant studies. We sought to minimize this risk through a rigorous review process involving two independent reviewers and a tiebreaker at each step when disagreements arose. Another confounding issue was the variable definitions of apnea across articles; we address this issue in our accompanying article[131] that analyzes raw data from articles identified by this systematic review and meta-analysis.

Reported rescue interventions across 98 studies ranged from simple stimulation to bag–mask ventilation, upgrade to the intensive care unit, endotracheal intubation, and, in two infants, chest compressions. The timing of the first[79,127] and last[6,88,95,117] postanesthesia apnea events and monitoring recommendations varied widely across studies.[5–8,12,28,32,38,51,55,78,80,83,88,101] To define a precise range of postmenstrual age at risk and make recommendations for the duration of postanesthesia monitoring, we conducted an individual participant data meta-analysis using original data sets provided by investigators. This analysis, which evaluates the optimal cutoff postmenstrual age for admission and duration of monitoring, is reported in the accompanying article.[131]

Conclusions

Our review of more than 6,000 articles confirms that postmenstrual age at the time of anesthesia is the most important and independent predictor of postanesthesia apnea in former preterm infants. We also found that longer duration of anesthesia is associated with increased risk of apnea, which is a new finding. Finally, the use of neuraxial anesthesia (spinal or caudal) may reduce postanesthesia apnea risk compared with general anesthesia.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Dalal: H187, 500 University Drive, Penn State College of Medicine, Penn State Health Children's Hospital, Hershey, Pennsylvania 17033. pdalal@pennstatehealth.psu.edu

Supplemental Digital Content

Supplemental Tables, https://links.lww.com/ALN/E444
Supplemental Table S1. Data extracted.
Supplemental Table S2. Studies included in the meta-analysis with meta-regressor data.
Supplemental Table S3. Case reports/case series descriptive data.
Supplemental Figures, https://links.lww.com/ALN/E444
Risk of Bias: Critical Appraisal Skills Program (CASP) checklists, traffic light plots

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Appendix 1: Medical Subject Heading Search Terms Used for Querying the Database

(("Infant"[MeSH Terms] OR "infant, extremely premature"[MeSH Terms] OR "infant, extremely low birth weight"[MeSH Terms] OR "infant, very low birth weight"[MeSH Terms] OR "infant, small for gestational age"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, newborn"[MeSH Terms] OR "infant, low birth weight"[MeSH Terms] OR "gestational age"[MeSH Terms] OR "premature birth"[MeSH Terms] OR ("intensive care, neonatal"[MeSH Terms] OR "intensive care units, neonatal"[MeSH Terms]) OR ("ex-premature"[Title/Abstract] OR "extremely preterm"[Title/Abstract] OR "extremely-premature"[Title/Abstract] OR "infant"[Title/Abstract] OR "neonate"[Title/Abstract] OR "newborn"[Title/Abstract] OR "premature"[Title/Abstract] OR "prematurely born"[Title/Abstract] OR "premie"[Title/Abstract] OR "premies*"[Title/Abstract] OR "premature*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "microprem*"[Title/Abstract] OR "exprem*"[Title/Abstract] OR "gestational age"[Title/Abstract] OR "post conceptional age"[Title/Abstract] OR "postmenstrual age"[Title/Abstract] OR "PMA"[Title/Abstract] OR "NICU"[Title/Abstract] OR "apnea of prematurity"[Title/Abstract] OR "neonatal"[Title/Abstract] OR "ex-prematurity"[Title/Abstract])) AND ("anesthe*"[Title/Abstract] OR "anesthesia"[Title/Abstract] OR "anesthetics"[Title/Abstract] OR "anesthe*"[Title/Abstract] OR "anaesth*"[Title/Abstract] OR "anesth*"[Title/Abstract] OR "anesthetized"[Title/Abstract] OR "sedation"[Title/Abstract] OR "analgesia"[Title/Abstract] OR ("anesthesia"[MeSH Terms] OR "anesthesia and analgesia"[MeSH Terms] OR ("anesthetics"[MeSH Terms] OR "analgesics"[MeSH Terms]) OR "deep sedation"[MeSH Terms])) AND ("apnoe*"[Title/Abstract] OR "bradycardia"[Title/Abstract] OR "pulse oximeter"[Title/Abstract] OR "breathing rate"[Title/Abstract] OR "apnea*"[Title/Abstract] OR "bradycardi*"[Title/Abstract] OR "bradyarrhythm*"[Title/Abstract] OR "periodic breathing"[Title/Abstract] OR "low heart"[Title/Abstract] OR "apnea of prematurity"[Title/Abstract] OR ("signs and symptoms, respiratory"[MeSH Terms] OR "apnea"[MeSH Terms] OR "bradycardia"[MeSH Terms] OR "respiratory rate"[MeSH Terms] OR "hypoxia/adverse effects"[MeSH Terms] OR "sleep apnea syndromes"[MeSH Terms])) AND ("management"[Title/Abstract] OR "therapy"[Title/Abstract] OR "prophylactic"[Title/Abstract] OR "therapeutics"[Title/Abstract] OR "postoperative"[Title/Abstract] OR "monitoring"[Title/Abstract] OR "monitor"[Title/Abstract] OR "manage"[Title/Abstract] OR "post-anesthesia"[Title/Abstract] OR "recovery room"[Title/Abstract] OR "PACU"[Title/Abstract] OR "post-anesthesia care unit"[Title/Abstract] OR "postop*"[Title/Abstract] OR "post operat*"[Title/Abstract] OR "postanesth*"[Title/Abstract] OR "postanaesth*"[Title/Abstract] OR "post anaesth*"[Title/Abstract] OR "recover*"[Title/Abstract] OR "postoperative care"[Title/Abstract] OR "postoperative complications"[Title/Abstract] OR "post anaesth*"[Title/Abstract] OR "postoperative"[Title/Abstract] OR "perioperative"[Title/Abstract] OR "pulse oximeter"[Title/Abstract] OR "electrocardiography"[MeSH Terms] OR "impedance pneumograms"[Title/Abstract] OR "pneumocardiograms"[Title/Abstract] OR "pain management"[MeSH Terms] OR "peripheral nerve blocks"[Title/Abstract] OR "acetaminophen"[Title/Abstract] OR "caffeine"[Title/Abstract] OR "theophylline"[Title/Abstract] OR "chloral hydrate"[Title/Abstract] OR "pentobarbital"[Title/Abstract] OR "supplemental oxygen"[Title/Abstract] OR "thermal regulation"[Title/Abstract] OR "kangaroo"[Title/Abstract] OR "pentobarbital"[Title/Abstract] OR "aminophylline"[Title/Abstract] OR "chloral hydrate"[Title/Abstract] OR "oximetry"[Title/Abstract] OR "postoperative"[Title/Abstract] OR "perioperative"[Title/Abstract] OR "recovery room"[Title/Abstract] OR "therapy"[Title/Abstract] OR ("perioperative period"[MeSH Terms] OR "perioperative nursing"[MeSH Terms] OR "perioperative care"[MeSH Terms] OR "recovery room"[MeSH Terms] OR "postanesthesia nursing"[MeSH Terms] OR "postoperative care"[MeSH Terms] OR "postoperative complications"[MeSH Terms] OR "postoperative period"[MeSH Terms] OR "oximetry"[MeSH Terms] OR "disease management"[MeSH Terms] OR "therapeutics"[MeSH Terms] OR "caffeine"[MeSH Terms] OR "theophylline"[MeSH Terms] OR "aminophylline"[MeSH Terms] OR "drug monitoring"[MeSH Terms] OR "kangaroo-mother care method"[MeSH Terms] OR "pentobarbital"[MeSH Terms] OR "chloral hydrate"[MeSH Terms]))) NOT "review"[Publication Type]

Appendix 2: Stages and Workflow for Systematic Review