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Review

Towards standardized and clinically relevant definitions of hypoxemia and hyperoxemia in preterm infants: A systematic review

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Educational Aims

The aims of this article regarding hyperoxaemia and hypoxaemia in preterm infants are to:

- Identify definitions based on continuous monitoring technologies
- Recognise the role of different oxygen monitoring techniques
- Provide an overview of definitions and the association with neonatal outcomes
- Identify the limitations of current definitions using continuous monitoring devices
- Interpret the hypoxemia and hyperoxemia burden as measured with continuous oxygen monitoring devices taking into account that the definition influences the total measured burden

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ABSTRACT

In neonatal care, maintaining oxygen levels in the target range is essential to minimize adverse outcomes. Both episodes of hyperoxemia and hypoxemia are associated with adverse neonatal outcomes. Criteria to determine the hypoxemic and hyperoxemic burden are currently not standardized or generally applied in clinical care. This results in difficulty to identify clinically relevant events in preterm infants. Clinical decisions and interventions are therefore mostly based on the experience of the clinical team. This systematic review aims to provide an overview of the used definitions for hypoxemia and hyperoxemia in preterm infants, based on continuous monitoring techniques and the relation to neonatal outcome (PROSPERO: CRD42023493201).

INTRODUCTION

Preterm infants often suffer from transient hypoxemic events due to immaturity of the respiratory system and its control. Respiration can be supported with invasive and non-invasive ventilation, oxygen supplementation, and medication [1,2]. Maintenance of oxygen levels within narrow target ranges is important to avoid adverse outcomes. Low oxygen levels are associated with a higher risk of death, impaired neurodevelopment, persistent ductus arteriosus, and necrotizing enterocolitis [3]. High oxygen levels are associated with retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) [3]. Intermittent hypoxemia, calculated as a percentage of time below a certain oxygen saturation measured

Abbreviations: cFTOE, fractional cerebral oxygen extraction; CI, Confidence interval; FiO_2, fraction of inspired oxygen; FTOE, fractional tissue oxygen extraction; GA, gestational age; IH, intermittent hypoxemia; IQR, interquartile range; NICU, neonatal intensive care unit; NIRS, near-infrared spectroscopy; OR, odds ratio; PMA, postmenstrual age; PNA, postnatal age; $rcSO_2$, regional cerebral tissue oxygenation saturation; RCT, randomized controlled trial; ROP, retinopathy of prematurity; RR, relative risk; $rStO_2$, regional tissue oxygen saturation; rSO_2C, regional cerebral tissue oxygen saturation; SD, standard deviation; $SctO_2$, StO_2, cerebral tissue oxygen saturation; SGA, small for gestational age; SpO_2, oxygen saturation measured with pulse oximetry; $TcPO_2$, transcutaneous partial pressure of oxygen.

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with pulse oximetry (SpO_2), has been associated with an increased risk of late death or disability at a corrected age of 18 months [4].

Clinical target ranges are mainly used to optimize oxygenation and to avoid exposure to both low and high oxygen levels. No standard definitions are available to determine the burden of hypoxemia and hyperoxemia, or to identify clinically relevant events. As a consequence, interventions and clinical decisions are largely based on the experience of the clinical team. Pulse oximetry is by far the most frequently applied technique for measuring oxygenation continuously and noninvasively to support clinical decisions. Despite its invasiveness, intermittent arterial blood gas analysis remains the gold standard for measuring oxygen levels due to its accuracy. Transcutaneous oxygen monitoring can be used as well to estimate arterial blood gas levels noninvasively [5]. Near-infrared spectroscopy (NIRS) is applied for the assessment of end-organ perfusion and, combined with arterial oxygen levels, can provide information on the balance between oxygen delivery and consumption [6].

Treatment and respiratory support can be adjusted to prevent hypoxemia and hyperoxemia when their harmful limits are clearly defined. There is a wide variety in definitions used in literature, making it difficult to concisely conclude upon a clinically relevant relation with neonatal outcome. This review aims to investigate the literature definitions of hypoxemia and hyperoxemia based on continuous monitoring techniques, and the association between applied definitions and outcome in preterm infants. The results of this systematic review could aid in the assessment of the hypoxemic and hyperoxemic burden in preterm infants in daily clinical care and provide more clarity on the relation with adverse outcome.

METHODS

Search strategy

A systematic search of electronic medical databases, including Embase, Medline, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, and Google Scholar, was conducted on March 30, 2022 and extended on August 18, 2023 by a reference librarian (Supplementary Methods). The search was restricted to studies including human participants and written in English. This systematic review has been registered in the international prospective register of systematic reviews database (PROSPERO: CRD42023493201).

Screening and data extraction

The following inclusion criteria were defined prior to the search and review: 1) preterm infants with a gestational age of $\leq$ 32 weeks; 2) continuous oxygen monitoring techniques; 3) quantifiable definition of hypoxemia and/or hyperoxemia. Monitoring techniques could have varying sampling rates and averaging intervals. All cerebral near-infrared oxygen measurements, regardless of their specific brand-specific parameter names, were included as NIRS. All types of published studies could be included, except for case reports, reviews and conference abstracts. Studies published before 1975, subjects other than human infants and written in a language other than English were also excluded. Studies on intermittent monitoring methods, such as laboratory values, do not fall within the scope of this review. All selected publications were managed in EndNote© X9 (Clarivate™, London, United Kingdom). Two reviewers (N.G.-P. and J.P.) screened titles and abstracts independently. Discrepancies were resolved by consensus and disagreement was resolved by consensus with two additional reviewers (W.W. and S.S.). Full text articles were screened for eligibility by two reviewers (N.G.-P. and J.P.) and data were extracted independently. Data extraction included information on (I) study characteristics, (II) participant characteristics, (III) hypoxemia and/or hyperoxemia definitions, (IV) device specifications, (V) monitoring periods, and (VI) investigated associations with adverse outcomes.

Quality assessment

Quality assessment of the studies including the association of definitions with clinical outcomes was performed independently by two reviewers (N.G.-P. and J.P.). Discrepancies and disagreement were resolved similarly to the data screening and extraction methods. The Newcastle-Ottawa Scale tool was used for quality assessment of observational and cross-sectional studies [7]. Studies are judged on the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest. A study can be awarded with a star for quality for each item in the scale, with a maximum of nine stars.

Outcome measures

The primary outcome measure of this systematic review was defined as a quantified definition of hypoxemia and/or hyperoxemia based on continuous monitoring data. This included the type of data source, monitoring technique, sampling rate, averaging time and gestational age. In addition, secondary outcome measures assessed the associations between hypoxemia and/or hyperoxemia and neonatal outcomes, including mortality and morbidity, during or after neonatal intensive care unit (NICU) admission.

Data analysis

A description of all used definitions is provided. Data on the definition of hypoxemia and hyperoxemia were synthesized structurally according to the characteristics of the study population, data source, and measurement details. Descriptive methods, including frequencies, were used to summarize the data. Descriptive methods were also used to present the association between hypoxemia and/or hyperoxemia and adverse outcomes. The outcome measures were not suitable for *meta*-analyses, as this was a descriptive systematic review on the definition of hypoxemia and/or hyperoxemia. Data analyses were performed using *R* (version 4.2.3, The *R* Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The search strategy resulted in 1914 potentially relevant studies. Of these, 1703 were excluded based on title and abstract, resulting in the selection of 211 studies for full-text screening. Ultimately, 91 studies were extracted for further analyses (Fig. 1) [4,6,8–96]. Eighty-six (86/91) articles explicitly stated one or more definitions of hypoxemia (N = 135) [4,6,8–39,41–44,46–81,83,84,86–93,95,96] and thirty-six provided definitions of hyperoxemia (N = 47) [6,8,13,19–21,32–34,38,40,45,47,49,50,54,56–59,67,68,72,73,78,80,82,83,85,89–95].

Definition of hypoxemia

Hypoxemia was defined as a threshold or a percentage deviation from a baseline. Additionally, time could be included in the definition as a threshold with a specified time limit, and as a specific interval or time period (intermittent hypoxemia) (Table 1). Pulse oximetry (N = 117), NIRS (N = 16) and transcutaneous blood gas monitoring (N = 2) were applied in the studies with

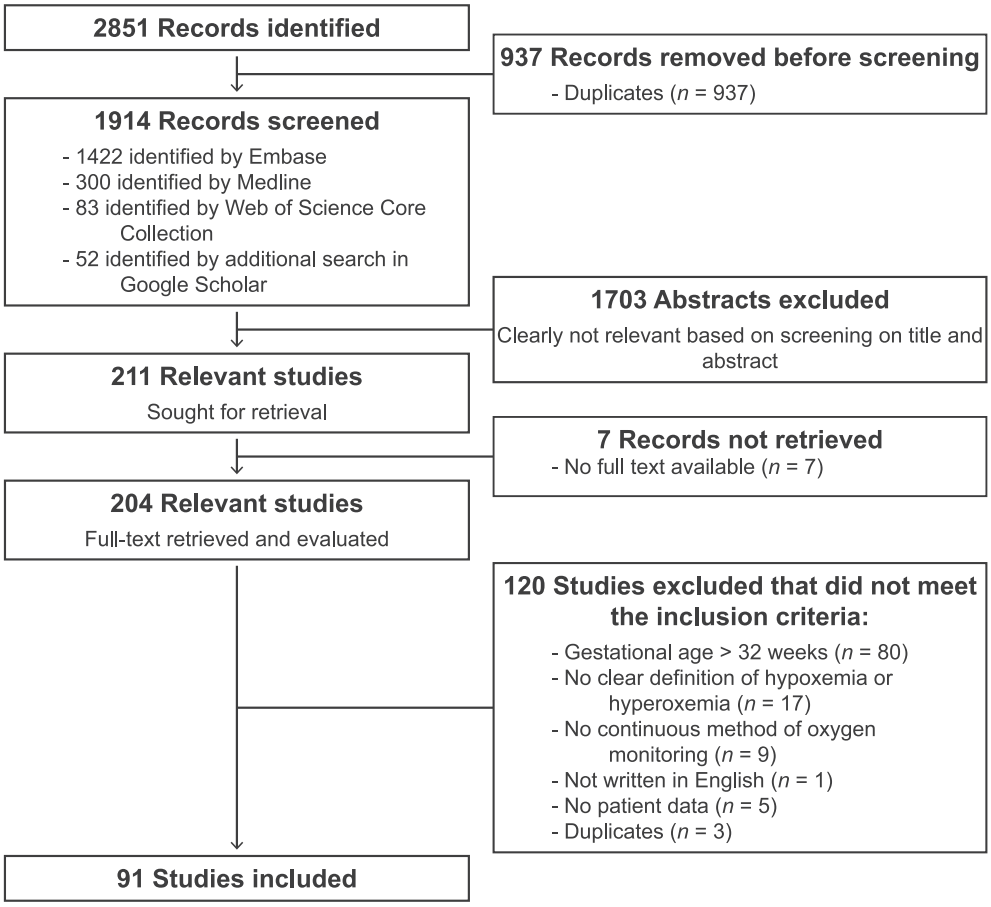

Fig. 1. Flow diagram of the systematic selection of literature.

corresponding definitions. The most frequently used definition of hypoxemia with pulse oximetry was an SpO_2 threshold of < 80 % (28/117; 24 %) (Fig. 2**A**). For cerebral NIRS, a threshold of < 55 % was most commonly used (9/16; 56 %). Two definitions of hypoxemia were found for transcutaneous blood gas monitoring; a deviation of more than 20 % from the baseline and a threshold of < 40 torr. In 39/135 definitions, time was taken into account, mostly in studies using pulse oximetry (38/39), applied as a limit (22/39) or as intermittent hypoxemia (13/39) (Fig. 2**B**). Intermittent hypoxemia was most frequently defined as SpO_2 exposure < 81 % with a duration between 10 s and 180 s.

Definition of hyperoxemia

Few articles provided a definition for hyperoxemia, which was specified as either a threshold or a threshold with a specific time limit (Supplementary Table 1). Most frequently, a threshold of > 95 % for pulse oximetry was applied (16/35) (Fig. 3). Levels > 85 % were used in most studies (8/9) in which NIRS was applied for tissue oxygen monitoring. No definitions for transcutaneous blood gas monitoring were found. Time with hyperoxemia was taken into account in two articles, with limits varying greatly from 10 s to 30 min.

Association with adverse outcomes

Twenty-two studies tested the difference in hypoxemic and/or hyperoxemic exposure for the development of adverse outcomes, including ROP, mortality, BPD, symptomatic childhood wheezing, necrotising enterocolitis, intraventricular hemorrhage, and neurodevelopmental impairment [4,9,12,25,34–36,42,53,55–57,59,69,72,73,77,78,82,87,93,94]. The quality assessment of these studies is presented in Supplementary Tables 2 and 3. Eight out of 22 studies scored 8 to 9 points on the 9-point quality assessment scale. Five out of 22 studies scored 6 or less points. The associations of ROP, mortality, BPD, neurodevelopmental impairment and other adverse outcomes with hypoxemic and hyperoxemic exposure are presented in Table 2. Exposure to hypoxemia was found to be associated with a higher risk of ROP in 5/7 studies, with mortality in 3/5 studies, with BPD in 2/3 studies, with neurodevelopmental impairment in 1/2 studies, and with combined death or disability in 3/3 studies. In the remaining studies no association was found between hypoxemic exposure and adverse outcomes.

In associations describing a higher risk for certain outcomes, varying SpO_2 limits of 80 % (N = 8), 83 % (N = 2), 85 % (N = 4) and 90 % (N = 1) were used to define hypoxemia. In 5 of these associations a time interval was used to define hypoxemia, varying from a duration below the defined saturation target of at least 10 s to 1 min up to a maximum duration of 3 to 5 min.

DISCUSSION

This systematic review presents an overview of literature definitions of hypoxemia and hyperoxemia in preterm infants, based on continuous monitoring techniques. Pulse oximetry, NIRS, and transcutaneous blood gas monitoring were used to detect hypoxemia and hyperoxemia. A large range of thresholds and time variables was described to define the burden of hypoxemia and hyperoxemia. A higher burden of hypoxemia was related to an

Table 1
Characteristics of included studies with a hypoxemia definition.

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
Abu Jawdeh, 2014, USA	The effect of red blood cell transfusion on intermittent hypoxemia in ELBW infants	Retrospective cohort study	130	24 to 27 6/7	Group 1:4 (IQR 2–5) Group 2:13 (IQR 10–18) Group 3:33 (IQR 31–38)	Intermittent hypoxemia: $SpO_2 \leq 80$ % for ≥ 4 s and ≤ 3 min	Pulse oximetry (Radical, Masimo, Irvine, CA, USA)	Averaging time: 2 s Sample rate: 0.5 Hz	Incidence of hypoxemic events in the 24 h period before, 24 h after and 24 – 48 h after transfusion	Day 1 to 8 weeks
Abu Jawdeh, 2017, USA	Prenatal opioid exposure and intermittent hypoxemia in preterm infants: a retrospective assessment	Prospective cohort study	82	< 30	Follow-up till: 56	Percent time spent with $SpO_2 < 80$ % Intermittent hypoxemia: number of events per day with $SpO_2 < 80$ % during 4–180 s	Pulse oximetry (Radical 7, Masimo, Irvine, CA, USA)	Averaging time: 2 s Sample rate: 1 Hz	Percent time spent with $SpO_2 < 80$ %	Day 1 to 8 weeks
Abu Jawdeh, 2021, USA	Extubation readiness in preterm infants: evaluating the role of monitoring intermittent hypoxemia	Prospective cohort study	50	< 30	Group 1:18 (IQR 5–37) Group 2:21 (IQR 9–33)	Percent time spent with $SpO_2 < 80$ % Intermittent hypoxemia: number of events per day with $SpO_2 < 80$ % during 4–180 s	Pulse oximetry (Radical 7, Masimo, Irvine, CA, USA)	Averaging time: 2 s Sample rate: 1 Hz	Percent time spent with $SpO_2 < 80$ % and the number of events	24 h pre-extubation until 72 h post-extubation or when reintubation was necessary
Abi Jawdeh, 2021, USA	Intermittent hypoxemia in preterm infants: a potential proinflammatory process	Prospective cohort study	26	< 30	30 (IQR: 29–32)	$SpO_2 < 80$ %	Pulse oximetry (Radical 7, Masimo, Irvine, CA, USA)	Averaging time: 2 s Sample rate: 1 Hz	$SpO_2 < 80$ %	At 30 days of PNA, a week prior to c-reactive protein collection
Afshar, 2018, Canada	The impact of hypoxemia on the development of retinopathy of prematurity in infants less than 29 weeks of gestation	Retrospective cohort study	112	< 29	Follow-up till: 70	$SpO_2 \leq 80$ %	Pulse oximetry (Masimo, Irvine, CA, USA)	Averaging time: NA Sample rate: NADaily percentage of time periods ($SpO_2 \leq 80$ %) converted to minutes	Association between ROP and cumulative exposure to hypoxemia	Weeks 1 to 10
Atanasov, 2023, Germany	Fluctuations in oxygen saturation during synchronized nasal intermittent positive pressure ventilation and nasal high-frequency oscillatory ventilation in very low birth weight infants: a randomized crossover trial	Retrospective cohort study	22	< 32	26.5 (range: 10.0–84.0)	$SpO_2 < 88$ % Severe: $SpO_2 < 80$ % Intermittent hypoxemia: $SpO_2 < 80$ % during > 30 s Desaturations: $SpO_2 < 70$ % during > 1 min $SctO_2 < 65$ % $SctO_2 < 60$ %	Pulse oximetry (IntelliVue MP50 monitor, Philipps, Amsterdam, The Netherlands) NIRS (Root kit 3.0 device, Massimo, CA)	Averaging time: SpO_2 8 s Sample rate: 0.5 Hz	Time spent within the SpO_2 target (SpO_2 88–95 %)	Two periods of 8 h on two consecutive days, recovery period of 16 h
Baerts, 2011, The Netherlands	Cerebral oxygenation and oxygen extraction in the preterm infant during desaturation: Effects of increasing FiO_2 to assist recovery	Prospective cohort study	24	< 32	Follow-up till: 3	$SpO_2 < 75$ % during > 30 s	Pulse oximetry (Nellcor, Boulder, Colo., USA)INVOS 4100 (Somanetics, Troy, Mich., USA)	Averaging time: NA Sample rate: 10 Hz	Absolute and relative differences in saturations and cFTOE values between episodes that were not managed with an increase in FiO_2 levels and which were not	Starting as soon as possible after birth during 6 desaturation episodes for a period of 72 h

Table 1 (*continued*)

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
Bauschatz, 2008, Switzerland	A preliminary report of nursing in the three-stair-position to prevent apnoea of prematurity	Prospective cohort study	20	< 31	30 3/7 (Range 26 6/7–34 6/7)	SpO_2 < 85 %	Siemens SC7000	Averaging time:NA Sample rate: NA	Difference in bradycardic or hypoxemic episodes between the three positions	Three times 24 h
Blanchard, 1991, Canada	Effects of tactile stimulation on physical growth and hypoxemia in preterm infants	RCT	9	30 to 32	Enrollment: 15 ± 1	SpO_2 ≤ 80–85 %, during ≥ 60 s	Pulse oximetry (Nellcor N-100)	Averaging time:NA Sample rate: NA	Physical growth as measured by weight, height and head circumference	During 10 days, twice daily measurements of 20 min
Bohnhorst, 2000, Germany	Pulse oximeters' reliability in detecting hypoxemia and bradycardia: Comparison between a conventional and two new generation oximeters	Prospective cohort study	17	25 (Range 24–30)	35 (Range 8–77)	$TcPO_2$ < 40 torr	Pulse oximetry (Nellcor N-200) Pulse oximetry with OXISMART technology (Nellcor N-3000) instrument with Signal Extraction Technology (Masimo SET) $TcPO_2$ monitoring at 44 °C (Kontron 7640, Kontron Instruments, Watford, UK)	Averaging time: 6–7 s Variable averaging 8 s Sample rate: 1 Hz	Number of hypoxemic episodes ($TcPO_2$ < 40 torr) and bradycardic events missed with pulse oximetry	Reported median recording duration of 13 (Range 5–36) hours
Bohnhorst, 2010, Germany	Oral versus nasal route for placing feeding tubes: No effect on hypoxemia and bradycardia in infants with apnea of prematurity	Randomized controlled crossover trial	32	< 32	32 (IQR 30 – 35)	SpO_2 ≤ 80 %	Pulse oximetry (Noninxx in beat-to beat-mode, Nonin Medical, Inc., Plymouth, Minn., USA)	Averaging time: NA Sample rate: NA	Combined rate of bradycardia and desaturation per hour	A 24 h recording period after consent
Bucher, 1988, Switzerland	Does caffeine prevent hypoxaemic episodes in premature infants? A randomized controlled trial	Double blinded RCT	50	≤ 32	Enrollment: 2	$TcPO_2$ < 20 % from baseline within 20 s	NA	Averaging time: NA Sample rate: 0.3 Hz	Difference in the incidence of hypoxaemic and bradycardic episodes	From 24 h to 100 h of age
Clarke, 2015, Australia	A randomised crossover trial of clinical algorithm for oxygen saturation targeting in preterm infants with frequent desaturation episodes	RCT	16	< 32	30.5 ± SD 2.4	SpO_2 ≤ 85 % SpO_2 ≤ 85 % during > 5 s SpO_2 < 70 %	Pulse oximetry (Radical 7, Masimo, Irvine, CA, USA)	Averaging time: 8 s Sample rate: 0.015 Hz	Proportion of time spent within the target saturation range	4-hour period in each control modality
Dani, 2021, Italy	Cerebral and splanchnic oxygenation during automated control of inspired oxygen (FiO_2) in preterm infants	Randomized controlled crossover trial	20	< 32	18.9 ± SD 19.4	SpO_2 < 80 %	Pulse oximetry (IntelliVue MP40 Neonatal, Philips, DA Best) NIRS (INVOS 5100®, Somanetics Corporation, Troy)	Averaging time: NA Sample rate: 0.03 Hz	Comparison of rSO_2C changes during the two phases of the study	Two 12-hour periods
Dassios, 2022, UK	Cumulative hypoxia, socioeconomic deprivation and neurodevelopmental outcomes in preterm infants	Retrospective cohort study	80	< 30	Follow-up until 36 weeks PMA	SpO_2 < 85 %, SpO_2 < 80 %, SpO_2 < 75 %	Pulse oximetry	Averaging time: NA Sample rate: NA	Bayley-III assessment	From admission to 36 weeks PMA
Di Fiore, 2010, USA	A higher incidence of intermittent hypoxemic episodes Is associated with severe retinopathy of prematurity	Retrospective cohort study	79	24 0/7–27 6/7	Follow-up till: 56	Intermittent hypoxemia: SpO_2 ≤ 80 %, during ≥ 10 – ≤180 s	Pulse oximetry (Radical, Masimo, Irvine, CA, USA)	Averaging time: 2 s Sample rate: 0.5 Hz	Duration of hypoxemic and hyperoxemic events	First 8 weeks of life
Di Fiore, 2012, USA	Low oxygen saturation target range is associated with increased incidence of intermittent	RCT post-hoc analysis	115	24 0/7–27 6/7	Follow-up until 36 weeks PMA	Intermittent hypoxemia: SpO_2 ≤ 80 % during ≥ 10 –	Pulse oximetry (Radical SET, Masimo, Irvine, CA, USA)	Averaging time: 2 s Sample rate:	Incidence of intermittent hypoxemia	Within 2 h after birth, continued until 36 weeks PMA or until the

(*continued on next page*)

Table 1 (*continued*)

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
	hypoxemia					≤180 s		0.5 Hz		infant was breathing room air without respiratory support for ≥ 72 h
Di Fiore, 2012, USA	The relationship between patterns of intermittent hypoxia and retinopathy of prematurity in preterm infants	Retrospective cohort study	79	24 0/7 – 27 6/7	Not described	Intermittent hypoxemia: SpO_2 ≤ 80 % during ≥ 10 – ≤180 s	Pulse oximetry (Radical, Masimo, Irvine, CA, USA)	Averaging time: 2 s Sample rate: 0.5 Hz	Number of intermittent hypoxemic episodes	First 8 weeks of life
Di Fiore, 2017, USA	Patterns of oxygenation, mortality, and growth status in the surfactant positive pressure and oxygen trial cohort	RCT post-hoc analysis	1054	24 0/7 – 27 6/7	Follow-up till 3	SpO_2 < 80 % Intermittent hypoxemia: SpO_2 < 80 %, during ≥ 20 - ≤ 300 s	Pulse oximetry (Radical, Masimo, Irvine, CA, USA)	Averaging time: 16 s Sample rate: 0.1 Hz	Comparison of achieved oxygen saturation between infants born SGA and AGA	First three days of life
Di Fiore, 2019, USA	Early inspired oxygen and intermittent hypoxemic events in extremely premature infants are associated with asthma medication use at 2 years of age	Retrospective cohort study	137	24 0/7 – 27 6/7	Follow-up till 28	Intermittent hypoxemia: SpO_2 ≤ 80 %, during ≥ 10 - ≤180 s	Pulse oximetry (Radical, Masimo, Irvine, CA, USA)	Averaging time: 2 s Sample rate: 0.5 Hz	Prescription asthma medication use at 2-year follow-up	First 4 weeks of age
Dijkman, 2021, The Netherlands	Predictive Intelligent Control of Oxygenation (PRICO) in preterm infants on high flow nasal cannula support: a randomised cross-over study	Randomized controlled crossover trial	27	< 30	31 (IQR 23 – 42)	SpO_2 < 80 %	Pulse oximetry (Masimo, Irvine, CA, USA) (Philips IntelliVue MX800, Böblingen, Germany).	Averaging time: 10 s 8 s Sample rate: 1 Hz 0.03 Hz	Time spent within target range (88 %-95 %)	Two consecutive 24-hour treatment periods
Dobson, 2017, USA	Caffeine decreases intermittent hypoxia in preterm infants nearing term-equivalent age	RCT subcohort combined with a prospective cohort study	27	< 32	Enrollment: Group 1: 33.1 ± SD 2.8 Group 2: 34.9 ± SD 1.1	SpO_2 ≥ 10 % from the baseline, during ≥ 5 s Baseline was defined as the 90th percentile of all baselines recorded	Pulse oximetry (Masimo Rad 8, Irvine, CA, USA)	Averaging time: NA Sample rate: NA	SpO_2 < 90 % in s/24 h	When weaned off supplemental oxygen and discontinuation of caffeine treatment until continued at home until 40 weeks PMA
Dormushian, 2022, USA	Pulse oximetry reliability for detection of hypoxemia under motion in extremely premature infants	Post-hoc analysis	20	≤ 28	13 (IQR 8 – 20)	Intermittent hypoxemia: SpO_2 < 90 % during > 10 s, SpO_2 < 80 % during > 10 s	Pulse oximetry (non-rainbow X2, DSP V4.6.0.2, Masimo Signal Extraction Technology pulse oximeter12 SET®, Masimo, Irvine, CA)	Averaging time: 10 s Sample rate: 0.9765 Hz, 1.024 Hz	Episodes of intermittent hypoxemia	Periods of 24 to 72 h duration
Dormushian, 2023, USA	Etiology and Mechanism of Intermittent Hypoxemia Episodes in Spontaneously Breathing Extremely Premature Infants	Secondary analysis of a prospective observational study	51	< 29	At 32 weeks PMA 38.7 ± (SD)11.1	Intermittent hypoxemia: SpO_2 < 90 % during ≥ 5 s Severe: SpO_2 < 80 % during ≥ 5 s	Pulse oximetry (Radical 7, Masimo, Irvine, CA, USA)	Averaging time: 8 s Sample rate: 100 Hz	Prevalence of the different mechanisms that lead to daytime intermittent hypoxic episodes	4 h at 32 weeks PMA and 4 h at 36 weeks PMA
Elsayed, 2021, Canada	Titration of inspired oxygen in preterm infants with hypoxemic respiratory failure using near-infrared spectroscopy and pulse oximetry: A new approach	Retrospective cohort study	38	< 28	Group 1: 32 (IQR 17 – 56) Group 2: 25 (IQR 11 – 46)	SpO_2 < 80 %	Pulse oximetry (Masimo Rad 7 Masimo®, Masimo Corporation, Masimo, Irvine, CA, USA) NIRS (FORE-SIGHT® Absolute Tissue Monitor, Casmed®)	Averaging time: NA Sample rate: 0.5 Hz	The achievement of significantly lower FiO_2 at 72 h after the start of the integrated monitoring	24 h before CAR test until 72 h after CAR test or until weaning FiO2 to < 0.3
Firme, 2005, USA	Episodes of hypoxemia during synchronized	RCT	18	≤ 30	43 ± SEM 6 41 (IQR 24 – 48)	SpO_2 < 90 %, SpO_2 < 85 %,	Pulse oximetry (Nellcor N-200, Nellcor-Puritan,	Averaging time:	Duration and severity of hypoxemic episodes	Two periods of 1 h

Table 1 (*continued*)

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
	intermittent mandatory ventilation in ventilator-dependent very low birth weight infants					SpO_2 < 80 %	Inc., Pleasanton, CA, USA)	NA Sample rate: NA		
Gentle, 2022, USA	Intermittent Hypoxemia and Bronchopulmonary Dysplasia with Pulmonary Hypertension in Preterm Infants	Matched case-control study	80	22 0/7 – 28 6/7	Follow up: day 28 and the preceding week Control group: at echo 37 (IQR 33–40) weeks	SpO_2 < 80 %, SpO_2 < 70 %	Pulse oximetry (Philips IntelliVue MP70 or MP50, using Nellcor sensors)	Averaging time: 8 s Sample rate: 125 Hz	Bronchopulmonary dysplasia-associated pulmonary hypertension	The week preceding echocardiography (after PNA day 28)
Gottlob, 2019, Germany	Randomized controlled trial on the effects of morning versus evening primary vaccination on episodes of hypoxemia and bradycardia in very preterm infants	Two RCTs	26	26–30	Group 1: 60.2 ± 0.83 Group 2: 61.0 ± 1.35	SpO_2 < 80 %	Pulse oximetry (VitaGuard® VG3100; Getemed, Teltow, Germany)	Averaging time: NA Sample rate: NA	The number of additional episodes of hypoxemia or bradycardia during the first 24 h after vaccination compared to the number of episodes in the 24 h before vaccination	24 h before and after vaccination
Hanke, 2022, Germany	Early skin-to-skin contact does not affect cerebral tissue oxygenation in preterm infants < 32 weeks of gestation	Two observational convenience samples	76	Group 1: 26 0/7 – 31 6/7 Group 2: 24 0/7 – 28 6/7	Follow-up till: 5	$rcSO_2$ < 55 %	NIRS (INVOS 5100 near infrared spectrometer, Somanetics Corp, Medtronic, Meerbusch, Germany)	Averaging time: NA Sample rate: 0.2 – 0.1 Hz	Differences in $rcSO_2$ values	The first 120 h of life
Hyttel-Sorensen, 2013, Denmark	Clinical use of cerebral oximetry in extremely preterm infants is feasible	observational pilot study of the experimental arm of the SafeBoosC phase II	10	24 0/7 – 27 6/7	Follow-up till: 3	$rStO_2$ < 55 %	INVOS 5100C (Covidien, Boulder, CO, USA) Adult SomaSensor NONIN EQUANOX 7600 (NONIN, Plymouth, MN, USA) 8000CA sensor model	Averaging time: NA Sample rate: 0.2 Hz 0.25 Hz	Time with $rStO_2$ below 55 % and above 85 % multiplied by the extent of deviation	Within three hours of birth until 72 h of age
Hyttel-Sorensen, 2015, France, Denmark, Spain, Ireland, The Netherlands, Austria, Italy, UK	Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial	RCT	166	< 27 6/7	Follow-up till: 3	The multiplication of duration and magnitude of $rStO_2$ < 55 %	INVOS 5100C with adult SomaSensor, NIRO 300, and NIRO 200NX with small probe holder (Hamamatsu Phototonics, Hamamatsu City, Japan) NONIN EQUANOX 7600 with adult sensor, model 8004CA (Nonin Medical, Plymouth, MN)	Averaging time: NA Sample rate: NA	The time spent outside the target range of 55–85 % $rStO_2$ multiplied by the mean absolute deviation, expressed in %hours	Within three hours of birth until 72 h of life
Ibonia, 2018, USA	Blood transfusions in preterm infants: changes on perfusion index and intermittent hypoxemia	Prospective cohort study	39	< 30	Group 1: 4.6 ± SD 1.6 Group 2: 18.0 ± SD 6.4 Group 3: 43.5 ± SD 8.9	Percent time spent with SpO_2 < 80 % Intermittent hypoxemia: SpO_2 < 80 %, during ≥ 4 – ≤ 180 s	Pulse oximetry (Radical 7, Masimo, Irvine, CA, USA)	Averaging time: 2 s Sample rate: 1 Hz	A decrease in SpO_2 to < 80 % for at least 4 sec and not more than 3-min duration and the overall percent time spent with SpO_2 of < 80 %	First 2 months of life
Jain, 2016, USA	Volume guarantee ventilation: effect on preterm infants with frequent hypoxemia episodes	RCT	24	< 32	32 ± SD 22	SpO_2 < 85 %, SpO_2 < 75 % Intermittent hypoxemia: SpO_2 < 85 %, during ≥ 20 s	Pulse oximetry (Radical 7, Masimo, Irvine, CA, USA)	Averaging time: 8 s Sample rate: 1 Hz	Difference in frequency or duration of hypoxemic events	Two consecutive 24-hour periods
Jain, 2017, USA	Hypoxemia episodes during day and night and their impact on oxygen	Randomized controlled crossover trial	24	< 32	32 ± SD 22	SpO_2 < 85 %, SpO_2 < 75 % SpO_2 < 85 %,	Pulse oximetry (Radical 7, Masimo, Irvine, CA, USA)	Averaging time: 8 s	Difference in frequency or duration of hypoxemic events	Two consecutive 24-hour periods

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Table 1 (*continued*)

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
	saturation targeting in mechanically ventilated preterm infants	post-hoc analysis				during ≥ 20 s		Sample rate: 1 Hz		
Jenni, 1997, Switzerland	Effect of nursing in the head elevated tilt position (15°) on the incidence of bradycardic and hypoxemic episodes in preterm infants	Randomized controlled crossover trial	12	< 31	Range 6 – 38	SpO_2 < 80 %	Pulse oximetry (Nellcor N-200, Pleasanton, CA)	Averaging time: NA Sample rate: NA	Difference in the frequency of hypoxemic and bradycardic episodes	Two periods of 24 h
Jensen, 2021, Canada, USA, Argentina, Finland, Germany, Israel	Association between intermittent hypoxemia and severe bronchopulmonary dysplasia in preterm infants	Prospective cohort study post-hoc analysis	1018	23–27	Follow-up until at least 36 weeks of PMA	SpO_2 < 80 % Intermittent hypoxemia: SpO2 < 80 % during ≥ 60 s	Pulse oximetry	Averaging time: 16 s Sample rate: 0.1 Hz	Severe BPD defined according to the 2001 NIH Workshop Summary	Within 24 h after birth, continued until at least 36 weeks of PMA
Johnson, 2018, USA	Reducing alarm fatigue in two neonatal intensive care units through a quality improvement collaboration	Prospective cohort study	48	< 30	29.4 ± SD 2.6	SpO_2 ≤ 80 %	Pulse oximetry (Masimo Corporation, Irvine, CA) (Nellcor oximeter technology, Medtronic, Minneapolis, MN)	Averaging time: NA Sample rate: NA	The total number of nonactionable SpO_2 alarms per patient per hour and the number of nonactionable low SpO_2 alarms per patient per hour	NA
Katheria, 2021, USA	Association between early cerebral oxygenation and neurodevelopmental impairment or death in premature infants	Prospective cohort study	127	< 32	Follow-up till: 3	StO_2 < 67 %	Fore-Site Elite monitor	Averaging time: NA Sample rate: NA	Death or neurodevelopmental impairment	First 72 h of life
Kaufman, 2014, USA	Time outside targeted oxygen saturation range and retinopathy of prematurity	Prospective cohort study	102	< 32	NA	SpO_2 < 83 % for infants with oxygen supplementation SpO_2 < 85 %for infants in room air	Pulse oximetry (Nellcor N600 OXIMAX, Covidien, CA)	Averaging time: NA Sample rate: 0.5 Hz	Threshold retinopathy of prematurity	The entire hospital admission
Kenosi, 2015, Ireland	Effects of Fractional Inspired Oxygen on Cerebral Oxygenation in Preterm Infants following Delivery	Prospective cohort study	47	< 32	Follow-up till: 2	$rcSO_2$ total area < 55 %	INVOS 5100 NIRS (Covidien, Mansfield, Massachusetts) Neonatal transducer (OxyAlertTM NIRSensor, Covidien)	Averaging time: NA Sample rate: 0.2–0.17 Hz	The $rcSO_2$ area < 55 % and area > 85 %	First 48 h of life
Kenosi, 2018, Ireland	Monitoring cerebral oxygenation of preterm infants using a neonatal specific sensor	Prospective cohort study	120	< 32	Follow-up till: 2	$rcSO_2$ total area < 55 % $rcSO_2$ total area < 60 % for very preterm infants	INVOS 5100 NIRS (Covidien, Mansfield, MA, USA) OxyAlertTM NIRSensor (Covidien IIc, Mansfield, MA, USA)	Averaging time: NA Sample rate: 0.2–0.17 Hz	The $rcSO_2$ area < 55/60 % and area > 85/90 %	First 48 h of life
Klevebro, 2019, Sweden	Adherence to oxygen saturation targets increased in preterm infants when a higher target range and tighter alarm limits were introduced	Retrospective cohort study	399	23 0/7–30 6/7	Follow-up til: 21	SpO_2 < 85 %	Philips Fourier Artifact-Suppression Technology (Philips Medical Systems, Andover, MA, USA) Masimo Signal-Extraction Technology (Masimo, Irvine, CA, USA)	Averaging time: 10 s Sample rate: 0.008 Hz	Differences in mean SpO_2	First three postnatal weeks
Kothari, 2021, Australia	Time to desaturation in preterm infants undergoing endotracheal	RCT secondary analysis	78	≤ 32	36 (10–312) hours	SpO_2 < 90 %, SpO_2 < 80 %, SpO_2 < 70 %,	Pulse oximetry (Radical 7, Masimo, Irvine, California, USA)	Averaging time: 10 s	The time from the last positive pressure inflation or spontaneous breath	

Table 1 (*continued*)

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
	intubation					SpO_2 < 60 %		Sample rate: 0.5 Hz	until desaturation (SpO_2 < 90 %)	
Kovatis, 2020, USA	Effect of blood transfusions on intermittent hypoxic episodes in a prospective study of very low birth weight infants	Prospective cohort study	41	23 0/7 – 28 6/7	Group 1: 28.11 ± SD 2.34 Group 2: 27.17 ± 1.16 weeks	Intermittent hypoxemia: SpO_2 ≤ 80 %, during ≥ 10–– 180 s	Pulse oximetry (Radical 87, Masimo, Irvine, California)	Averaging time: 2 s Sample rate: 0.5 Hz	Number of intermittent hypoxemia events	First day of enrollment or after one week of age, until six weeks of age
Kurtom, 2022, USA	Effect of the target range on arterial oxygen saturation stability in extremely premature infants	Prospective crossover study	18	≤ 28	56 ± (SD) 28	Intermittent hypoxemia: SpO_2 < 90 % during ≥ 10 s Severe: SpO2 < 80 % during ≥ 10 s	Pulse oximetry (Radical 7, Masimo, Irvine, CA, USA)	Averaging time: 8 s Sample rate: 100 Hz	Episodes of severe hypoxemia defined as SpO_2 < 80 % during ≥ 10 s	Two periods of 2 h each
Lee, 2006, Canada	Frequency of apnea, bradycardia, and desaturations following first diphtheria-tetanus-pertussis-inactivated polio-Haemophilus influenzae type B immunization in hospitalized preterm infants	Retrospective cohort study	248	≤ 32	Group1: 74 (range 58–125) Group 2: 74 (range 56–120) days	SpO_2 ≤ 85 %	NA	Averaging time: NA Sample rate: NA	Frequency of events	72 h pre-immunization and 72 h post-immunization (for controls 72 h prior to equivalent age and 48 h post)
Lehtonen, 2002, USA	Relation of sleep state to hypoxemic episodes in ventilated extremely-low-birth-weight infants	Prospective cohort study	13	Mean 24.9 (Range 23–27)	Mean 28.3 (Range 25–34)	SpO_2 ≤ 85 %	Pulse oximetry (Datex-Ohmeda 3900, Madison, Wis)	Averaging time: 3 s Sample rate: NA	Proportion of time spent in hypoxemia	3 h
Martini, 2020, Italy	Cardiorespiratory events in infants born preterm during the transitional period	Prospective cohort study	32	< 32	Follow-up til: 3	SpO_2 < 85 % Mild: SpO_2 80 %-84 %, during ≤ 60 s Moderate: SpO_2 70 %-79 %, and/or during 61–120 s Severe: SpO2 < 70 %, and/or during > 120 s	Pulse oximetry (Radical 7, Masimo Corporation, Irvine, CA, USA)	Averaging time: 2 s Sample rate: 1 Hz	Daily incidences of isolated desaturation, isolated bradycardia, and combined desaturation and bradycardia	Time of enrollment to up to 72 h of life
McEvoy, 1997, USA	Prone positioning decreases episodes of hypoxemia in extremely low birth weight infants (1000 g or less) with chronic lung disease	Prospective crossover study	55	Mean 26.0 (Range 23 – 30)	42 ± SD 2 (range 28–83)	SpO_2 < 90 %, SpO_2 < 85 %, SpO_2 < 80 %	Pulse oximetry (Nellcor N-200 monitor, Nellcor Inc., Hayward, Calif.)	Averaging time: NA Sample rate: 1 Hz	Mean oxygen saturation	Consecutively 1-hour time intervals
MacFarlane, 2023, USA	Plasma serotonergic biomarkers are associated with hypoxemia events in preterm neonates	Prospective cohort study	168	< 31	Group 1: 7 ± 3 (range: 5–14) Group 2: 30 ± 5 (range: 27–43)	SpO_2 < 80 % Intermittent hypoxemia: SpO_2 < 80 % during > 10 s and < 5 min	Pulse oximetry (Masimo, Radical 7, Irvine, CA)	Averaging time: 8 sSample rate:1 Hz	Parameters of hypoxemia (frequency of intermittent hypoxemia and percentage of time < 80 %)	Two 6 h periods post-blood draw
Martin, 2023, Germany	Association of response time and intermittent hypoxemia in extremely preterm infants	Prospective cohort study	20	≤ 28	Range: 11 – 37	Intermittent hypoxemia: SpO_2 < 80 % during ≥ 10 s	Pulse oximetry (IntelliVue MX700, Philips Healthcare with RD-Set (Masimo Corp) and Radical-7 (Masimo	Averaging time: NA Sample rate: 0.5 Hz	Response time and relative intermittent hypoxic frequency during rest	Six consecutive 24 h periods

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Table 1 (*continued*)

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
							Corp) with LNCS Neo (Masimo Corp))			
Mueller, 2022, Germany	Incidence of intermittent hypoxemia increases during clinical care and parental touch in extremely preterm infants	Prospective cohort study	20	≤ 28	22 (range 11 – 37)	Intermittent hypoxemia: SpO_2 < 80 % during ≥ 10 s	Pulse oximetry (Masimo, Radical 7, Yorba, CA, USA)	Averaging time: 2 s Sample rate: 1 Hz	Intermittent hypoxemia	Six consecutive 24 h periods
Mitchell, 2013, USA	Effects of daily kangaroo care on cardiorespiratory parameters in preterm infants	RCT post hoc analysis of one arm	38	27 – 30	Enrollment: 5 Follow-up till: 10	SpO_2 < 80 %	Pulse oximetry (Nellcor)	Averaging time: NA Sample rate: NA	Hourly means of oxygen saturation	Starting at 5 days of life and continuing for 5 days
Morozoff, 2009, Canada	Evaluation of three automatic oxygen therapy control algorithms on ventilated low birth weight neonates	Prospective cohort study	7	Range 25 – 31	Range 8 – 23	SpO_2 < 90 %	Pulse oximetry	Averaging time: NA Sample rate: NA	Percent time spent at SpO_2 target (92, 93, and 94 %)	NA
Morozoff, 2017, Canada	Applying computer models to realize closed-loop neonatal oxygen therapy	Prospective cohort study	7	Range 25 – 31	Range 8 – 23	SpO_2 < 90 %	Pulse oximetry	Averaging time: NA Sample rate: 1 Hz	Duration in normoxemia	≥ 1 h of manual oxygen therapy and ≥ 1 h of closed-loop therapy
Ng, 2020, UK	Burden of hypoxia and intraventricular haemorrhage in extremely preterm infants	Prospective cohort study	44	< 28	Group 1: 6.92 (SD 3.04) hours Group 2: 6.54 (SD 3.00) hours	$rStO_2$ < 55 %	NIRO-200NX NIRS monitor	Averaging time: NA Sample rate: NA	Percentage of time in hypoxia and burden of hypoxia below each threshold	First 24 h of life
Noroozi-Clever, 2023, USA	Preterm infants off positive pressure respiratory support have a higher incidence of occult cerebral hypoxia	Prospective cohort study	174	≤ 32	NA	NIRS < 67 %, SpO_2 < 85 %	NIRS (ForeSight Elite, Edwards LifeSciences, Irvine, CA) Pulse oximetry (Nellcor OxiMax, Medtronic, Minneapolis, MN)	Averaging time: NA Sample rate: 0.5 Hz	Cerebral hypoxia	Until 35 weeks corrected age for 4 – 6 h per session
Petrova, 2006, Canada	Near-infrared spectroscopy in the detection of regional tissue oxygenation during hypoxic events in preterm infants undergoing critical care	Observational cross-sectional study	10	24 – 32	Enrollment: 7	SpO_2 ≤ 80 %, during ≥ 4 s rSO_2C ≤ 44 %	GE DASH 4000 (GE Healthcare, WI) NIRS equipment (INVOS 5100, Somanetics Corporation, Troy, MI)	Averaging time: NA Sample rate: 0.2 Hz (SpO_2) 0.08––0.1 Hz (NIRS)	Association between decreased SpO_2 to 70–80 % with reduction in cerebral and renal tissue oxygenation	A 2-hour period
Pirr, 2013, Germany	Closed versus open endotracheal suctioning in extremely low-birth-weight neonates: A randomized, crossover trial	Randomized controlled crossover trial	15	< 32	Mean 4 (range 2 – 27)	SpO_2 < 85 %, SpO_2 < 80 %	Pulse oximetry (Medcare Embletta PDS)	Averaging time: NA Sample rate: NA	Frequency, duration and severity of hypoxemia < 85 %, < 80 % and bradycardia < 80 bpm	Two 4-hour periods
Plomgaard, 2017, France, Denmark, Spain, Ireland, The Netherlands, Austria, Italy, UK	Early biomarkers of brain injury and cerebral hypo- and hyperoxia in the SafeBoosC II trial	RCT post-hoc analysis	164	< 28	Follow-up till: 3	The time spent below target limits multiplied by the mean deviation from the lower (55 %) limit	NIRS	Averaging time: NA Sample rate: NA	The burden of hypoxia and hyperoxia	The first 72 h of life
Plomgaard, 2022, France, Denmark, Spain, Ireland, The Netherlands, Austria, Italy, UK	Early cerebral hypoxia in extremely preterm infants and neurodevelopmental impairment at 2 year of age: A post hoc analysis	RCT post-hoc analysis	114	< 28	Follow-up till: 3	The time spent below target limits multiplied by the mean deviation from the lower (55 %)	NIRS	Averaging time: NA Sample rate: NA	Medical examination, Bayley II or III test and the parental Ages and Stages Questionnaire	The first 72 h of life

Table 1 (*continued*)

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
	of the SafeBoosC II trial					limit				
Poets, 1999, Germany	Effect of doxapram on episodes of apnoea, bradycardia and hypoxaemia in preterm infants	Prospective cohort study	15	< 32	27 (Range 12 – 60)	$SpO_2 \leq 80$ %	Pulse oximetry (Nellcor N200 in beat-to-beat mode; Nellcor Puritan Bennett, Pleasington, Calif., USA)	Averaging time: NA Sample rate: beat-to-beat recordings, not specifically described	Rate of apnea, desaturations, bradycardia	Four 6 h periods
Poets, 2015, 25 hospitals in Canada, USA, Argentina, Finland, Germany, Israel	Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants	Post-hoc analysis of data from inception cohort	1019	23 0/7 – 27 6/7	Enrollment: 17.8 (IQR 11.8–22.1) hours	$SpO_2 < 80$ %	Pulse oximetry	Averaging time: 16 s Sample rate: 0.1 Hz	Composite of death after 36 weeks' postmenstrual age, motor impairment, cognitive or language delay, severe hearing loss, or bilateral blindness at 18 months' corrected age	Until 36 weeks' PMA, and 40 weeks when receiving supplemental oxygen or any other respiratory support at 35 weeks' PMA
Poets, 2020, Australia	Oxygenation and intermittent hypoxia in supine vs prone position in very preterm infants	Prospective crossover study	14	< 32	29 (IQR 28 – 31)	$SpO_2 < 80$ %	Pulse oximetry (Masimo Radical, Masimo Inc)	Averaging time: 2 – 4 s Sample rate: 1 Hz	Baseline oxygenation and rates of intermittent hypoxemia	Two 4-hour periods
Poets, 2021, Australia	Mask versus nasal prong leak and intermittent hypoxia during continuous positive airway pressure in very preterm infants	RCT secondary analysis	20	< 32	17 (IQR 14 – 24)	$SpO_2 < 80$ %, during ≥ 10 s	Pulse oximetry (Masimo Radical, Masimo, Irvine, California, USA)	Averaging time: 2 – 4 s Sample rate: 1 Hz	Episodes of intermittent hypoxemia or bradycardia	Two 12 h periods
Raffay, 2019, USA	Neonatal intermittent hypoxemia events are associated with diagnosis of bronchopulmonary dysplasia at 36 weeks postmenstrual age	Retrospective cohort study	137	< 28	Enrollment: 1 Follow-up till: 28	$SpO_2 \leq 80$ %, during ≥ 10 – ≤180 s	Pulse oximetry (Masimo Radical, Irving, CA)	Averaging time: 2 s Sample rate: 0.5 Hz	Number of intermittent hypoxemia episodes	From the first postnatal day until 28 days
Raffay, 2023, USA	Hypoxemia events in preterm neonates are associated with urine oxidative biomarkers	Prospective cohort study	170	< 31	Group 1: 7 ± 3 Group 2: 30 ± 5 days	$SpO_2 < 80$ % Intermittent hypoxemia: $SpO_2 < 80$ % during > 10 s and < 5 min	Pulse oximetry (Masimo, Radical 7, Irvine, CA)	Averaging time: 8 s Sample rate: 1 Hz	Hypoxemia events	Two 24-hour periods preceding urine collection
Ramanand, 2023, USA	Comparison of oxygen supplementation in very preterm infants: Variations of oxygen saturation features and their application to hypoxemic episode based risk stratification	Secondary analysis RCT	25	< 32	25 (IQR 4 – 86)	Intermittent hypemoxia: $SpO_2 < 85$ % during > 10 s	Pulse oximetry	Averaging time: 7 s Sample rate:NA	Dynamic measures of oxygen saturation patterns	Four 24 h periods
Rantakari, 2021, Finland	Early oxygen levels contribute to brain injury in extremely preterm infants	Retrospective cohort study	73	< 28	Follow-up till: 3	Cumulative $SpO_2 < 85$ %, cumulative $SpO_2 < 90$ %	NA	Averaging time: 120 s Sample rate: 0.1 Hz	White matter injury, secondary cortical somatosensory processing in magnetoencephalography, Hempel neurological examination, and developmental quotients of Griffiths Mental Developmental Scales	During the first 3 postnatal days

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Table 1 (*continued*)

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
Reher, 2008, Germany	Randomised crossover trial of different postural interventions on bradycardia and intermittent hypoxia in preterm infants	Randomized controlled crossover trial	18	≤ 32	29 (Range 11 – 56)	SpO_2 < 85 %	Pulse oximetry (Radical, Masimo Inc, USA)	Averaging time: 2 s Sample rate: NA	Combined event rate of desaturations (SpO_2 < 85 %) and bradycardias (heart rate < 80 bpm)	three 4-hour periods
Reynolds, 2019, UK	Randomised cross-over study of automated oxygen control for preterm infants receiving nasal high flow	Randomized controlled crossover trial	30	Range 23 – 32	29 (IQR 18 – 53) (Range 5 – 109)	SpO_2 < 90 %, during ≥ 60 s, SpO_2 < 80 %, during ≥ 60 s	Pulse oximetry (Masimo, Irvine, USA)	Averaging time: 8 s Sample rate: NA	Percent of time spent within target SpO_2 range	Two 24-hour periods
Rhein, 2014, USA	Effects of caffeine on intermittent hypoxia in infants born prematurely: A randomized clinical trial	RCT	95	< 32	Enrollment: Group 1: 35.6 (SD 1.1) Group 2: 35.4 (SD 1.1)	SpO_2 decrease of at least 5 % from the baseline to less than 90 %, during ≥ 5 s	Pulse oximetry (Masimo Rad 8, USA)	Averaging time: 2 s Sample rate: NA	Number of intermittent hypoxemia events per hour of recording and seconds with SpO_2 < 90 % per hour of recording	Monitoring continued until the infant was home for at least one week and had reached a PMA of at least 40 weeks
Ruiz, 2014, USA	Transcribed oxygen saturation vs oximeter recordings in very low birth weight infants	Retrospective cohort study	51	< 30	NA	SpO_2 between 80 – 84 %	Pulse oximetry (Masimo Radical 7 SET oximeters, Masimo Corporation, Irvine, CA, USA)	Averaging time: 8 s Sample rate: 0.5 Hz	Proportion of SpO_2 values recorded by the oximeter at each saturation value between 80 and 100 % compared to the proportion of hand-transcribed values at the same saturation value	from birth through 36 weeks PMA
Salverda, 2023, The Netherlands	Comparison of two automated oxygen controllers in oxygen targeting in preterm infants during admission: an observational study	Retrospective cohort study	186	24 – 29	Follow-up till: 30 weeks PMA	SpO_2 < 80 %, SpO_2 80 % –84 %, SpO_2 85 % –90 %, SpO_2 ≤ 90 %	Pulse oximetry (Masimo SET, Irvine, CA, USA)	Averaging time: 2 – 4 s 8 s Sample rate: 0.5 Hz	Time spent within SpO_2 target range (91–95 % for either epoch) and other SpO_2 ranges	Up to 30 weeks PMA
Sher, 2002, USA	Effect of nursing in the head elevated tilt position (15 degrees) on the incidence of bradycardic and hypoxemic episodes in preterm infants	Randomized controlled crossover trial	12	26 – 31	Range 6 – 38	SpO_2 < 80 %	Pulse oximetry	Averaging time: NA Sample rate: NA	Number of events (hypoxemic, bradycardic, mixed)	48 h
Tabacaru, 2017, USA	Impact of caffeine boluses and caffeine discontinuation on apnea and hypoxemia in preterm Infants	Retrospective cohort study	302	≤ 32	Group 1: 36 ± SD 24 Group 2: 39 ± SD 21 Group 3: 39 ± SD 24	SpO_2 < 88 %, SpO_2 < 75 %	Pulse oximetry	Averaging time: 8 s Sample rate: 0.5 Hz	Number of apnea, bradycardia, desaturation events (central apnea of at least 10 s with associated decline in heart rate to < 100 bpm and oxygen saturation to < 80 %)	Around the time of serum caffeine levels, caffeine boluses while on maintenance therapy, and caffeine discontinuation
Thewissen, 2021, Ireland, Belgium, Czech Republic, Canada	Cerebral oxygen saturation and autoregulation during hypotension in extremely preterm infants	Prospective cohort study within a RCT	89	< 28	NA	$rScO_2$ < 63 %	INVOS 5100 and the neonatal OxyAlert NIRSensor (Covidien, Mansfield, MA) neonatal monitors (IntelliVue MP70, Philips Healthcare, Best, The Netherlands, or equivalent).	Averaging time: NA Sample rate: NA	Difference in $rScO_2$ between dopamine- and placebo-treated hypotensive infants, for a period of 2 h following commencement of the study drug	2-hour epochs before, after start, and after stop of the study drug
Thoyre, 2003, USA	Occurrence of oxygen	Prospective	22	Range 25 – 32	36.5 (SD 1.6)	SpO_2 < 90 %,	Pulse oximetry	Averaging	Percentage of the feeding	5 min before and

Table 1 (*continued*)

Study	Title	Study design	n	GA (w)	PNA (d)	Definition of hypoxemia	Measurement	Monitoring specifications	Primary outcome	Monitoring period
	desaturation events during preterm infant bottle feeding near discharge	cohort study			range 33.5 – 40	during ≥ 1 s Mild: SpO_2 85 – 89 % Moderate: SpO_2 81 – 84 % Severe: SpO_2 ≤ 80	(Ohmeda Biox 3700, Boulder, CO)	time: lowest response averaging time Sample rate: NA	time with SpO_2 < 90 %, number of desaturation events	throughout an entire bottle feeding
Van Zanten, 2014, The Netherlands	The risk for hyperoxaemia after apnoea, bradycardia and hypoxaemia in preterm infants	Retrospective cohort study	56	< 32	NA	SpO_2 ≤ 80 %	NA	Averaging time: NA Sample rate: 0.017 Hz	Occurrence of apnoea, bradycardia, cyanosis	NA
Van Zanten, 2017, The Netherlands	The effect of implementing an automated oxygen control on oxygen saturation in preterm infants	Prospective cohort study	42	< 30	NA	SpO_2 ≤ 80 %	Pulse oximetry (Masimo Radical, Masimo Corporation, Irvine, California, USA)	Averaging time: 8 s Sample rate: NA	Percentage of time spent with SpO_2 within the intended target range (90–95 %) when FiO_2 was > 0.21	Starting from receiving respiratory support by the AVEA ventilator and supplemental oxygen, until a GA of 32 weeks
Van Zanten, 2017, The Netherlands	Improving manual oxygen titration in preterm infants by training and guideline implementation	Prospective cohort study	136	< 30	NA	SpO_2 ≤ 80 %	Pulse oximetry (Masimo SET Radical pulse oximeter, software version 46.02, Masimo Radical, Masimo Corporation, Irvine CA, USA)	Averaging time: NA Sample rate: 0.017 Hz	Time spent within the SpO_2 target range (85–95 %)	During respiratory support
Van Zanten, 2018, The Netherlands	Effect of a smaller target range on the compliance in targeting and distribution of oxygen saturation in preterm infants	Prospective pre–post implementation study	104	< 30	NA	SpO_2 < 80 %	Pulse oximetry (Masimo pulse oximeter, Masimo Radical, Masimo, Irvine, California, USA)	Averaging time: 8 s Sample rate: 0.017 Hz	Percentage of time spent with SpO_2 levels between 90 % and 95 % when FiO_2 > 0.21	Monitoring was continued until infants were transferred out of NICU or to another hospital
Variane, 2023, Brazil	Cerebral oxygen saturation in neonates: a bedside comparison between neonatal and adult NIRS sensors	Prospective cohort study	44	< 32	6 (Range 0 – 100)	NIRS < 55 % SpO_2 < 80 %	NIRS (INVOS™ OxyAlert™ Infant/ Neonatal NIRSensor, IS, Medtronic and INVOS™ Small Adult SomaSensors, SAFB-SM, Medtronic)	Averaging time: NA Sample rate: 0.3 – 0.14 Hz	$rScO_2$ values between the neonatal sensor measurement and the adult sensor measurement	Two 3-hour periods
Vesoulis, 2019, USA	Early hypoxemia burden is strongly associated with severe intracranial hemorrhage in preterm infants	Prospective cohort study	645	< 32	Follow-up til: 7	SpO_2 ≤ 70 %	Pulse oximetry (Masimo, UVA and CUMC) Nellcor (WU)	Averaging time: 8 s Sample rate: 0.5 Hz	High-grade ICH	From birth through 7 days
Waitz, 2015, Germany	Effects of automated adjustment of the inspired oxygen on fluctuations of arterial and regional cerebral tissue oxygenation in preterm infants with frequent desaturations	Randomized controlled crossover trial	15	< 30	34 (Range, 19 – 74)	SpO_2 < 80 %	Pulse oximetry (Radical, Masimo, Irvine, California, USA)	Averaging time: 8 s Sample rate: 0.5 Hz	Time within the SpO_2 target range (88 %-96 %) and the area under the curve above and below a defined $SctO_2$ range (±5% of the individual $SctO_2$ median of each infant)	Two 24-hour periods
Zanardo, 1995, Italy	Oxygen saturation in premature neonates with bronchopulmonary dysplasia in a hammock	Prospective cohort study	15	Range 27 – 30	Range 33 – 48	SpO_2 < 85 %	Pulse oximetry (Ohmeda B105 3760 Pulse Oximeter)	Averaging time: NA Sample rate: NA	Differences in SpO_2 values	15 min before during, and after hammock 'containing' position

Overview of the included articles with a hypoxemia definition. cFTOE = fractional cerebral oxygen extraction; d = days; FiO_2 = fraction of inspired oxygen; GA = gestational age; IQR = interquartile range; n = number; min = minutes; NICU = neonatal intensive care unit; NIRS = near-infrared spectroscopy; PMA = post menstrual age; PNA = postnatal age; RCT = randomized controlled trial; $rStO_2$ = regional tissue oxygen saturation; $rcSO_2$ = regional cerebral tissue oxygenation saturation; rSO_2C = regional cerebral tissue oxygen saturation; s = seconds; SD = standard deviation; $SctO_2$ = cerebral tissue oxygen saturation; SpO_2 = oxygen saturation measured with pulse oximetry; StO_2 = cerebral tissue oxygen saturation; $TcPO_2$ = transcutaneous partial pressure of oxygen; w = weeks.

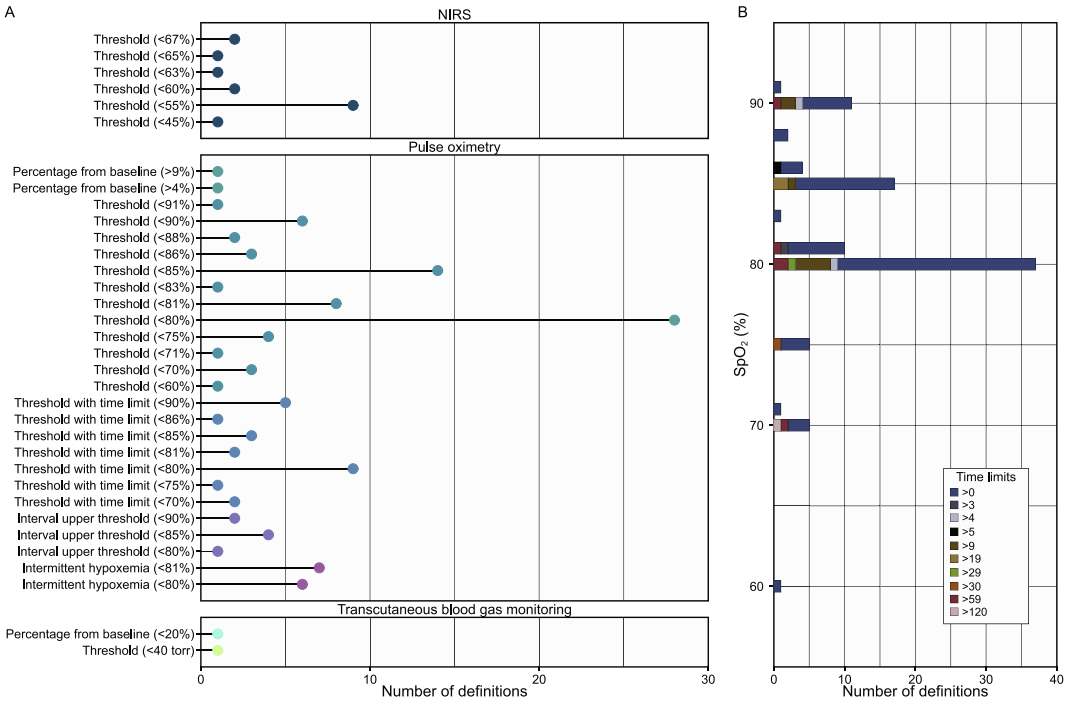

Fig. 2. a. Frequency graph on the different hypoxemia definitions (threshold, threshold with time limit, percentage from baseline, interval and intermittent) for NIRS, pulse oximetry and transcutaneous blood gas monitoring. b. Histogram of pulse oximetry definition based on a threshold or a threshold with a specific time limit.

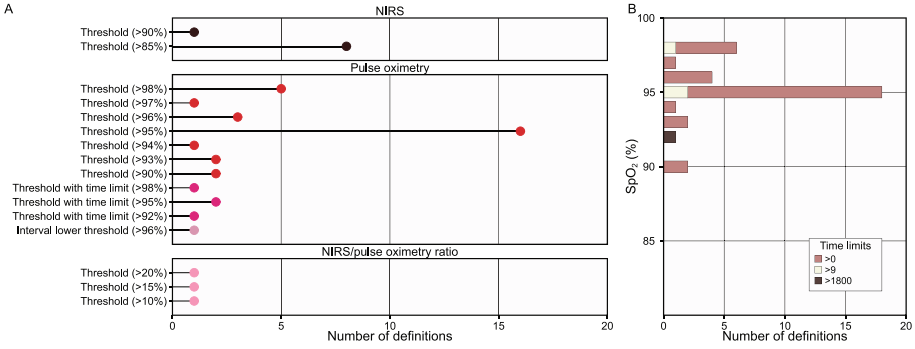

Fig. 3. a. Frequency graph on the different hyperoxemia definitions (threshold, threshold with time limit) for NIRS, pulse oximetry and NIRS/pulse oximetry ratio. b. Histogram of pulse oximetry definition based on a threshold or a threshold with a specific time limit.

increased risk of ROP, mortality, BPD, neurodevelopmental impairment, and the combined outcome of death and disability. A higher burden of hyperoxemia was related to an increased risk of ROP and overall mortality. However, the evidence on clinically relevant definitions remains sparse, due to the retrospective nature of most studies and relatively small samples sizes.

Definitions of hypoxemia and hyperoxemia were most frequently reported for pulse oximetry, likely due to its widespread use in neonatal clinical care and its non-invasive aspect. Upon application, SpO_2 levels are available almost within seconds. However, the accuracy and reliability of pulse oximetry is affected by incorrect sensor placement, motion artefacts, skin pigment, or low blood perfusion and can decrease even further during periods of hypoxemia and hyperoxemia [30,97]. During anemic periods pulse oximetry readings might appear within normal ranges, while hypoxemia occurs at a tissue level. Given the shape of the oxygen hemoglobin dissociation curve, pulse oximetry has certain limitations when measuring hyperoxemia, as exposure of tissue to high oxygen levels is frequently underestimated [97]. Measurement of hypoxemia is also underestimated as low levels of oxygen might not be visible in pulse oximetry measurements due to the S-shaped curve [97]. Varying pulse oximeter averaging times and sample rates were applied in the identified studies, which influences the estimation of the actual burden of hypoxemia and hyperoxemia by inaccurate assessment of oxygen fluctuations [98,99]. Due to the absence of both a safe range of cerebral oxygenation as well as evidence for clinical benefits on the reduction of the cerebral burden of hypoxemia and hyperoxemia, NIRS monitoring is not commonly applied in neonatal care [6,100]. Transcutaneous oxygen monitoring is limited by the degree of arterialisation of the skin, relatively slow response times, and the need for frequent calibrations [97]. Inaccurate oxygen measurements can result in an underestimation or overestimation of the burden of hypoxemia and hyperoxemia, hampering adequate interventions.

Our study shows a broad spectrum of definitions of hypoxemia and hyperoxemia, which included other variables such as time within the definition [8,10,11,13–16,18,19,22–24,26,28,32,34–37,39,40,42,48,49,53,61,64,70,76,77,80,81]. It has been hypothe-

Table 2
Association of defined hypoxemia or hyperoxemia with neonatal outcomes.

	Exposure	Association	Remarks	Article
ROP requiring treatment/severe ROP				
Hypoxemia	Cumulative exposure to hypoxemia (SpO_2 < 80 %)	Higher risk	No association after adjustment for confounders	Afshar, 2018
	Desaturation events: a drop in arterial oxygen saturation (SpO_2) of ≤ 80 % for ≥ 10 s and ≤ 3 min duration	Higher risk		Di Fiore, 2010
	IH: SpO_2 ≤ 80 %, ≥10 s and ≤ 3 min	Higher risk	Associated with duration of IH, variability of the time interval between IH, IH nadir, time interval between IH of 1–20 min, and spectral power in the range of 0.002–0.008 Hz	Di Fiore, 2012
	Number of times the saturation was below the targeted range (alarm limits were set at 83 % while infants required oxygen supplementation and 85 %for neonates in room air)	Higher risk	The cumulative amount of time spent below an accepted targeted range of oxygen saturations correlates with the incidence of threshold ROP. The duration of hypoxemia was associated with the future development of threshold ROP or mortality.	Kaufman, 2014
	SpO_2 of < 85 %	No association	No significant differences between two oxygen saturation target ranges	Klevebro, 2019
	The time spent below target limits multiplied by the mean deviation from the 55 % limit (NIRS)	No association	OR 95 %CI between 0.1–10	Plomgaard, 2017
	Pulse oximeter oxygen saturation < 80 %	Higher risk	RR 1.95 (95 % CI 1.22–3.11)	Poets, 2015
Hyperoxemia	Hyperoxemic events: SpO_2 increase of > 95 % for ≥ 10 s	Lower risk		Di Fiore, 2010
	The time spent above the target limits multiplied by the mean deviation from the upper limit of 85 % (NIRS)	No association	OR 95 %CI between 0.01–10	Plomgaard, 2017
	Percentage of the total SpO_2 exceeding defined thresholds 90/93/95 %	No association		Vesoulis, 2016
	Percentage of the total FTOE exceeding defined thresholds 20/15/10 % (NIRS)	Higher risk	Association with severe ROP at the 15 % (p = 0.04) and 10 % (p = 0.03) thresholds	Vesoulis, 2016
	Cerebral ($rcSO_2$ NIRS) and arterial (SpO_2) hyperoxia, defined as the percentage of time spent at saturation thresholds exceeding 85 and 90 %, respectively	Higher risk (cerebral), no association (arterial)	Adjusted OR (95 % CI) > Cerebral: 1.50 (1.09–2.06) > Arterial: 0.86 (0.62–1.21)	Richter, 2019
Death within 90 days after birth/overall mortality				
Hypoxemia	IH: SpO_2 < 80 % for ≥ 20 s and ≤ 5 min (hypoxemia < 80 %)	Higher risk	Only in SGA infants. > Shorter IH (HR 6.1; 95 % CI, 3.2–11.8, p < 0.0001, interaction p = 0.0255) > Longer IH (HR 3.6; 95 % CI, 2.0–6.3, p < 0.0001, interaction p = 0.1747)	Di Fiore, 2017
	Number of times the saturation was below the targeted range (alarm limits were set at 83 % while infants required oxygen supplementation and 85 %for neonates in room air)	Higher risk	Greater number of desaturation, as well as longer duration of time belowthe saturation limits.	Kaufman, 2014
	SpO_2 of < 85 %	No association	No significant differences between two oxygen saturation target ranges	Klevebro, 2019
	The time spent below target limits multiplied by the mean deviation from the 55 % limit (NIRS)	Higher risk	OR 95 %CI between 1–10	Plomgaard, 2017
	SpO_2 ≤ 70 %	No association		Vesoulis, 2019
Hyperoxemia	Number of times the saturation was above the targeted range (alarm limits were set at 93 % while infants required oxygen supplementation and 100 %for neonates in room air)	Higher risk	Greater number of high saturation events, as well as longer duration of time above the saturation limits.	Kaufman, 2014
	SpO_2 of > 95 %	No association	No significant differences between two oxygen saturation target ranges	Klevebro, 2019
	The time spent above the target limits multiplied by the mean deviation from the upper limit of 85 % (NIRS)	No association	OR 95 %CI between 0.1–10	Plomgaard, 2017
(Severe) bronchopulmonary dysplasia				
Hypoxemia	Hypoxemia: SpO_2 values < 80 %; hypoxemic episodes: SpO_2 < 80 % for ≥ 1 min	Higher risk	Adjusted RR (95 % CI) > Frequency of intermittent hypoxemic episodes: 1.72 (1.55–1.90) at the 2nd decile and 20.40 (12.88–32.32) at the 10th decile > The proportion of time per day with SpO2 < 80 %: 1.69 (1.52–1.88) at the 2nd decile and 14.90 (9.51–23.36) at the 10th decile	Jensen, 2021

(*continued on next page*)

Table 2 (*continued*)

	Exposure	Association	Remarks	Article
	The time spent below target limits multiplied by the mean deviation from the 55 % limit (NIRS)	No association	OR 95 %CI between 0.1–10	Plomgaard, 2017
	SpO_2 of ≤ 80 % for ≥ 10 s and ≤ 180 s duration	Higher risk	Increased IH event frequency and durations, and elevated IH nadirs In infants with BPD	Raffay, 2019
Hyperoxemia	The time spent above the target limits multiplied by the mean deviation from the upper limit of 85 % (NIRS)	Lower risk	OR 95 %CI between 0.1–1	Plomgaard, 2017
Neurodevelopmental impairment at 2 years of age				
Hypoxemia	The time spent below target limits multiplied by the mean deviation from the 55 % limit (NIRS)	No association	Moderate or severe neurodevelopmental impairment, OR 1.95 (0.61–6.02)	Plomgaard, 2022
	Cumulative time SpO_2 < 85 % and < 90 %	Higher risk	More SpO_2 measurements < 85 % and higher cumulative times when having SpO2 < 85 %	Rantakari, 2021
Death and disability/neurodevelopment impairment (combined)				
Hypoxemia	Hourly StO_2 average of 67/StO_2 threshold of 67 % (NIRS)	Higher risk	StO_2 < 67 was the only predictor for death or neurodevelopmental impairment (OR 2.75, 95 % CI 1.006, 7.5132, p = 0.049)	Katheria, 2021
	$rcSO_2$ total area below 55 %, and increased thresholds by 5 % for the very preterm group (NIRS)	Higher risk	a greater degree of hypoxia for the moderate compared to the normal outcome group and moderate compared to the severe outcome group.	Kenosi, 2018
	Pulse oximeter oxygen saturation < 80 %	Higher risk	RR 1.53 (95 % CI 1.21–1.94)	Poets, 2015
Neurodevelopmental impairment or death (combined)				
Hyperoxemia	$rcSO_2$ total area above 85 %, and increased thresholds by 5 % for the very preterm group (NIRS)	No association		Kenosi, 2018
Composite of death after 36 weeks' PMA, motor impairment, cognitive or language delay, severe hearing loss, or bilateral blindness at 18 months' corrected age.				
Hypoxemia	Pulse oximeter oxygen saturation < 80 %	Higher risk	RR 1.53 (95 % CI 1.21–1.94)	Poets, 2015
Cognitive or language delay				
Hypoxemia	SpO_2 < 80 %	Higher risk	RR 1.47 (95 % CI 1.13–1.90)	Poets, 2015
	Time with SpO_2 < 75 %	Higher risk and no association resp.	Rho = − 0.237, p = 0.034 (cognitive delay)Rho = − 0.078, p = 0.333 (language delay)	Dassios, 2022
Motor impairment				
Hypoxemia	SpO_2 < 80 %	Higher risk	RR 3.59 (95 % CI 2.02–6.40)	Poets, 2015
	Time with SpO_2 < 75 %	Higher risk	Rho = − 0.243, p = 0.031	Dassios, 2022
Early intraventricular haemorrhage or death (combined)				
Hypoxemia	% time $rScO_2$ < 63 %	Higher risk	OR 1.027 (95 % CI 1.004–1.051)No significance after correcting for GA	Thewissen, 2021
Intraventricular haemorrhage				
Hypoxemia	Threshold of 55 % and reference values from 60 %–87 % were investigated in conjunction with the threshold from our X2 analysis to calculate burden of hypoxia and percentage of time spent below each threshold	Higher risk	With a threshold of 71 %, percentage of time in hypoxia was lower by 12.2 % with a 95 % CI of (−25.7 to 1.2) (p = 0.073), and the burden of hypoxia was lower by 29.2 % hour (%h) (95 % CI − 55.2 to − 3.1)%h (p = 0.012) in infants without IVH than those with IVH.	Ng, 2020
	The time spent below target limits multiplied by the mean deviation from the lower (55 %) limit	Higher risk	OR 95 %CI between 1–10	Plomgaard, 2017
	SpO_2 ≤ 70 %	Higher risk	OR 6.56	Vesoulis, 2019
Hyperoxemia	The time spent above the target limits multiplied by the mean deviation from the upper limit (85 %)	No association	OR 95 %CI between 0.1–10	Plomgaard, 2017
	proportion of measured SpO_2 samples > 95 %	Lower risk		Vesoulis, 2019
Necrotising enterocolitis				
Hypoxemia	The time spent below target limits multiplied by the mean deviation from the lower (55 %) limit	No association	OR 95 %CI between 0.1–10	Plomgaard, 2017
Hyperoxemia	The time spent above the target limits multiplied by the mean deviation from the upper limit (85 %)	No association	OR 95 %CI between 0.01–10	Plomgaard, 2017
Symptomatic childhood wheezing requiring prescription asthma medication				
Hypoxemia	Intermittent hypoxemia: SpO_2 ≤ 80 % for ≥ 10 s and ≤ 180 s	Higher risk	Adjusted RR (95 % CI) > Day 1–3: 1.01 (1.004, 1.01) > Day 1–7: 1.01 (1.01,1.02) > Day 1–28: 1.00 (1.00, 1.00)	Di Fiore, 2019
Bronchopulmonary dysplasia-associated pulmonary hypertension (BPD-PH)				
Hypoxemia	IH: defined as SpO_2 < 80 % and < 70 %	Higher risk	IH events of longer duration threshold < 80 % (6; IQR, 5–8 vs. 7; IQR, 6–8; P = 0.03) or < 70 % (58; IQR, 41–89 vs. 105; IQR, 54–150; P = 0.008)	Gentle, 2022

Overview of the association between hypoxemia and hyperoxemia definition and clinical outcome. IH = intermittent hypoxemia; ROP = retinopathy of prematurity; SGA = small for gestational age; FTOE = fractional tissue oxygen extraction; NIRS = near-infrared spectroscopy; $rcSO_2$ = regional cerebral tissue oxygen saturation; StO_2 = tissue oxygen saturation; SpO_2 = oxygen saturation measured with pulse oximetry; CI = Confidence interval; RR = relative risk; OR = odds ratio.

sized that the harmful effects of intermittent hypoxemia depend on the frequency, timing, severity, and duration of hypoxemic events [101]. Using these parameters, high risk oxygenation patterns can be distinguished from low risk oxygenation patterns to identify the cumulative burden of hypoxemia and hyperoxemia. Multiple studies calculated other compound parameters as secondary outcomes, including the number of episodes above or below a certain threshold, a relative or absolute time spent at a threshold, area under or above a threshold, time between events, and variability in oxygenation [4,8–10,12–20,22,24,25,28–30,32,33,35–39,41,42,46,48–51,53–56,59,61,64–67,70–75,77,78,80–82,85–87,89–96]. In the case of hyperoxemia, measurements need to be corrected for the administration of supplemental oxygen. Measured hyperoxemia without additional support is likely to be less damaging than hyperoxemia while breathing more than 21 % oxygen. Although these compound parameters could provide more insight into the actual burden of hypoxemia and hyperoxemia, their clinical relevance and the applicability of these methods are unknown. This is complicated by the constantly evolving postnatal course of oxygenation in preterm infants [34].

Strengths and limitations

The results of this systematic review can guide the application of definitions for hypoxemia and hyperoxemia in current guidelines and future research. Using a systematic approach, this study provides a thorough overview of the available literature definitions. It allows for a step towards clinical integration of scientifically used definitions for hypoxemia and hyperoxemia. Evidence on the relationship between exposure to hypoxemia, hyperoxemia and adverse outcomes is still scarce and limited to studies with mostly small sample sizes and thus remains uncertain. The median sample size of the included studies investigating associations with adverse outcomes was 117, with the studies of Poets et al., Di Fiore et al., and Jensen et al. as outliers with more than 1000 participants [4,36,53]. In addition, while numerous definitions were found, a limited number was associated with neonatal outcome. As a result, the clinical relevance and therefore the shortcomings could not be sufficiently investigated. The heterogeneity of the presented hypoxemia and hyperoxemia definitions, with varying monitoring techniques and settings, may misdirect the search for clinically relevant quantifications of harmful and beneficial levels of oxygenation. No hyperoxemia definition using transcutaneous blood gas monitoring was identified in the systematic search, which can be explained by our inclusion and exclusion criteria, including studies with a gestational age $\leq$ 32 weeks, while some studies used birth weight for subject inclusion [102,103]. Less definitions of hyperoxemia were related to neonatal outcome, while, among others, studies investigating pulse oximetry target ranges, such as the STOP-ROP and BOOST trials have shown the link between high SpO_2 targets and poor outcome. Previous reviews suggested an upper limit of 80 torr for transcutaneous oxygen monitoring [97,104]. Studies reporting relevant associations between exposure to hypoxemia and hyperoxemia and adverse outcome could have been missed or excluded if no quantifiable definition was provided. The availability of a quantifiable definition was the main outcome of this systematic review, which could have resulted in these omissions.

Implications for clinical care and future research directions

In current clinical care, oxygen therapy is mostly titrated based on pre-set target ranges, although the optimal SpO_2 target ranges are still uncertain and adherence is suboptimal as shown in the NeOProM studies [105]. It is also unknown what alarm settings should be applied to reach optimal adherence to target ranges. The patient-specific hypoxemia and hyperoxemia burden is not commonly quantified for clinical use and guidelines provide no information for management based on the burden, despite the known associations between the oxygen burden and adverse outcomes. Introducing new methods to maintain oxygen levels within the specific range could lead to better, more efficient and individualized neonatal care. Monitoring techniques should be combined to increase the measurement accuracy of the hypoxemic and hyperoxemic burden. Respiratory interventions should not be based on alarm limits and target ranges only, the hypoxemic and hyperoxemic burden should be accounted for. The data infrastructure of NICUs needs to allow for processing and integrating currently available data streams. This is essential to achieve quantification of hypoxemia and hyperoxemia. Quantification of hypoxemia and hyperoxemia should at least be based on the most frequently used definitions in former studies (i.e. threshold of < 80 % and > 95 % for pulse oximetry, < 40 torr and > 80 torr for transcutaneous blood gas monitoring, and < 55 % and > 85 % for NIRS). The feasibility and added value of the use of more compound parameters to determine the hypoxemic and hyperoxemic burden needs to be investigated. The association between exposure to hypoxemia or hyperoxemia and short-term and long-term outcomes needs to be investigated more extensively to identify optimal oxygen management in neonatal care. Future studies should be conducted in a structured manner to enhance the knowledge on clinically relevant oxygenation levels and the hypoxemic or hyperoxemic burden and to enhance development of guidelines for interventions.

CONCLUSION

In the large range of hypoxemia and hyperoxemia definitions in preterm infants we found similarities, most frequently a threshold of < 80 % and > 95 % for pulse oximetry, < 40 torr and > 80 torr for transcutaneous blood gas monitoring, and < 55 % and > 85 % for cerebral NIRS. Exposure to hypoxemia and hyperoxemia is found to be associated with the development of adverse outcomes, including ROP, mortality, BPD, neurodevelopmental impairment, and the combined outcome of death and disability. The findings of our review suggest that the relation between clinical application of found definitions and adverse neonatal outcomes is insufficient for direct implementation.

Future directions for research

- Detailed analysis on the duration, frequency, timing and severity of hypoxemic and hyperoxemic events is required to define the actual burden.
- Clinical guidelines that uniformly apply a single definition and method to determine the burden of hypoxemia and hyperoxemia are required for early interventions that could potentially improve neonatal outcomes.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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APPENDIX A. SUPPLEMENTARY DATA

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