BMJ Paediatrics Open

Cumulative sucrose exposure for repeated procedural pain in preterm neonates and neurodevelopment at 18 months of corrected age: a prospective observational longitudinal study

Mariana Bueno,[1] Marilyn Ballantyne,[1,2] Marsha Campbell-Yeo,[3,4] Carole Estabrooks,[5] Sharyn Gibbins,[6,7] Denise Harrison,[8,9] Carol McNair,[10] Shirine Riahi ,[11] Janet Squires,[9,12] Anne R Synnes ,[13,14] Anna Taddio,[11,15] Charles Victor,[16,17] Janet Yamada,[18] Bonnie Stevens[1,11]

To cite: Bueno M, Ballantyne M, Campbell-Yeo M, *et al*. Cumulative sucrose exposure for repeated procedural pain in preterm neonates and neurodevelopment at 18 months of corrected age: a prospective observational longitudinal study. *BMJ Paediatrics Open* 2024;**8**:e002604. doi:10.1136/bmjpo-2024-002604

Received 28 February 2024
Accepted 27 June 2024

For numbered affiliations see end of article.

Correspondence to
Bonnie Stevens; bonnie.stevens@sickkids.ca

ABSTRACT

Introduction Oral sucrose is repeatedly administered to neonates in the neonatal intensive care unit (NICU) to treat pain from commonly performed procedures; however, there is limited evidence on its long-term cumulative effect on neurodevelopment. We examined the association between total sucrose volumes administered to preterm neonates for pain mitigation in the NICU and their neurodevelopment at 18 months of corrected age (CA).

Methods A prospective longitudinal single-arm observational study that enrolled hospitalised preterm neonates <32 weeks of gestational age at birth and <10 days of life was conducted in four level III NICUs in Canada. Neonates received 0.1 mL of 24% sucrose 2 min prior to all commonly performed painful procedures during their NICU stay. Neurodevelopment was assessed at 18 months of CA using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). Multiple neonatal and maternal factors known to affect development were adjusted for in the generalised linear model analysis.

Results 172 preterm neonates were enrolled and 118 were included in the analysis at 18 months of CA. The total mean sucrose volume administered/neonate/NICU stay was 5.96 (±5.6) mL, and the mean Bayley-III composite scores were: cognitive 91 (±17), language 86 (±18) and motor 88 (±18). There was no association between Bayley-III scores and the total sucrose volume: cognitive (p=0.57), language (p=0.42) and motor (p=0.70).

Conclusion Cumulative sucrose exposure for repeated procedural pain in preterm neonates was neither associated with a delay in neurodevelopment nor neuroprotective effects at 18 months of CA. If sucrose is used, we suggest the minimally effective dose combined with other non-pharmacological interventions with demonstrated effectiveness such as skin-to-skin contact, non-nutritive sucking, facilitated tucking and swaddling.

Trial registration number NCT02725814.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pain experienced in early life negatively affects development. There is moderate-certainty evidence that oral sucrose is clinically effective for reducing pain in neonates from single heel lance procedures.

WHAT THIS STUDY ADDS

⇒ Cumulative sucrose administered for repeated procedural pain in preterm neonates in the neonatal intensive care unit was not associated with neurodevelopment at 18 months of corrected age (CA) as measured by the Bayley Scales of Infant and Toddler Development, Third Edition.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We anticipate the results of this study will inform future research on neurodevelopment beyond 18 months of CA and other factors that may exert neuroprotective effects on development.

INTRODUCTION

Rising preterm birth rates and subsequent life-saving medical care provided in neonatal intensive care units (NICUs) have amplified exposure to pain in early life.[1] Painful procedures over the full NICU stay range into the hundreds.[2] Frequent skin-breaking (SB) and non-skin-breaking (NSB) procedures, coupled with underlying painful medical conditions, leave highly vulnerable preterm neonates repeatedly exposed to pain.[3] Early pain stress-related experiences negatively impact neurodevelopmental outcomes in the postnatal period and beyond,[4] potentially driven by epigenetic modulation and structural changes in the brain.[5] Therefore, finding effective treatments to prevent or ameliorate procedural pain in the NICU is essential for the improvement of neurodevelopmental outcomes.[6]

Table 1 Examples of minor SB and NSB painful procedures

Adhesive (tape) removal	Bandages, electrode tape, dressing tape, endotracheal/nasopharyngeal tape, gastric tube tape, intravenous/arterial line tape, low flow cannula tape, oxygen saturation probe tape, transcutaneous probe tape, ostomy bag changes, dressing changes, etc
Blood work	Capillary, venous and arterial blood draws
Injections	Intramuscular and subcutaneous
Vascular access attempts/ insertions	Peripheral intravenous lines, peripheral arterial lines, and long lines/peripherally inserted central catheters
Other procedures	Lumbar punctures, bladder taps, chest tube insertions and removals, eye examinations and urinary catheterisations

NSB, non-skin-breaking; SB, skin-breaking.

Multiple lines of systematically reviewed and synthesised evidence support the clinical effectiveness of oral sweet solutions,[7–10] breastfeeding,[11] skin-to-skin contact,[12] and non-nutritive sucking, facilitated tucking and swaddling[13] to prevent or treat pain from commonly performed procedures in the NICU. Of these, sucrose is one of the most implemented and studied treatments to mitigate procedural pain, either alone or in combination with other strategies, and there is moderate-certainty evidence on its effectiveness for single heel lances.[7] There is less evidence on the long-term effectiveness and safety of repeated sucrose use in the NICU population, although it suggests that it is effective and safe,[14 15] and few non-animal studies addressing its impact on neurodevelopment. Four randomised controlled trials looking at repeated sucrose use in the NICU over the first week of life to the full NICU stay found no differences between sucrose and non-sucrose exposure groups in neurobiological risk or neurobehavioural scores within the postnatal period.[16–19] However, a dose-related group effect was reported in one study,[19] with 10 or more doses of sucrose over a 24-hour period related to poorer neurodevelopment scores at term equivalent age.[20] Longer term effects of sucrose on neurodevelopment beyond the postnatal period warrant further study to see if these findings are sustained.

Table 2 Association between Bayley-III composite scores and total sucrose volume at 18 months of CA*

Bayley-III composite score	Slope (SE)	P value
Cognitive (n=112/91)	0.73 (1.30)	0.57
Language (n=108/88)	−1.08 (1.35)	0.42
Motor (n=112/91)	−0.54 (1.39)	0.70

*Adjusted for gestational age (GA), sex, total number of procedures, total number of non-pharmacological interventions, BPD, brain injury (including IVH 3 or 4), composite of NEC/ROP, SNAPPE-II scores, any opioid during stay, maternal education (postsecondary or more vs high school or less), maternal prenatal use of medications for depression or anxiety, maternal low-income neighbourhood and marital status (single vs married/common law).
Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; BPD, bronchopulmonary dysplasia; CA, corrected age; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity; SNAPPE-II, Score for Neonatal Acute Physiology-Perinatal Extension II.

Our aim was to examine the cumulative effect of total oral sucrose volumes administered to preterm neonates for procedural pain while in the NICU on their neurodevelopment at 18 months of corrected age (CA), adjusted for neonatal and maternal factors known to affect development.

METHODS

Study design and sample

In this prospective longitudinal single-arm observational study, preterm hospitalised neonates <32 weeks of gestational age at birth and <10 days of life were enrolled prospectively in four level III NICUs in Canada between March 2016 and June 2018, with data collection completed for the 18 months of CA time point in March 2020. Neonates with contraindications for oral sucrose use were excluded. Although there is no precise formula for calculating sample size in a longitudinal study, we estimated that 40 neonates per site would adequately represent the population of interest and meet the study goals. We oversampled by 10% to account for losses to follow-up.[15] A total of 172 preterm neonates were enrolled.

Study intervention

The study intervention was introduced in participating NICUs by the research nurses through unit-wide presentations and one-to-one teaching. Bedside staff nurses were directed to administer the minimally effective dose of 0.1 mL of 24% sucrose[21] to enrolled neonates prior to every minor SB and NSB painful procedure (table 1) during their NICU stay. The doses were given from primarily Canadian commercial 24% sucrose vials (ie, 3 drops of 0.04 mL/drop concentration). The sucrose was orally administered drop by drop onto the anterior surface of the tongue over no more than 1 min, 2 min before the painful procedure started. A pacifier was offered for non-nutritive sucking if the neonate could hold it in their mouth independently. The study dose was repeated at the discretion of the bedside staff nurse if the procedure continued over 1 min or if the neonate showed signs of moderate to severe distress as demonstrated by increased

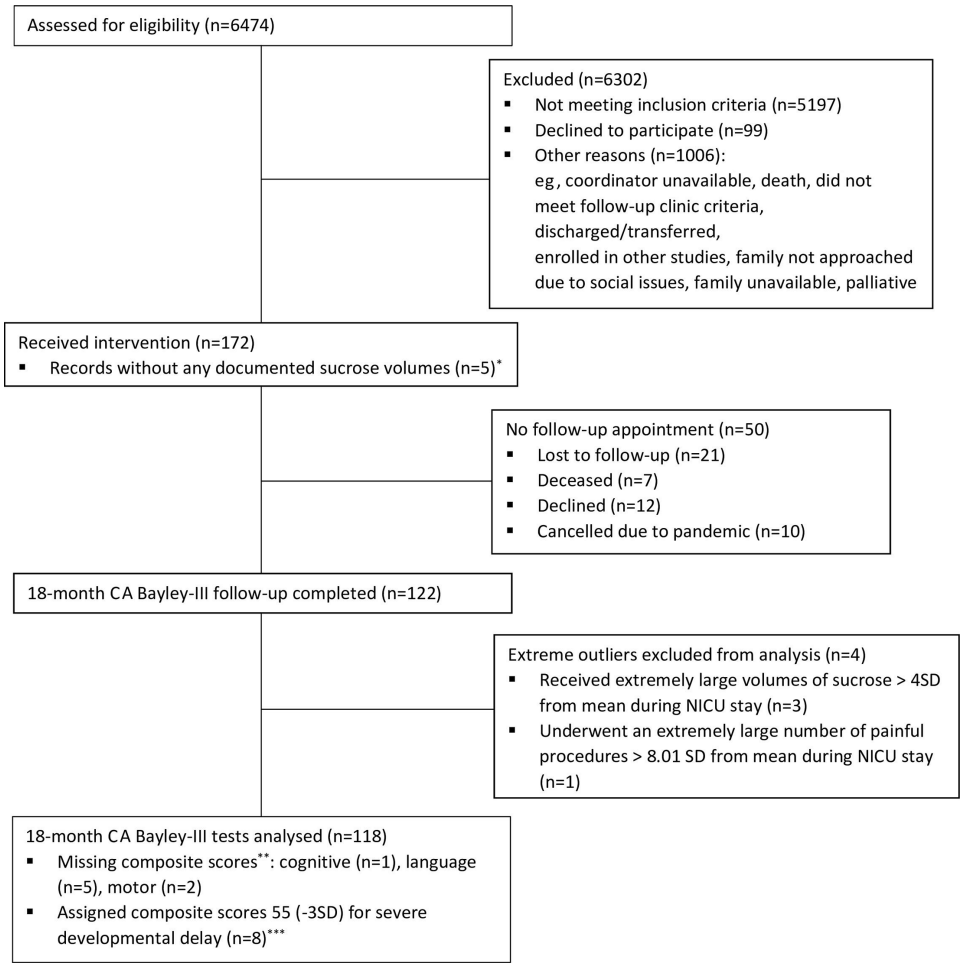

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. *Five participants did not have any documented sucrose volumes during their neonatal intensive care unit (NICU) stay for unknown reasons. **From partially completed Bayley-III tests (included in the analysis), where the assessor was unable to score every domain for reasons unrelated to developmental delay (eg, child was tired or distracted). ***Includes seven participants who were assigned Bayley-III composite scores of 55 (–3 SD) in all three domains (cognitive, language and motor), and one additional participant who was assigned Bayley-III composite scores of 55 (–3 SD) in two domains. Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition.

crying, changes in vital signs and moderate to maximal changes in facial grimacing. There was no limit set for the maximum procedural, daily or cumulative sucrose dose. Bedside staff nurses recorded the volume of sucrose administered, the associated painful procedure(s) and any non-pharmacological interventions used for pain mitigation in conjunction with sucrose (ie, skin-to-skin contact, non-nutritive sucking/pacifier use, facilitated tucking and swaddling) in a 24-hour study log. Research nurses followed up with bedside staff nurses caring for enrolled neonates to ensure the accuracy of 24-hour study log documentation, and to reinforce intervention fidelity using reminders and feedback. Standardised study supply kits containing oral sucrose, administration instructions and 24-hour study logs were kept at participant bedsides to facilitate intervention fidelity.

Study outcomes

The primary outcome was participant neurodevelopment, assessed at 18 months of CA by a trained psychometrist or nurse in the neonatal follow-up clinic at each site using the validated Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). Assessors were not blinded to the participants' enrolment in the study. The standardised mean composite score for each Bayley-III component (cognitive, language and motor development) was reported. The Bayley-III composite scores are standardised to a mean of 100 with one SD=15. Participants who were not tested due to severe developmental delay or had scores below –3 SD were given a composite score of 55 (–3 SD).[22] Outcome data on the efficacy of repeated sucrose[15] and the epidemiology of painful procedures and sucrose administration[23] over the course of hospitalisation in the NICU were reported elsewhere.

Data collection and management

Research nurses entered data into Research Electronic Data Capture (REDCap) software[24 25] hosted at the primary study site. Data monitoring was performed

Table 3 Neonatal and maternal demographics at 18 months of CA

Demographics	Participants included in analysis at 18 months of CA N=118	Participants not in analysis at 18 months of CA N=50	Difference P value
Neonatal demographics			
Sex, n (%)			0.28
Male	71 (60.2)	25 (51.0)	
Female	47 (39.8)	24 (49.0)	
GA at birth in weeks, mean (SD)	28.3 (2.1)	28.7 (2.5)	0.30
BW in grams, mean (SD)	1098 (356)	1118 (439)	0.76
SNAPPE-II score, mean (SD)	20.5 (19.0)	19.5 (20.4)	0.77
NEC, n (%)	3 (2.5)	3 (6.0)	0.25
ROP, n (%)	1 (0.8)	1 (2.0)	0.50
BPD, n (%)	24 (19.7)	11 (22.0)	0.73
Brain injury (includes IVH 3 or 4), n (%)	9 (7.4)	5 (10.0)	0.57
Opioid use during stay, n (%)			0.96
Yes	50 (42.4)	21 (42.0)	
No	68 (57.6)	29 (58.0)	
Total number of procedures during stay, mean (SD)	68.2 (66.5)	43.3 (58.4)	0.025
Total number of non-pharmacological interventions during stay excluding sucrose, mean (SD)*	79.4 (103.9)	78.4 (120.2)	0.95
Maternal demographics			
Education, n (%)			0.10
High school or less	24 (22.6)	15 (35.7)	
Postsecondary or more	82 (77.4)	27 (64.3)	
Prenatal use of medication for depression or anxiety, n (%)			0.85
Yes	13 (11.0)	5 (10.0)	
No	105 (89.0)	45 (90.0)	
Marital status, n (%)			0.39
Single	11 (9.4)	6 (12.2)	
Married/common law	100 (85.5)	38 (77.6)	
Not reported	6 (5.1)	5 (10.2)	
Low-income neighbourhood, n (%)			0.57
Yes	20 (17.9)	10 (21.7)	
No	92 (82.1)	36 (78.3)	

*Skin-to-skin contact, non-nutritive sucking/pacifier use, facilitated tucking and swaddling.
BPD, bronchopulmonary dysplasia; BW, birth weight; CA, corrected age; GA, gestational age; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; ROP, retinopathy of prematurity; SNAPPE-II, Score for Neonatal Acute Physiology-Perinatal Extension II.

throughout data collection. In addition to checking the accuracy of 24-hour study log documentation with bedside nurses, research nurses at each site undertook further intervention fidelity checks by reconciling data from the 24-hour study logs with other medical records with documented patient care before inputting the results into the REDCap database. The lead site project coordinator monitored the REDCap database for completeness and oversaw data cleaning activities.

Data analysis

Descriptive statistics were conducted to describe the sample and study outcomes. Generalised linear models accounting for the clustering of participants within sites were performed to evaluate the relationship between neurodevelopment at 18 months of CA and total sucrose volume administered during the NICU stay. Outcomes were adjusted for neonatal factors and maternal factors (table 2).

Table 4 Bayley-III composite scores at 18 months of CA

Bayley-III composite scores	
Cognitive score, mean (SD)	91 (17) n=117
Language score, mean (SD)	86 (18) n=113
Motor score, mean (SD)	88 (18) n=116

Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; CA, corrected age.

RESULTS

Of the 172 enrolled preterm neonates, 118 were included in the analysis (68.6%). The recruitment and final numbers of participants evaluated are summarised in figure 1.

Neonatal and maternal demographic characteristics are presented in table 3. Characteristics are compared between the sample analysed and the sample that did not have Bayley-III test results, excluding the outliers (n=4). There were no significant differences except for the mean number of procedures during the neonates' NICU stay which was greater in the analysis sample (p=0.025).

Total exposure to sucrose, expressed as the mean (SD) volume of sucrose administered per neonate per NICU stay, was 5.96 mL (5.60). Bayley-III composite scores were within the normal range for cognitive, language and motor development (table 4).

There was no association between Bayley-III composite scores (cognitive, language and motor) at 18 months of CA and total sucrose volume, when adjusted for neonatal and maternal characteristics (table 2). A sensitivity analysis performed with and without the outliers showed no difference in the direction of effects, no statistically significant p values and no difference in the interpretation of results.

DISCUSSION

We did not find a relationship between total oral sucrose volume administered to preterm neonates during their NICU stay and neurodevelopment at 18 months of CA as assessed by the Bayley-III. Cumulative sucrose exposure was neither associated with a delay in neurodevelopment nor neuroprotective effects within the period of this study, only its pain-relieving impact at the time of individual SB procedures.[15] Our results are consistent with findings reporting no effects of cumulative sucrose on neurodevelopment in the postnatal period.[16–18]

At the time the protocol for this study was developed, no research had examined neurodevelopmental outcomes in relation to sucrose beyond the first month of life. However, since then, a prospective longitudinal study reported that oral glucose exposure for pain mitigation in preterm neonates during their NICU admission was associated with lower Bayley-II motor development scores at 18 months of CA and slower brain growth/smaller brain volumes by term equivalent age.[26] Separating the effects of pain stress-related exposure, different pain treatments, prematurity and other modifying factors on neurodevelopment is complex and may be contributing to mixed findings. We addressed some of this complexity by adjusting for a variety of neonatal and maternal factors in the analyses (table 2) known to influence developmental outcomes. Unfortunately, it is difficult to know if this list was sufficiently comprehensive, although it was more extensive than the oral glucose study.[26] For example, little is known about how the NICU environment impacts neurodevelopment at later stages[27 28] and identifying the most salient factors that impact long-term neurodevelopment are still to be determined. Furthermore, no studies that we are aware of accounted for sucrose/glucose/sweeteners in medications and food. More research is needed to establish consistency in results.

Other limitations of this research related to managing pre-existing differences in sucrose administration and documentation practices across sites when the intervention was being administered by clinical versus research staff. For example, imprecise reporting of sucrose volumes prior to study enrolment meant that more complete sucrose volumes for the entire NICU stay were not available.[23] We attempted to minimise practice differences through staff nurse education and the use of standardised study supply kits kept at participant bedsides. These strategies, in conjunction with routine intervention fidelity checks by the research nurses, lead us to have reasonable confidence in the sucrose volume estimates in this study.

There was a greater than expected loss to follow-up towards the end of the study related to the onset of the COVID-19 pandemic. 10 participants were lost to follow-up either because clinical research activities were suspended, or parents did not want to bring their child to the hospital/outpatient clinic during the pandemic after clinical research activities resumed. The overall loss to follow-up rate for this study (43/172 or 25%, excluding deceased participants) was in line with Canadian neonatal follow-up clinic attendance rates.[27] Similar long-term follow-up studies should anticipate a loss to follow-up rate of at least 25%, excluding deaths, in the sample size calculation. Further follow-up at 36 months of CA and beyond needs to be considered, with attention given to maximising the feasibility of following children for this long.

CONCLUSION

Balancing the adverse effects of untreated procedural pain on the developing brain against the potential side effects of pain-relieving interventions such as sucrose is challenging, especially in preterm neonates. Since there is increased exposure to SB and NSB procedures in this population, pain prevention and treatment dictate repeated intervention. Given that cumulative

sucrose exposure was neither associated with a delay in neurodevelopment nor neuroprotective effects, and given the significant body of evidence on the effectiveness of non-pharmacological interventions, if sucrose is used, we suggest the minimally effective dose in combination with other non-pharmacological interventions with demonstrated effectiveness such as skin-to-skin contact, non-nutritive sucking, facilitated tucking and swaddling. Researchers must address the most effective and safe combinations of pain mitigation strategies for preterm neonates who are repeatedly exposed to pain and must commit to examining cumulative impacts on neurodevelopment over the long term.

Author affiliations
[1]University of Toronto Lawrence Bloomberg Faculty of Nursing, Toronto, Ontario, Canada
[2]Holland Bloorview Kids Rehabilitation Hospital, Toronto, Ontario, Canada
[3]School of Nursing, Faculty of Health and Departments of Pediatrics, Psychology and Neuroscience, Dalhousie University, Halifax, Nova Scotia, Canada
[4]Centre for Pediatric Pain Research, IWK Health Centre, Halifax, Nova Scotia, Canada
[5]Edmonton Clinic Health Academy, University of Alberta, Edmonton, Alberta, Canada
[6]Neonatology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[7]Trillium Health Partners, Mississauga, Ontario, Canada
[8]Nursing, University of Melbourne School of Health Sciences, Melbourne, Victoria, Australia
[9]School of Nursing, University of Ottawa Faculty of Health Sciences, Ottawa, Ontario, Canada
[10]Neonatology, The Hospital for Sick Children, Toronto, Ontario, Canada
[11]Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada
[12]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[13]Neonatology, BC Women's Hospital and Health Centre, Vancouver, British Columbia, Canada
[14]Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada
[15]University of Toronto Leslie Dan Faculty of Pharmacy, Toronto, Ontario, Canada
[16]Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada
[17]University of Toronto Dalla Lana School of Public Health, Toronto, Ontario, Canada
[18]Toronto Metropolitan University Daphne Cockwell School of Nursing, Toronto, Ontario, Canada

Contributors Conceptualisation/design and methodology: BS, JY, MC-Y, DH, MB, CV, ARS, AT, CE, JS. Data acquisition: BS, MC-Y, DH, SG, CM, SR. Data analysis and interpretation: BS, CV, MB, SR. Manuscript preparation: all authors. Study accountability: BS.

Funding This study was funded by a Foundation Grant from the Canadian Institutes of Health Research (CIHR) (FDN-148452).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study protocol was reviewed and approved by the Research Ethics Boards at each participating study site including: The Hospital for Sick Children (1000051066), IWK Health Centre (1020268), The Ottawa Hospital (20150910-01H) and Sunnybrook Health Sciences Centre (354-2013). Following approval, the research nurses explained the study and obtained written consent from parents of eligible neonates. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available upon request.

ORCID iDs
Shirine Riahi http://orcid.org/0009-0006-6827-9409
Anne R Synnes http://orcid.org/0000-0002-6917-0978

REFERENCES

1 Williams MD, Lascelles BDX. Early neonatal pain—a review of clinical and experimental implications on painful conditions later in life. *Front Pediatr* 2020;8:30.
2 Orovec A, Disher T, Caddell K, *et al*. Assessment and management of procedural pain during the entire neonatal intensive care unit hospitalization. *Pain Manag Nurs* 2019;20:503–11.
3 Shiff I, Bucsea O, Pillai Riddell R. Psychosocial and neurobiological vulnerabilities of the hospitalized preterm infant and relevant non-pharmacological pain mitigation strategies. *Front Pediatr* 2021;9:568755.
4 Valeri BO, Holsti L, Linhares MBM. Neonatal pain and developmental outcomes in children born preterm: a systematic review. *Clin J Pain* 2015;31:355–62.
5 Boggini T, Pozzoli S, Schiavolin P, *et al*. Cumulative procedural pain and brain development in very preterm infants: a systematic review of clinical and preclinical studies. *Neurosci Biobehav Rev* 2021;123:320–36.
6 McPherson C, Miller SP, El-Dib M, *et al*. The influence of pain, agitation, and their management on the immature brain. *Pediatr Res* 2020;88:168–75.
7 Yamada J, Bueno M, Santos L, *et al*. Sucrose analgesia for heel-lance procedures in neonates. *Cochrane Database Syst Rev* 2023;8:CD014806.
8 Bueno M, Yamada J, Harrison D, *et al*. A systematic review and meta-analyses of nonsucrose sweet solutions for pain relief in neonates. *Pain Res Manag* 2013;18:153–61.
9 Lin T, Qiu H, Huang R, *et al*. There are already enough studies on sweet solutions for neonatal procedural pain and more would be unethical and unnecessary. *Acta Paediatr* 2023;112:1434–6.
10 Weng Y, Zhang J, Chen Z. Effect of non-pharmacological interventions on pain in preterm infants in the neonatal intensive care unit: a network meta-analysis of randomized controlled trials. *BMC Pediatr* 2024;24:9.
11 Benoit B, Martin-Misener R, Latimer M, *et al*. Breast-feeding analgesia in infants: an update on the current state of evidence. *J Perinat Neonatal Nurs* 2017;31:145–59.
12 Johnston C, Campbell-Yeo M, Disher T, *et al*. Skin-to-skin care for procedural pain in neonates. *Cochrane Database Syst Rev* 2017;2:CD008435.
13 Pillai Riddell RR, Bucsea O, Shiff I, *et al*. Non-pharmacological management of infant and young child procedural pain. *Cochrane Database Syst Rev* 2023;6:CD006275.
14 Gao H, Gao H, Xu G, *et al*. Efficacy and safety of repeated oral sucrose for repeated procedural pain in neonates: a systematic review. *Int J Nurs Stud* 2016;62:118–25.
15 Bueno M, Ballantyne M, Campbell-Yeo M, *et al*. The effectiveness of repeated sucrose for procedural pain in neonates in a longitudinal observational study. *Front Pain Res (Lausanne)* 2023;4:1110502.
16 Campbell-Yeo M, Johnston CC, Benoit B, *et al*. Sustained efficacy of Kangaroo care for repeated painful procedures over neonatal intensive care unit hospitalization: a single-blind randomized controlled trial. *Pain* 2019;160:2580–8.
17 Banga S, Datta V, Rehan HS, *et al*. Effect of sucrose analgesia, for repeated painful procedures, on short-term neurobehavioral outcome of preterm neonates: a randomized controlled trial. *J Trop Pediatr* 2016;62:101–6.
18 Stevens B, Yamada J, Beyene J, *et al*. Consistent management of repeated procedural pain with sucrose in preterm neonates: is it effective and safe for repeated use over time *Clin J Pain* 2005;21:543–8.
19 Johnston CC, Filion F, Snider L, *et al*. Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age. *Pediatrics* 2002;110:523–8.
20 Johnston CC, Filion F, Snider L, *et al*. How much sucrose is too much sucrose. *Pediatrics* 2007;119:226.
21 Stevens B, Yamada J, Campbell-Yeo M, *et al*. The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial. *BMC Pediatr* 2018;18:85.
22 Finder M, Boylan GB, Twomey D, *et al*. Two-year neurodevelopmental outcomes after mild hypoxic ischemic

encephalopathy in the era of therapeutic hypothermia. *JAMA Pediatr* 2020;174:48–55.
23 Bueno M, Ballantyne M, Campbell-Yeo M, *et al*. A longitudinal observational study on the epidemiology of painful procedures and sucrose administration in hospitalized preterm neonates. *Paediatr Neonatal Pain* 2024;6:10–8.
24 Harris PA, Taylor R, Minor BL, *et al*. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
25 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
26 Schneider J, Duerden EG, Guo T, *et al*. Procedural pain and oral glucose in preterm neonates: brain development and sex-specific effects. *Pain* 2018;159:515–25.
27 Synnes A, Luu TM, Moddemann D, *et al*. Determinants of developmental outcomes in a very preterm Canadian cohort. *Arch Dis Child Fetal Neonatal Ed* 2017;102:F235–F234.
28 Synnes AR, Petrie J, Grunau RE, *et al*. Family integrated care: very preterm neurodevelopmental outcomes at 18 months. *Arch Dis Child Fetal Neonatal Ed* 2022;107:76–81.