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Early neurobehavior at 30 weeks postmenstrual age is related to outcome at term equivalent age

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ABSTRACT

Aims: To determine 1) the relationship between infant medical factors and early neurobehavior, and 2) the relationship between early neurobehavior at 30 weeks postmenstrual age (PMA) and neurobehavior at term equivalent age.

Study design: In this prospective longitudinal study, 88 very preterm infants born ≤30 weeks estimated gestational age (EGA) had neurobehavioral assessments at 30 weeks PMA using the Premie-Neuro and at term equivalent age using the NICU Network Neurobehavioral Scale (NNNS) and Hammersmith Neonatal Neurological Evaluation (HNNE).

Results: Lower Premie-Neuro scores at 30 weeks PMA were related to being more immature at birth ($p = 0.01$; $\beta = 3.87$); the presence of patent ductus arteriosus (PDA; $p < 0.01$; $\beta = -16.50$) and cerebral injury ($p < 0.01$; $\beta = -20.46$); and prolonged exposure to oxygen therapy ($p < 0.01$; $\beta = -0.01$), endotracheal intubation ($p < 0.01$; $\beta = -0.23$), and total parenteral nutrition ($p < 0.01$; $\beta = -0.35$). After controlling for EGA, PDA, and number of days of endotracheal intubation, lower Premie-Neuro scores at 30 weeks PMA were independently related to lower total HNNE scores at term ($p < 0.01$; $\beta = 0.12$) and worse outcome on the NNNS with poorer quality of movement ($p < 0.01$; $\beta = 0.02$) and more stress ($p < 0.01$; $ß = -0.004$), asymmetry ($p = 0.01$; $\beta = -0.04$), excitability ($p < 0.01$; $\beta = -0.05$) and suboptimal reflexes ($p < 0.01$; $ß = -0.06$).

Conclusion: Medical factors were associated with early neurobehavioral performance at 30 weeks PMA. Early neurobehavior at 30 weeks PMA was a good marker of adverse neurobehavior at NICU discharge.

1. Introduction

Despite advances in medical care, developmental challenges following preterm birth remain high [1]. Preterm infants have high rates of motor, cognitive and language delays [2–6]. They also have higher rates of social-emotional, behavioral and learning problems [6–13]. Due to the high rates of morbidity, early identification of developmental difficulties is important, as it can lead to activation of therapeutic interventions aimed at optimizing outcomes [14]. Neonatal neurobehavioral assessments consist of the evaluation of neurological integrity (largely involving observing motor function and eliciting reflexes) and behavioral functioning (largely involving observation of arousal, excitability, and the infant's ability to cope with environmental stressors). Neonatal therapy interventions that begin in the neonatal intensive care unit (NICU) are common and can be implemented for those with identified impairments from the neurobehavioral assessment [15].

Due to the rapid changes in development prior to term equivalent age and through the first months corrected age, tools that are used in later infancy and early childhood are not appropriate for or do not discriminate alterations in function in high-risk infants during the neonatal period [16–18]. However, tools have been developed for infants prior to and at term equivalent age in the NICU environment [19–27], and their use is typically appropriate until 6–8 weeks

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corrected age. Some tools are appropriate for infants as they approach term equivalent age [21,25], and others use a limited number of assessment items to assess function in infants who are very early in gestation and may still have endotracheal intubation [20]. Some assessments are observational [27], and others require the tester to elicit infant responses [20,21,24]. However, it is not well understood if early neurobehavioral tests discriminate those with neurobehavioral alterations from those without. Furthermore, medical complications during NICU hospitalization can complicate the neurobehavioral performance of high-risk infants, and it is not well understood if early neurobehavior, during a time of medical challenges, can predict later outcomes.

Neurobehavioral exams performed during NICU hospitalization have been shown to be good markers of early function, with specific patterns of behavior predicting long term disability in preterm infants [28–32]. These studies demonstrate that neurobehavior, as early as 36 weeks postmenstrual age (PMA), is related to developmental outcomes. Yet to date, there is a paucity of studies that have reported serial neurobehavior assessment of preterm infants across PMA, with none starting as early as 30 weeks PMA [33,34]. In addition, medical factors such as patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and cerebral injury have been related to poorer long term outcome [30,35–37], but their impact on early neurobehavior is not well understood. It is also not well-understood how medical and environmental factors associated with early birth and hospitalization in the NICU can impact neurobehavioral performance and development [38].

The objectives of the current study were to determine 1) the relationship between infant medical factors and early neurobehavior and 2) the relationship between early neurobehavior at 30 weeks PMA and neurobehavior at term equivalent age.

2. Methods

This study was approved by the study site institutional review board, and parents signed informed consent for participation in this prospective longitudinal cohort study. The study site was a 75-bed level III-IV NICU in the Midwestern United States. Eighty-eight preterm infants born ≤30 weeks estimated gestational age (EGA) were enrolled by the 3rd day of life. Infants were excluded if there was a known or suspected congenital anomaly or if they were not expected to survive, according to the attending physician. Medical and environmental factors were collected from the medical chart during the course of NICU hospitalization. Study procedures included serial neurobehavioral assessments conducted within 14 days of birth, 30 weeks PMA, 34 weeks PMA, and at term equivalent age. However, the current investigation included assessments at 30 weeks PMA and at term. Assessments conducted within 14 days of birth were not utilized, due to the variability in EGA, resulting in them occurring at different PMAs. Assessments at 34 weeks PMA have previously been reported by this study team [30].

2.1. Medical and Environmental Factors in the NICU

The following medical and environmental factors were collected from the electronic medical record during NICU hospitalization: EGA, birth weight, Clinical Risk Index for Babies (CRIB) score, delivery type (vaginal or Caesarean), whether part of a multiple birth, sex, race (Caucasian or non-Caucasian), prenatal exposure to illicit drug use (by toxicology screen), PDA (requiring indomethacin or surgical ligation), NEC (all stages), confirmed sepsis, retinopathy of prematurity (ROP; all stages), total oxygen hours, days of continuous positive airway pressure (CPAP), days of total parenteral nutrition (TPN), exposure to postnatal steroid use, days on endotracheal ventilation, PMA at discharge, and length of stay. In addition, cerebral injury was defined by a single trained neurologist using cranial ultrasound (CUS) and magnetic resonance imaging (MRI) and was dichotomized into 'moderate to severe injury' (cerebellar hemorrhage, grade 3–4 intraventricular hemorrhage, and/or cystic periventricular leukomalacia) or 'no to mild injury' (the absence of the aforementioned injuries).

2.2. Neurobehavioral assessments

Neurobehavioral performance was evaluated at 30 weeks PMA using the Premie-Neuro and at term equivalent age (between 37 and 41 weeks) using the NICU Network Neurobehavioral Scale (NNNS) and the Hammersmith Neonatal Neurological Evaluation (HNNE).

2.3. Premie-Neuro

The Premie-Neuro is a 24-item neurologic examination appropriate for infants between 23 and 37 weeks PMA. While the Premie-Neuro is defined as a neurologic examination, 14 out of 24 items relate to assessment of reflexes and motor responses, with 10 of the 24 items assessing stress signs, excitability, arousal, and other behaviors. Premie-Neuro scores range between 24 and 120. Raw scores are used to categorize infant performance into abnormal, questionable or normal. An abbreviated form is available for infants < 28 weeks PMA or who are intubated and includes 16 items from the Premie-Neuro that do not require moving the infant away from the supine position. The abbreviated form includes 8 items on reflexes and motor responses and 8 items on behavioral observations. Raw scores for the abbreviated form range from 16 to 80 and also can be categorized into abnormal, questionable or normal. The Premie-Neuro can be learned by reading a manual and through practice. Validity has been established, and the Premie-Neuro has fair to moderate reliability [39]. It takes approximately 5 min to conduct the standard form and approximately 1–2 min to conduct the abbreviated form. The Premie-Neuro was used to assess neurobehavior at 30 weeks PMA. If the infant was assessed using the abbreviated form, scores were calibrated to the scores for the standard form by multiplying the raw score by 1.2.

2.4. The NICU Network Neurobehavioral Scale (NNNS)

The NNNS is a 115-item test that takes approximately 20 min to administer. The first 45 items are administered/elicited by the examiner, and the remaining are observations made throughout the assessment. The NNNS includes the assessment of reflexes, observations of motor patterns, elicitation and observation of visual and auditory responses, and behavioral observations related to how well the infant copes with the demands of the environment and what strategies he/she uses. Raw scores are converted to 13 summary scores: habituation, orientation, arousal, self-regulation, quality of movement, suboptimal reflexes, asymmetry, hypertonicity, hypotonicity, lethargy, excitability, tolerance of handling, and stress. The NNNS can be performed by certified evaluators who have completed a comprehensive training and certification course, and certification is achieved after the examiner demonstrates reliability. Assessments for the described study were conducted by a single, certified examiner. The NNNS has been used extensively to evaluate preterm infants and has good predictive validity [25] and excellent reliability [40].

2.5. The Hammersmith Neonatal Neurological Evaluation (HNNE)

The HNNE is a 34-item evaluation that takes approximately 10–15 min to administer. Although identified as a neurological evaluation, it includes assessment of orientation/behavior, in addition to tone, tone patterns, reflexes, movement, and abnormal signs/patterns. Scores range from 0 to 34. The HNNE Optimality Score has been used to describe outcome with the HNNE, with scores below 31 deemed 'suboptimal'. The HNNE has been used extensively for neurobehavioral assessment of preterm infants and has been found to be valid and reliable [40,41]. Evaluations were performed by a single examiner who was trained in the use of the HNNE.

It is common for longitudinal cohorts of preterm infants to assess

neurobehavior using both the NNNS and HNNE at term equivalent age. When this is done, the NNNS is administered according to standard procedures first, followed by conducting the remaining three items that are unique to the HNNE [42–44]. This procedure was undertaken for this study to combine the overlapping data and allow comparisons between the two neurobehavioral tools.

2.6. Statistical analysis

Statistical analyses was conducted using SPSS Version 22 (IBM, Chicago). Linear regression models as well as chi-square analyses were used to explore relationships between medical and environmental factors and Premie-Neuro scores at 30 weeks PMA. Among medical and environmental factors that were related ($p < 0.05$), collinearity was evaluated to determine which factors to include in a multivariate model to evaluate relationships between early neurobehavior at 30 weeks PMA and neurobehavior at term equivalent age. Medical and environmental factors that were related to neurobehavior at 30 weeks PMA, but that were not collinear with others, were chosen to be in the model to control for variables that may confound outcome. When variables were collinear, the variable with highest statistical significance and appropriate biological validity was chosen to be included in the model. Univariate and multivariate linear regression models were used to explore relationships between Premie-Neuro scores at 30 weeks PMA and HNNE scores as well as Premie-Neuro scores at 30 weeks PMA and NNNS summary scores, while controlling for medical and environmental factors related to early neurobehavior. Using a Bonferroni adjustment for each family of outcome variables (2, HNNE and NNNS), a significance level of $\alpha < 0.025$ was used for the main analyses investigating relationships between neuroebehavior at 30 weeks PMA and neurobehavior at term equivalent age. Analyses were re-run controlling for PMA at the time of testing, as PMA has previously been reported to impact neurobehavioral outcome [34].

3. Results

Eighty-eight very preterm infants were included in this study. Table I identifies baseline and acquired medical and environmental factors for the infants.

Lower Premie-Neuro scores at 30 weeks PMA were related to being Caucasian ($p = 0.03$; $\beta = -10.88$), having lower EGA at birth ($p = 0.01$; $\beta = 3.87$), presence of PDA ($p < 0.01$; $\beta = -16.50$) and cerebral injury ($p < 0.01$; $\beta = -20.46$), and respiratory factors of receiving more days of endotracheal intubation ($p < 0.01$; $\beta = -0.23$) and more oxygen therapy hours ($p < 0.01$; $\beta = -0.01$), in addition to more days of TPN ($p < 0.01$; $\beta = -0.35$). There were no other relationships between baseline and acquired medical and environmental factors related to neurobehavior at 30 weeks. The following infant factors were found to have high collinearity - race and EGA, patent ductus arteriosus and cerebral injury, total oxygen hours and total days of TPN, and total days of TPN and total days of endotracheal intubation. Medical factors chosen to go in the multivariate model had high statistical significance and biological validation. These included EGA, PDA, and number of days of endotracheal intubation. EGA was chosen due to literature identifying that the earlier the EGA, the higher the risk of poor outcome [45,46]. PDA was chosen due to its relationship with altered functional outcome [36]. Days of endotracheal intubation was included in the model, because it is a known factor related to adverse outcome [47–50]. Although the initial multivariate model controlled for EGA, PDA and days of endotracheal intubation, the analyses were re-run controlling for EGA, cerebral injury and days of endotracheal intubation as well as PMA at the time of testing.

Table II identifies the relationships between neurobehavioral performance at 30 weeks PMA and term equivalent age. Lower Premie-Neuro scores at 30 weeks PMA were related to lower HNNE scores at term equivalent age ($p < 0.01$; $\beta = 0.12$) and poorer quality of movement ($p < 0.01$; $\beta = 0.02$), more suboptimal reflexes ($p < 0.01$; $\beta = -0.06$), more stress ($p < 0.01$; ß $= -0.004$), more asymmetry ($p = 0.01$; ß $= -0.04$), and more excitability ($p < 0.01$; ß $= -0.05$) on the NNNS, after controlling for EGA, PDA, and number of days of endotracheal intubation. No other significant relationships were found. Including PMA at the time of testing in the model did not alter the key findings. Analyses were also re-run controlling for EGA, cerebral injury, and days of endotracheal intubation, which did not alter the key findings.

Table I
Baseline and acquired infant factors.

	N % or median (IQ) or mean (SD)	Relationship with Premie-Neuro score at 30 weeks PMA *P-value (ß)
EGA	26.5 (1.7)	**0.01** (3.87)
Birth weight, g	936.8 (241.9)	0.06 (0.02)
CRIB	2 (1–6)	0.32 (−0.73)
Vaginal delivery	46 (52%)	0.80 (−1.33)
Multiple birth	29 (33%)	0.52 (−3.50)
Sex, female	46 (52%)	0.62 (−2.52)
Race, Caucasian	46 (52%)	**0.03** (−10.88)
Prenatal drug exposure	6 (7%)	0.85 (2.05)
Patent ductus arteriosus	48 (55%)	< **0.01** (−16.50)
Necrotizing enterocolitis	9 (10%)	0.31 (−6.89)
Retinopathy of prematurity	12 (14%)	0.30 (−10.21)
Cerebral injury**	15 (17%)	< **0.01** (−20.46)
Confirmed sepsis	24 (27%)	0.48 (−3.93)
Continuous positive airway pressure, days	4 (1−10)	0.42 (0.21)
Oxygen therapy, hours	1512 (894–2124)	< **0.01** (−0.01)
Endotracheal intubation, days	3 (1−20)	< **0.01** (−0.23)
Total parenteral nutrition, days	18 (11−32)	< **0.01** (−0.35)
Postnatal steroids	27 (31%)	0.12(−8.89)
PMA at discharge, wk	39.7 (3.3)	0.51 (−0.52)
Length of stay, d	88 (73–106)	0.11 (−0.15)

Note: There was collinearity among these infant factors: race and EGA ($p = 0.029$); total oxygen hours and total days of TPN ($p \leq 0.001$); total days of endotracheal intubation and total days of TPN ($p \leq 0.001$); patent ductus arteriosus and cerebral injury ($p = 0.03$); EGA = estimated gestational age; CRIB = Clinical Risk Index for Babies; PMA = postmenstrual age; TPN = total parenteral nutrition. $\alpha < 0.05$.
Bolded values reached significance at $p < 0.05$.

* *P* value from investigations of relationships of medical factors to neurobehavioral scores using linear regression models and chi-square analyses.

** $n = 85$; cerebral injury defined as cerebellar hemorrhage, grade 3–4 intraventricular hemorrhage and/or cystic periventricular leukomalacia from cranial ultrasound and MRI.

4. Discussion

The key finding of this study was that early neurobehavioral performance at 30 weeks PMA predicted neurobehavioral performance at term equivalent age, making it an excellent early marker of neurodevelopmental risk to focus NICU interventions. Specifically, lower scores on the Premie-Neuro were related to lower scores on the HNNE, in addition to poorer quality of movement, more suboptimal reflexes, more stress, more asymmetry and more excitability on the NNNS. In addition, this study identified that early medical factors that infants experience in the NICU were associated with poor neurobehavioral performance.

While poorer performance on early assessment was related to poorer performance at term equivalent age, the NNNS assessment enabled a better understanding of specific areas of function that could be impacted on later assessment. Specifically, infants with poorer

Table II
Relationships between neurobehavioral performance at 30 weeks PMA and neurobehavior at term equivalent age.

		Univariate regression analysis			Multivariate regression analysis		
Predictor	Term assessment score	p-Value*	Beta	95% confidence interval of beta	p-Value**	Beta	95% confidence interval of beta
Premie-Neuro score at 30 weeks PMA	HNNE optimality score	< 0.01	0.12	[0.07, 0.17]	< 0.01	0.11	[0.06, 0.17]
	NNNS quality of movement	< 0.01	0.02	[0.01, 0.03]	< 0.01	0.02	[0.01, 0.03]
	NNNS suboptimal reflexes	< 0.01	−0.05	[−0.08, −0.03]	< 0.01	−0.05	[−0.08, −0.03]
	NNNS stress	< 0.01	−0.004	[−0.01, −0.003]	< 0.01	−0.004	[−0.01, −0.003]
	NNNS asymmetry	< 0.01	−0.04	[−0.06, −0.02]	0.01	−0.04	[−0.07, −0.02]
	NNNS excitability	< 0.01	−0.04	[−0.07, −0.01]	< 0.01	−0.05	[−0.08, −0.02]

Note: Only significant findings ($p < .0.05$) are listed in the table.
$\alpha < 0.025$ (using Bonferroni correction for each family of outcome variable).
Bolded valued reached significance at $p < 0.025$.

* *p*-Value from investigations of relationships between neurobehavioral performance at 30 weeks PMA and neurobehavior at term equivalent age using univariate linear regression models.

** *p*-Value from investigations of relationships between neurobehavioral performance at 30 weeks PMA and neurobehavior at term equivalent age using multivariate linear regression models controlling for EGA, PDA, and days of endotracheal intubation.

performance on early assessment demonstrated fewer optimal newborn reflex responses, and movements of the arms and legs were not as modulated, being less smooth and mature and with more startles and tremors. Infants with poorer early performance were also noted to have more asymmetrical responses, with reflexes on one side of the body being stronger or weaker than the other side. In addition, infants with poorer early performance were noted to demonstrate more stress/abstinence signs and have more exitability or over-responsiveness by term equivalent age. All of these factors have been related to cerebral injury and/or poorer long term outcomes [51–56] and also can impact the infant's early experiences, therefore being early warning signs of neurodevelopmental impairment.

The finding that medical factors are related to neurobehavioral performance is consistent with previously published work [38,50,57,58]. The risk of disability has been shown to increase as EGA decreases [59]. In addition, lower EGA increases the risk of medical complications that can interfere with neurobehavioral performance and also increases length of NICU hospitalization, which may alter the developmental trajectory [60,61]. Consistent with our findings of adverse performance with prolonged oxygen use and intubation, others have demonstrated that longer periods of respiratory compromise have neurological and developmental consequences [47–49]. While such respiratory therapies could be related to periods of hypoxia, which can increase the risk of developmental alterations [62], it is also possible that positive sensory and motor exposures are limited in the infant with respiratory therapy, impacting appropriate neuronal activity during this time period [63]. The prolonged use of TPN has also been linked to poorer outcome [64]. While TPN could be a proxy for medical status, it has also been linked to bloodstream infections such as sepsis which can impact development [64,65]. Previous research has identified cerebral injury as a source of neurobehavioral alterations in the neonatal period [30,35], which are consistent with our findings. Also, our findings are consistent with other reports that PDA is related to adverse outcome [36]. Importantly, the findings from this study identify that alterations in neurobehavior can be detected by 30 weeks PMA, independent of concurrent medical factors.

Better neurobehavior at term, with an average of 10 points higher on the HNNE, was observed in infants who were Caucasian. This is consistent with other reports of poorer outcomes among infants who are not Caucasian [66]. Although socioeconomics may impact outcome [67,68], this study was done while infants were still in the hospital, prior to potential influences of the home environment. However, the early differences in neurobehavior across races that was observed can potentially be explained by there being a relationship of race to EGA at birth ($p = 0.03$), with non-Caucasians being more likely to have lower EGA. Lower EGA increases the risk of neurobehavioral impairment [45,46]. Our findings of non-Caucasian infants being more likely to be born at lower EGA is consistent with other reports of higher risk of preterm birth, including extremely low birth weight, in African American children, who made up the majority of the non-Caucasian group [66]. In addition, it remains unclear how early prenatal care may have differed among families of different socioeconomic backgrounds. However, further inquiry into racial differences can aid our understanding of how to improve the health and well-being of all infants in efforts toward improved health equity.

Neurobehavioral assessment scores on the Premie-Neuro at 30 weeks PMA were related to scores at term equivalent age on the HNNE and NNNS. This is consistent with other reports that have demonstrated that early neurobehavioral assessment as early as 36 weeks was related to outcome at term [30,34], however this is the first report, that we are aware of, that has investigated if neurobehavior at 30 weeks PMA, using the Premie-Neuro, can inform later neurobehavioral outcome. Previous research has identified structural abnormalities as well as decreased brain volumes and connectivity of infants born very preterm; however, it remains unclear if these translate to consistent alterations in function [58,69–73]. As alterations in function can be identified on neurobehavioral exam at 30 weeks, this enables the potential for greater targeting of developmental therapies that can optimize the environment, sensory motor experiences and potentially improve outcome to identified high risk infants.

Neurobehavioral exams, performed during NICU hospitalization prior to discharge, have been shown to be good markers of early function, with different patterns of behavior predicting long term disability in preterm infants [28–32]. Neonatal therapists use a variety of different therapy interventions [15], and targeted therapy interventions can be defined from the neurobehavioral assessment while the infant is in the NICU in order to individualize a therapeutic approach. For example, identification of stress signs and excitability may inform the need for positioning, graded handling/activity tolerance, calming, and environmental modifications; identification of asymmetry of movement can inform the focus of interventions on one side of the body; suboptimal reflexes and poor quality of movement can inform the need for functional mobility, weight bearing, positioning, and stretching. With assessment at 30 weeks PMA predicting performance at term equivalent age, assessing early neurobehavior can provide meaningful information to the health care team as the care plan is established during hospitalization and plans are made for discharge. Furthermore, neurobehavioral assessment can aid in detecting alterations in neurobehavior at bedside, as a low risk, low cost strategy, in lieu of or in addition to use of MRI. Unlike MRI, the neurobehavioral assessment enables observations that inform early therapy targets and can also provide meaningful information to share with families about areas of strength and challenge.

There were limitations to the current study, which included a small sample size that was not powered for the current investigation. Methodologically, there was variability in when the infants were assessed at term equivalent age, which was between 37 and 41 weeks PMA. The HNNE and NNNS assessment were conducted at the same time, which could affect the validity of our findings. Also, this investigation used a medically fragile sample with complex medical courses that could confound outcome. There are multiple factors that can influence health, and the variables collected may not fully represent other factors compounded in each. For example, race can be confounded by socioeconomic status and other environmental determinants of health. Although we corrected the main analysis using Bonferroni adjustment for each family of outcome variable, the use of multiple analyses can increase the risk of a Type I error. Also, the study was conducted in an urban setting with a population with many social challenges, so the findings may not be generalized to other populations.

Despite these limitations, this is the first study, that we are aware of, that has conducted and reported relationships between neurobehavioral assessment of very preterm infants at 30 weeks PMA to term equivalent age. The findings of the current study affirm that neurobehavioral assessment provides a low risk, low cost alternative for assessing outcome and can be conducted at the NICU bedside to inform the need for early therapeutic intervention. Early assessments are likely impacted by medical factors, but are also related to outcome at term equivalent age. Future research is needed on relationships of early neurobehavioral assessment after preterm birth on long-term neurodevelopmental outcomes.

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CRediT authorship contribution statement

Roberta Pineda: Conceptualization, Methodology, Investigation, Supervision, Formal analysis, Writing - original draft, Writing - review & editing. **Lara Liszka**: Formal analysis, Writing - original draft, Writing - review & editing. **Terrie Inder**: Conceptualization, Methodology, Funding acquisition, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare no conflicts of interest.

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