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ORIGINAL ARTICLE

Regulation of Stress Physiology Across Social Contexts in Preterm-Born Preschoolers

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ABSTRACT

Premature birth increases risk for socio-emotional difficulties and altered autonomic regulation, yet because physiological regulation supports development, dysregulation may have lasting consequences. We evaluated social functioning and physiological regulation in 70 preterm children aged 5.5 years compared to 32 matched full-term controls (total sample: 59 boys, 43 girls; 98% White). Heart rate and heart rate variability (HRV) were recorded during rest and structured social interactions with the mother and a stranger, including eye contact, conversations, and triadic play. Preterm children demonstrated significantly greater social difficulties and internalizing problems than full-term peers. Across conditions, the preterm children exhibited consistently elevated heart rate, whereas HRV patterns were comparable with the full-term group. Across both groups, RMSSD-HRV varied by interaction partner (stable with mother, fluctuating with stranger), while HF-HRV reflected general condition effects independent of partner familiarity. In both groups, conversation tasks elicited the strongest autonomic activation, with the lowest parasympathetic indices during negative interactions. In conclusion, preterm children show persistent cardiac hyperarousal and social-behavioral difficulties yet maintain context-dependent autonomic regulation similar to full-term peers. The distinct sensitivity of HRV indices suggests preserved regulatory mechanisms, indicating that prematurity's physiological signature may reflect heightened baseline arousal rather than impaired regulation.

1 | Introduction

Each year, an estimated 13.4 million infants are born prematurely (< 37 weeks gestation) (Di Renzo et al. 2018; Khandre et al. 2022; Vogel et al. 2018; World Health Organization 2023). Although advances in neonatal care have improved survival, preterm children frequently exhibit the "preterm behavioral phenotype", marked by attentional difficulties, socio-emotional challenges, and elevated risk of neurodevelopmental disorders, with lower gestational age conferring greater vulnerability (Pickler et al. 2010; Adams-Chapman 2006; Arpino et al. 2010; Rogers and Hintz 2016; Woodward et al. 2012; Arpi and Ferrari 2013; Allotey et al. 2018; Fitzallen et al. 2023). The autonomic nervous system (ANS) is a core mechanism supporting self-regulation, social engagement and environmental adaptation (Thayer et al. 2012). Characterizing autonomic functioning in preterm children is a necessary step toward understanding the physiological context in which their socio-emotional difficulties develop.

The ANS regulates stress responses through its sympathetic (fight-or-flight) and parasympathetic (rest-and-recovery) branches (Berntson et al. 2016). Heart rate (HR) is a general index of physiological arousal influenced by both autonomic and non-autonomic factors, whereas heart rate variability (HRV), the variation in intervals between consecutive heartbeats, arises

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from the modulation of the heart by both autonomic branches, with its vagally mediated components (such as the root mean square of successive differences (RMSSD) and high-frequency (HF) power) indexing parasympathetic cardiac regulation (Shaffer and Ginsberg 2017; Shaffer et al. 2014). Higher HRV is associated with better stress resilience, self-regulation, and cognitive flexibility, whereas lower HRV indicates maladaptive cardiac stress responses and has been linked to psychological vulnerability (Laborde et al. 2017; Quintana et al. 2016). The third trimester of gestation is a critical window for maturation of endocrine and autonomic stress-regulatory systems (Feldman 2009). Premature birth interrupts this developmental trajectory (Lammertink et al. 2021; Fenoglio et al. 2017; Mulkey and du Plessis 2019), with lasting implications for stress regulation across the lifespan (Lammertink et al. 2021). During infancy, preterm infants frequently show lower parasympathetic activity than full-term peers in resting-state assessments (De Rogalski Landrot et al. 2007). Although findings from later childhood suggest that these differences may become less pronounced over development, evidence from socially and emotionally challenging contexts indicates that regulatory differences can remain detectable beyond the neonatal period. As infants mature and become increasingly engaged in social interactions, group differences may become particularly apparent when regulatory systems are challenged. For example, in the still-face paradigm at 6 and 9 months, during which maternal responsiveness is briefly withdrawn, preterm infants made fewer attempts to re-engage their mothers and displayed less optimal social-communicative behavior than full-term peers (De Schuymer et al. 2011). Consistent with these behavioral findings, physiological studies indicate that infants born at lower gestational ages show heightened arousal and a diminished capacity to regulate heart rate during recovery from stress, whereas more mature infants exhibit more adaptive recovery patterns (Holsti et al. 2006). Moreover, short-term autonomic indices in preterm infants have been associated with concurrent self-regulatory capacities and stress-related neurobehavioral functioning (Donnellan et al. 2025). Together, these findings suggest that the developmental consequences of preterm birth may be most apparent when autonomic regulatory systems are actively engaged, rather than under resting conditions alone.

Such differences may partly originate from the atypical early environment associated with neonatal intensive care (Smith et al. 2011). Environmental stressors in the neonatal intensive care unit (NICU), including repeated painful procedures, caregiver separation, and sensory overstimulation, have been proposed to interfere with autonomic nervous system development (Lammertink et al. 2021; Lavanga et al. 2021; Nist et al. 2020; Wachman and Lahav 2011). By disrupting sleep–wake organization and physiological stability, these experiences may challenge the developing regulatory system and contribute to later difficulties in physiological, emotional, attentional, and behavioral regulation (Feldman 2009; Lammertink et al. 2021). Importantly, developmental care interventions such as kangaroo care (skin-to-skin contact) may buffer these effects by reducing stress exposure and supporting neurological and autonomic maturation (Feldman et al. 2014).

Whether autonomic alterations observed following preterm birth persist beyond the neonatal period remains unclear (Lavanga et al. 2021; Longin et al. 2006; Yiallourou et al. 2017; Gistelinck et al. 2026). Evidence from resting-state assessments suggests that autonomic group differences may normalize relatively early in development. Lower respiratory sinus arrhythmia in preterm infants diminishes by approximately 2 years of age when maturational delays are taken into account (Bradshaw et al. 2025). Parasympathetic indices derived from frequency-domain measures similarly appear to normalize by this age, with differences that are pronounced at term-equivalent age no longer detectable at 2–3 or 6–7 years (De Rogalski Landrot et al. 2007). By school age, children born moderate-to-late preterm likewise show HRV profiles comparable to those of term-born peers (Dantas et al. 2024), and autonomic functioning appears amenable to early support, with a NICU-based family nurture intervention associated with improved regulation at 4–5 years of age (Welch et al. 2020). However, findings remain mixed, with several studies reporting persistent autonomic differences relative to term-born controls (Yiallourou et al. 2017; Rakow et al. 2013; Urfer-Maurer et al. 2018). Moreover, alterations in HRV have been reported to re-emerge during adolescence (Haraldsdottir et al. 2018; Mathewson et al. 2015) and to extend into adulthood, particularly among males (Björkman et al. 2023; Jussinniemi et al. 2025). This developmental picture can be further contextualized within the normative maturation of parasympathetic control. In typically developing children, vagally mediated cardiac control increases rapidly across infancy and toddlerhood, reflected in rising resting respiratory sinus arrhythmia and declining heart rate (Wagner et al. 2021; Sacrey et al. 2021). For the parasympathetic indices most relevant to the present study, this early rise largely levels off during early childhood: pooled normative data indicate that RMSSD and high-frequency HRV stabilize across this period, with RMSSD reaching a relative plateau from approximately 4 years of age (Joyce et al. 2026), whereas the broader reorganization of sympathovagal balance continues more gradually and becomes most evident toward puberty and adolescence (Šišáková et al. 2024). Group differences observed around Age 5 are therefore less likely to primarily reflect ongoing rapid maturation, making this developmental stage particularly informative for evaluating whether early parasympathetic disruption associated with preterm birth has resolved.

The interpretation of physiological findings in preterm populations is further complicated by substantial methodological heterogeneity across studies, including differences in recording techniques (e.g., polysomnography (Yiallourou et al. 2017; Cohen et al. 2017; Fyfe et al. 2014) versus ambulatory (De Rogalski Landrot et al. 2007; Rakow et al. 2013; Aziz et al. 2013; Biala et al. 2012; Buchhorn et al. 2016; Cripps et al. 2009; Korkalainen et al. 2021)) and variation in assessment protocols (Björkman et al. 2023; Morin et al. 2014; Chifamba et al. 2015; Karvonen et al. 2019), which limits cross-study comparability. Moreover, much of the existing literature has relied on resting or sleep-based assessments, leaving the social contexts through which children regulate physiological and behavioral responses largely unexamined despite their developmental relevance.

Age 5 is also distinctive in its regulatory demands. Children of this age remain strongly dependent on parental support while, at the same time, entering the structured social environment of kindergarten, where they must increasingly manage their own behavior and emotions without direct parental

support (Armstrong-Carter et al. 2021). Within hierarchical models of self-regulation, physiological regulation indexed by HRV forms the foundational level on which emerging emotional and behavioral regulation builds (Blair and Ku 2022). Consistent with this view, high-frequency HRV at this age is associated with self-regulatory functioning and varies as a function of emotional demands (Clark et al. 2024), yet it has rarely been examined during naturalistic social interactions. As children's social worlds expand, the familiarity of the interaction partner becomes an increasingly relevant contextual factor. Interactions with a familiar caregiver and an unfamiliar adult are likely to place different demands on the regulatory system. A familiar caregiver allows the child to draw on the established relationship and on co-regulatory support, whereas interactions with an unfamiliar adult require greater reliance on the child's own regulatory capacities. Examining autonomic functioning across these contexts therefore provides insight into the flexibility with which children adapt physiological regulation to differing social demands. This capacity is especially relevant during the preschool years, when children are increasingly expected to engage with non-parental adults while maintaining effective emotional and behavioral control.

To address these limitations, the present study examines autonomic functioning during standardized real-life interaction paradigms, administered identically across preterm and full-term children. Social context is treated as a structured experimental factor by systematically varying interaction partner and interaction condition, enabling autonomic regulation to be evaluated across clearly defined social contexts. Given the duration of the interaction segments, parasympathetic regulation is indexed using both RMSSD and high-frequency HRV, two complementary measures of cardiac vagal activity derived from the time and frequency domains, respectively. The combined use of these indices provides a more comprehensive assessment of parasympathetic regulation than reliance on a single HRV metric alone. Our two primary objectives are: (1) to clarify inconsistent findings on ANS regulation beyond infancy by comparing HR and HRV in preterm and full-term 5-year-olds, and (2) to implement standardized interaction paradigms to investigate physiological adaptation in social contexts. To our knowledge, this is the first study to assess parasympathetic functioning in preterm versus full-term children during rest and structured social interactions with their mother or a stranger. We hypothesized that (a) social interactions would elicit greater physiological arousal (higher HR) and reduced parasympathetic regulation (lower RMSSD-HRV and HF-HRV) compared to rest, (b) arousal would be stronger during interactions with a stranger than with the mother, (c) non-contingent (e.g., replay) and negative affect conditions would elicit greater arousal than contingent and positive interactions, and (d) preterm children would exhibit heightened arousal and reduced regulation across contexts compared to full-term peers. Understanding ANS regulation at this critical developmental stage may inform interventions that support self-regulatory development in preterm populations.

2 | Methods

This research is part of the Resilience project, a longitudinal cohort study monitoring preterm infants from initial NICU admission at University Hospital Leuven, Belgium.

2.1 | Participants

The study sample comprised 102 children (mean age 5.5 years), all native Dutch speakers with normative or corrected hearing and vision, and IQ scores above 80. The sample consisted of 59 boys and 43 girls, all of whom were attending the third year of kindergarten at the time of testing. With regard to race and ethnicity, the majority of participants were White (98%), with one participant of African and one of North African descent. Children with major cerebral complications (Grade III-IV intraventricular hemorrhage, periventricular leukomalacia) or diagnosed neurological conditions (e.g., cerebral palsy, epilepsy) were excluded. The preterm cohort consisted of 70 preterm-born children (Bollen et al. 2025; Van den Broeck et al. 2026), defined by gestational age (GA) < 37 weeks and birth weight (BW) < 2500 g. This group was stratified as moderate-to-late preterm ($n = 37$, GA 32–36 weeks), very preterm ($n = 21$, GA 28–31 weeks), and extremely preterm ($n = 12$, GA < 28 weeks). The comparison group comprised 32 full-term participants, recruited through local schools, and matched for age and sex (Table 1). Full-term inclusion criteria were GA 37–42 weeks, BW > 2500 g, and absence of autism spectrum disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), or a first-degree family history of these conditions. Maternal and family demographic information are provided in Table 2.

TABLE 1 | Participant characteristics.

	Preterm ($N = 70$) Mean ± SD	Full-term ($N = 32$) Mean ± SD		*p*
Sex (M:F)	43:27	16:16	$X^2(3) = 1.52$	0.68
Age (years)	5.55 ± 0.09	5.62 ± 0.16	$w = 1321$	0.05
Gestational age (weeks)	31.31 ± 2.74	39.35 ± 1.31	$w = 2112$	< 0.0001
Birth weight (g)	1615.44 ± 472.44	3646.38 ± 512.18	$w = 2048$	< 0.0001
# skin breakings	39 ± 19	—	—	—
# hours kangaroo care	116 ± 60	—	—	—

Note: Chi-Square tests were used to compare ratios, and the Wilcoxon Rank Sum test was used to compare group means.
Abbreviations: # hours kangaroo care, total number of kangaroo care hours divided by the number of hospitalization days; # skin breakings, total amount during the first 5 days; F, female; M, male.

The study was approved by the [Ethics committee and reference number removed], and written informed consent was obtained from all parents, adhering to the Declaration of Helsinki.

2.2 | Questionnaires

The Social Responsiveness Scale (SRS-2) is a 65-item parent-report measure assessing autism-related social impairments (Channell 2020). The Child Behavior Checklist (CBCL 1.5-5) is a parent-report questionnaire quantifying behavioral problems and competencies in young children, yielding scores on internalizing problems (emotionally reactive behavior, anxiety/depression, somatic complaints, withdrawal) and externalizing problems (attention problems, aggressive behavior) (Hernández and Báez 2013).

TABLE 2 | Maternal and family characteristics.

	Family preterm ($N=70$)	Family full-term ($N=32$)
Age	37.7	37.54
Monthly netto income	4943 EUR	5645 EUR
Maternal education level	**Mothers preterm**	**Mothers full-term**
High school	18.3%	6.5%
Bachelor's degree	33.8%	35.5%
Master's degree	28.2%	51.6%
PhD	8.4%	6.4%
Other	9.3%	0%

Note: Family demographic characteristics and maternal education level, presented as percentages or means by group.
Abbreviations: EUR, euros; FT, full-term; PT, preterm.

2.3 | Experimental Procedure

The experimental set-up (Figure 1) employed a two-way video-call configuration, adapted from Hessels et al. (2018). Child and mother/stranger were seated in the same room, each in front of a wooden box with a half-silvered see-through mirror, allowing them to see each other and interact verbally. Web cameras behind the mirrors were placed at eye level, thereby allowing natural interaction and eye contact (Hessels et al. 2018). The dyadic setup enabled simultaneous ECG, EEG, galvanic skin response, audio/video, and eye-tracking measurements. The present report focuses solely on the ECG measurements of the child. Live, bidirectional video-mediated interaction has been shown to preserve key features of social engagement and to elicit autonomic responses to direct gaze that are comparable to those observed in live face-to-face interaction (Hietanen et al. 2020; Diana et al. 2023).

2.4 | Conditions

A series of social interactions were conducted between child–mother and child-stranger (i.e., a female experimenter). Prior to the session, the experimenter met with the mother alone and provided detailed instructions regarding the interaction procedures, while ensuring that the child remained unaware of the experimental manipulations. Conversation topics were agreed upon in advance. For the negative conversation condition, mothers were asked to discuss a recent disagreement or source of conflict involving the child (e.g., disputes with siblings, bedtime resistance, or refusal to get ready for school in the morning...). For the positive conversation condition, mothers were asked to talk about a shared positive experience with the child (e.g., a birthday party, baking together...). The experimenter remained present but out of view during all interactions and documented the content of each conversation using written notes and audio recordings. Conversations that substantially deviated from the agreed topic were excluded from

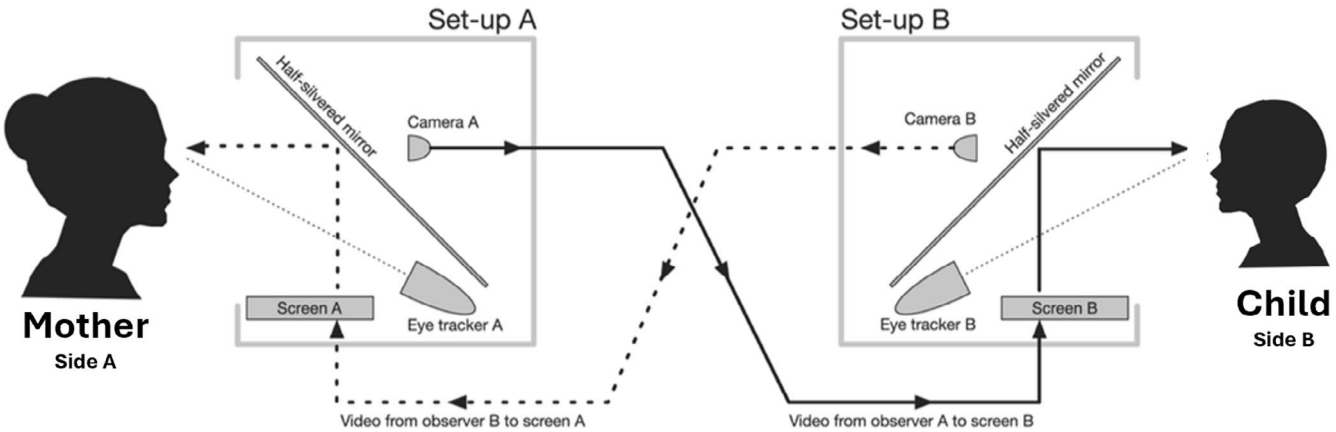


FIGURE 1 | Schematic representation of the dual-camera experimental configuration. The mother is positioned at side A and filmed by camera A, which is mounted behind a one-way mirror. The solid arrow indicates the video transmission pathway from the mother to the child, with maternal recordings displayed on monitor B for the child's viewing. The child is situated at side B and captured by camera B, likewise positioned behind a one-way mirror. Child recordings are transmitted to the mother via monitor A, as depicted by the dotted arrow. Both participants remain within the same experimental room throughout the session. Height-adjustable platforms enable direct eye-level contact between mother and child, facilitating naturalistic gaze interaction. Adapted from Hessels et al. (2018).

analysis. Child–mother interactions comprised six conditions in fixed order: (a) 2 min eyes-closed rest, (b) 2 min eyes-open (silent visual contact), (c) 2 min replay (child viewed recording of mother from previous condition while believing it was live), (d) 3 min positive conversation about shared experience, (e) 3 min negative conversation about recent disagreements, (f) 3 min triadic conversation with dragon puppet. The child-stranger protocol comprised three conditions in fixed order: (a) 2 min eyes-closed rest, (b) 2 min eyes-open, (c) 3 min conversation about school and activities. Order of mother and stranger interactions was counterbalanced.

2.5 | ECG Recording

Electrocardiographic (ECG) data were acquired using the ActiveTwo BioSemi system (Biosemi, The Netherlands) at 512 Hz sampling rate. For mother–child dyads, the Common Mode Sense (CMS) and Driven Right Leg (DRL) electrodes from the EEG cap served as references. Two external ECG electrodes were positioned on the thorax: the negative electrode medial to the right coracoid process, inferior to the clavicle, and the positive electrode on the lower left ribcage, approximating a simplified lead II configuration. Conductive paste and adhesive rings were used to ensure stable, high-quality signals. For strangers without EEG caps, four external electrodes were applied following similar placement principles.

2.6 | Child HR and HRV Analysis

HRV was assessed using both time- and frequency-domain metrics. In time-domain analysis, the root mean square of successive differences (RMSSD) was calculated, a well-established index of vagally-mediated HR fluctuations that strongly correlates with high-frequency (HF) power (Berntson et al. 2016; Laborde et al. 2017). The primary outcomes of the study were heart rate (bpm), RMSSD-HRV (ms), reflecting beat-to-beat variability and the natural logarithm of absolute HF-HRV power (0.24–1.04 Hz). Data were pre-processed using MATLAB (R2021b) and Kubios HRV Scientific (v4.1, University of Eastern Finland). R-peaks were detected using the Pan-Tompkins algorithm, with artifact correction based on Tarvainen et al. (2014), which identifies and corrects ectopic, missed, extra, or misaligned beats, and automatically detects noisy segments at moderate sensitivity thresholds. All recordings were additionally subjected to visual inspection, and irregularities were manually annotated.

2.7 | Statistical Analyses

Outliers were identified using Cook's Distance and excluded prior to group-level analyses. Outlier percentages varied by parameter and model: HR (7.67%–8.08%), RMSSD-HRV (6.47%–7.67%) and HF-HRV (8.58%–9.24%). Linear mixed models (LMMs) were run with the 'Afex' package (v1.2-1) (Henrik et al. 2012) in R (v4.2.0) (Team RC 2022).

Two LMMs were implemented. The first model (mother-only) included *Condition* (eyes closed, eyes open, replay, positive/negative/triadic conversation) as a within-subject factor and *Group* (preterm vs. full-term) as a between-subject factor. The second model (mother-stranger) incorporated *interaction partner* as an additional within-subject factor (mother vs. stranger), comparing three conditions (eyes closed, eyes open, and positive/neutral interaction). Both models included random intercepts per participant. Post hoc pairwise comparisons used Bonferroni corrections and Kenward-Roger approximation for degrees of freedom ('emmeans' package, v1.8.5) (Lenth 2023).

Spearman correlations were computed between physiological parameters (HR, RMSSD-HRV, HF-HRV) and developmental variables. In the preterm group, correlations included prematurity indices (GA, BW, skin breaking indices, kangaroo care) and behavioral measures (SRS-2, CBCL). In the full-term group, only associations with behavioral measures (SRS-2, CBCL) were tested. Significance for these multiple correlations was set at $p < 0.01$.

Group differences in participant characteristics were analyzed with Welch's *t*-test or Wilcoxon rank-sum test, depending on normality. Sex ratio was compared using chi-square tests. Significance for group comparisons was set at $p < 0.05$. Preterm children were analyzed as a single group rather than stratified by gestational age subgroup. Descriptive statistics for the main outcome variables are provided separately for moderate-to-late preterm, very preterm, and extremely preterm children in Table S1.

3 | Results

3.1 | Questionnaire Data

Preterm children scored higher on SRS-2 (M = 52.56, SD = 9.38) than full-term children (M = 46.91, SD = 6.46; w = 615, $p = 0.001$) and showed elevated CBCL internalizing problems (M = 49.92, SD = 11.60 vs. M = 43.97, SD = 9.31; w = 705.5, $p = 0.007$). No group differences emerged for externalizing problems (w = 939.5, $p = 0.38$).

3.2 | Physiological Regulation in Preterm and Full-Term Children While Interacting With Mother

3.2.1 | Heart Rate

Analysis of HR measurements revealed significant main effects of group ($F(1,388) = 5.77$, $p = 0.017$) and condition ($F(5,320) = 3.27$, $p = 0.007$), with no significant group-by-condition interaction ($F(5,320) = 1.56$, $p = 0.17$). The preterm group consistently exhibited higher HR than the full-term group, with a mean difference of 1.87 bpm (95% CI: 0.34, 3.40) (Figure 2A). These findings indicate that preterm children exhibit consistently elevated cardiovascular arousal across all conditions.

Post hoc comparisons showed that the negative conversation elicited significantly higher HR compared to both the eyes open

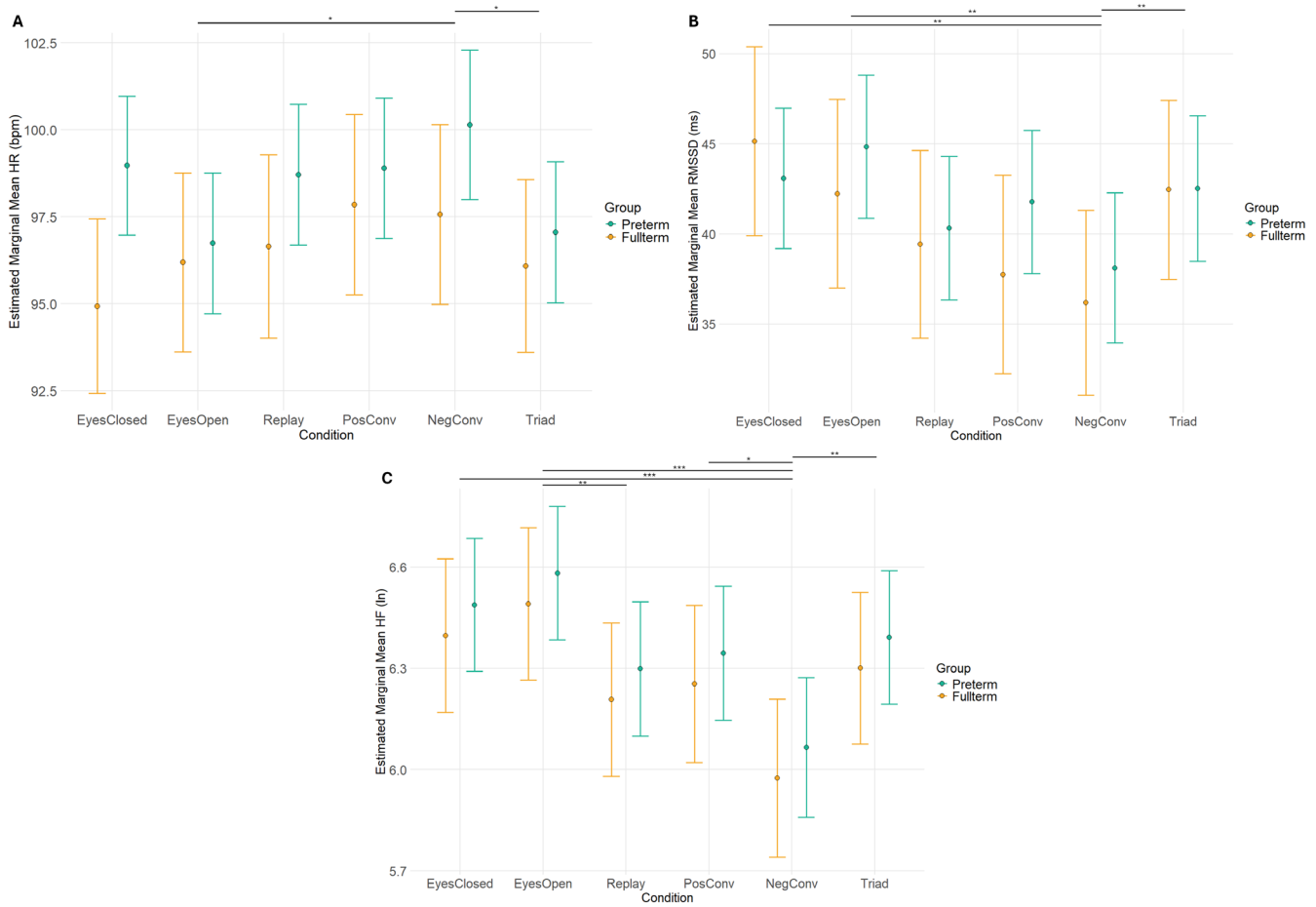


FIGURE 2 | Physiological responses of preterm and full-term children across interaction conditions with their mother. (A) Mean heart rate (HR, bpm), (B) root mean square of successive differences (RMSSD, ms), and (C) high-frequency heart rate variability power (HF, ln ms^2). Points represent estimated marginal means with error bars indicating 95% confidence intervals. PosConv, positive conversation; NegConv, negative conversation; Triad, triadic conversation. Asterisks denote significant differences between conditions (*$p<0.05$, **$p<0.01$, ***$p<0.001$).

(95% CI: 0.55, 4.23, $t(323)=3.02$, $p=0.032$) and the triadic condition (95% CI: 0.44, 4.12, $t(321)=2.98$, $p=0.037$).

3.2.2 | RMSSD-HRV

Analysis of RMSSD-HRV revealed a significant main effect of condition ($F(5,318)=5.47$, $p<0.001$), with no significant main effect of group ($F(1,392)=0.61$, $p=0.44$) or group-by-condition interaction ($F(5,318)=0.87$, $p=0.502$). Post hoc comparisons showed that RMSSD values were significantly lower during the negative conversation than during eyes closed ($t(323)=4.30$, $p=0.003$), eyes open ($t(323)=3.96$, $p=0.001$), and triadic condition ($t(322)=-3.41$, $p=0.009$) (Figure 2B).

3.2.3 | Hf-HRV

Analysis of HF-HRV revealed a significant main effect of condition ($F(5,316)=7.93$, $p<0.001$), while no significant effect of group ($F(1,396)=1.13$, $p=0.29$) was observed (Figure 2C). Post hoc analyses demonstrated that HF-HRV during the negative conversation condition was significantly lower compared to eyes closed ($t(323)=4.82$, $p<0.001$), eyes open ($t(325)=5.82$, $p<0.0001$), positive conversation ($t(323)=3.14$, $p=0.022$), and triadic condition ($t(321)=-3.78$, $p=0.002$). HF-HRV was also lower during replay versus eyes open ($t(323)=3.42$, $p=0.009$), suggesting real-time interaction supports greater parasympathetic activation.

In sum, these findings suggest that while both groups demonstrate a similar capacity for autonomic regulation during maternal interactions, the nature of the social interaction significantly affects parasympathetic activity, which was lowest during negative emotional exchanges.

3.3 | Physiological Regulation in Preterm and Full-Term Children During Interactions With Mother Versus Stranger

3.3.1 | Heart Rate

HR analysis revealed a significant main effect of condition ($F(2,309)=20.63$, $p<0.001$), with no other significant main effects ($p>0.05$). Significant interactions were observed between condition and interaction partner ($F(2,309)=5.57$, $p=0.004$) and between group and interaction partner ($F(1,313)=9.68$, $p=0.002$), whereas the interaction between group and condition ($F(2,309)=2.88$, $p=0.058$), and the three-way

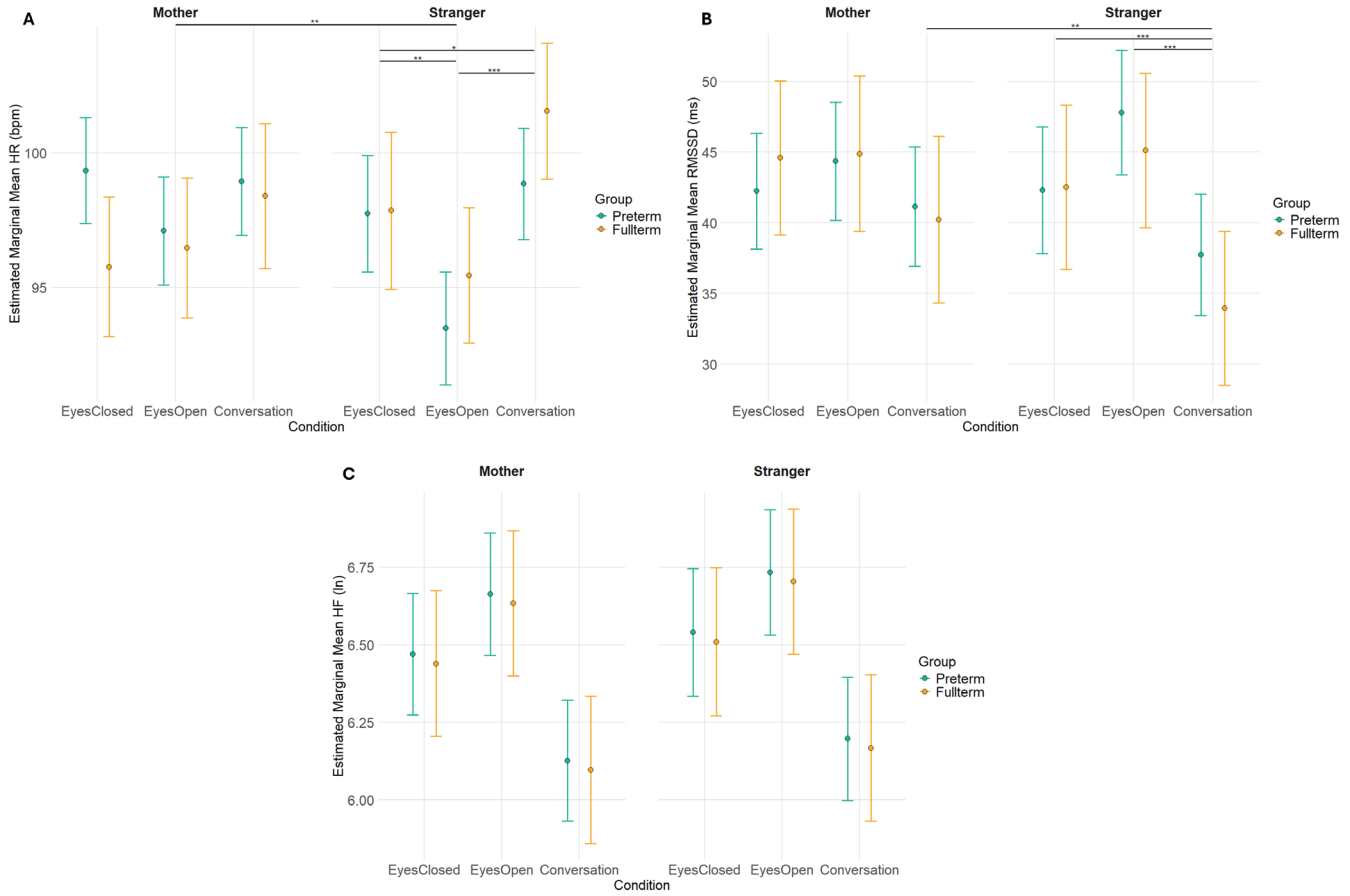


FIGURE 3 | Physiological responses of preterm and full-term children during interactions with mother versus stranger across different conditions. (A) Mean heart rate (HR, bpm), (B) root mean square of successive differences (RMSSD, ms), and (C) high-frequency heart rate variability power (HF, ln ms^2). Points represent estimated marginal means with error bars indicating 95% confidence intervals. Asterisks denote significant differences between conditions (*$p<0.05$, **$p<0.01$, ***$p<0.001$).

interaction of group×condition×partner were non-significant ($F(2,309)=0.10$, $p=0.91$) (Figure 3A).

Follow-up analyses of the condition-by-partner interaction indicated that HR patterns during interactions with the mother remained relatively stable across conditions, whereas interactions with the stranger showed greater variability, with significantly higher HR during conversation compared to both eyes closed (95% CI: 0.59, 4.23, $t(315)=2.59$, $p=0.027$) and eyes open (95% CI: 4.12, 7.36, $t(311)=6.94$, $p<0.001$). Furthermore, during the eyes open condition, HR was significantly higher when interacting with the mother than with the stranger (95% CI: 0.68, 3.96, $t(312)=2.77$, $p=0.006$). Breaking down the group-by-partner interaction revealed that full-term children showed no significant difference in HR between mother and stranger interactions ($t(314)=-1.69$, $p=0.092$), whereas preterm children exhibited significantly higher HR when interacting with the mother compared to the stranger (95% CI: 0.63, 2.91, $t(317)=3.04$, $p=0.003$). Preterm children showed heightened cardiovascular sensitivity specifically during maternal interactions. Separately, both groups showed greater HR variability with strangers, where conversation elicited significantly higher HR than passive condition, an effect less pronounced with mothers.

3.3.2 | RMSSD-HRV

Analysis of RMSSD-HRV revealed a significant main effect of condition ($F(2,315)=16.72$, $p<0.001$), but no significant effects of group ($F(1,392)=0.17$, $p=0.68$) or interaction partner ($F(1,318)=1.59$, $p=0.21$). A significant condition-by-partner interaction ($F(2,315)=3.52$, $p=0.031$) was observed, whereas no interactions involving group were significant (all $p>0.05$). The condition-by-partner interaction indicates that the effect of condition varied depending on interacting with mother versus stranger (Figure 3B). Specifically, interactions with mothers were characterized by relatively stable RMSSD-HRV values across conditions, with no significant differences between eyes closed, eyes open, and conversation (all $p>0.05$). In contrast, interactions with strangers showed clear condition effects: RMSSD-HRV was significantly lower during conversation compared to both eyes closed ($t(320)=-3.49$, $p=0.001$) and eyes open ($t(317)=-5.99$, $p<0.001$). Furthermore, during the conversation condition, RMSSD-HRV was significantly lower when interacting with strangers than with mothers ($t(320)=2.65$, $p=0.009$). These findings reveal partner-specific patterns: parasympathetic activity remained stable across conditions during maternal interactions, whereas interactions with the stranger showed condition-dependent variation, with the lowest values observed during conversation. This suggests

maternal interactions provide a regulatory buffer, whereas unfamiliar contexts demand flexible autonomic adjustment.

3.3.3 | Hf-HRV

Analysis of high-frequency HR fluctuations revealed a significant main effect of condition type ($F(2,306) = 30.83$, $p < 0.001$), but no significant main effect of group ($F(1,385) = 0.09$, $p = 0.76$) or interaction partner ($F(1,317) = 1.38$, $p = 0.24$) (Figure 3C). No significant interactions were found (all $p > 0.05$). Post hoc analyses revealed the following HF-HRV differences between conditions: conversation showed significantly lower values compared to both eyes closed ($t(312) = -4.88$, $p < 0.001$) and eyes open ($t(312) = -7.75$, $p < 0.001$), with eyes closed also showing significantly lower values than eyes open ($t(311) = -2.76$, $p = 0.017$). These findings indicate that social interaction, particularly active conversation, elicits the greatest parasympathetic withdrawal regardless of interaction partner or group status. The pattern suggests a hierarchy of autonomic regulation, with eyes open showing the highest HF power, followed by eyes closed, and conversation showing the lowest parasympathetic activity.

3.4 | Correlations

Exploratory correlational analyses between physiological parameters on the one hand, and neonatal and socio-affective variables on the other revealed no significant associations (Tables S2 and S3; all $p > 0.01$).

4 | Discussion

We examined autonomic nervous system functioning in 5-year-old preterm and full-term children during rest (eyes closed) and structured social interactions with mothers and strangers, using heart rate and heart rate variability indices (RMSSD/HF). Preterm children consistently exhibited elevated HR compared to full-term peers during maternal interaction paradigms, whereas no significant between-group differences were observed in parasympathetic regulation, as indexed by RMSSD-HRV and HF-HRV.

Research has documented altered autonomic cardiovascular regulation in premature infants, characterized by elevated mean HR, reduced HRV, and differences in blood pressure. This physiological adaptation likely serves a compensatory role, meeting heightened metabolic demands by elevating the heart pumping frequency. Makarov et al. (2010) reported that term infants exhibit marked HR decreases after birth, whereas preterm neonates (28–36 weeks GA) maintain elevated HR throughout the first postnatal week. Notably, this elevation persists into childhood, remaining evident at Age 9 (Johansson et al. 2007). Our finding hereby corroborates these observations by showing consistently increased HR in 5-year-old preterms, both during rest and social interactions.

Previous research also documented reduced HRV in preterm infants (Lammertink et al. 2021; Fyfe et al. 2015; Field and Diego 2008), yet the present study found no significant group differences at Age 5. These findings are consistent with literature suggesting autonomic regulation in preterm children may normalize by approximately Age 2 (De Rogalski Landrot et al. 2007; Dantas et al. 2024). However, the developmental trajectory appears complex, with evidence indicating potential deterioration during later stages. Studies have reported reduced HRV re-emerging in adolescence and early adulthood (Haraldsdottir et al. 2018; Mathewson et al. 2015), highlighting the need for longitudinal monitoring of autonomic functioning throughout development.

Further analysis revealed that negative conversational paradigms elicited significantly elevated HR and attenuated HRV compared to eyes-open and triadic conditions, reflecting increased cardiovascular arousal and reduced parasympathetic activity. Importantly, these effects were consistent across preterm and full-term children, indicating similar autonomic reactivity despite basic cardiac differences. Next, we use the term regulatory flexibility to refer to the extent to which parasympathetic activity is modulated across interaction conditions, that is, context-dependent modulation of parasympathetic activity. In the present models, the presence of such modulation is indexed by the main effect of condition, whereas group differences in the degree of modulation would be reflected in the group-by-condition interaction. Both groups showed significant condition-related modulation, and the group-by-condition interactions were non-significant, indicating comparable regulatory flexibility. This autonomic flexibility aligns with neurovisceral integration theory, which proposes that parasympathetic withdrawal represents an adaptive response to emotionally challenging stimuli, facilitating vigilance and readiness for threat or social engagement (Thayer and Lane 2009). The preservation of these regulatory dynamics in preterm children indicates that core autonomic mechanisms supporting emotional regulation and social engagement remain intact despite persistently elevated basic cardiac activity. These findings contribute to a growing body of evidence indicating that, while preterm birth alters basic cardiovascular function, parasympathetic regulatory flexibility appears preserved. This distinction between basic cardiac differences and preserved reactivity highlights the need for longitudinal autonomic-developmental relationships.

Another key finding is that preterm children demonstrated significantly higher heart rate during maternal versus stranger interactions. Two findings concerning the role of the interaction partner require separate interpretation. First, in both groups, heart rate varied less across conditions during interactions with the mother than during interactions with the stranger. This may indicate that the presence of a familiar caregiver buffers context-dependent fluctuations in arousal. However, attachment was not directly assessed, and we therefore present this as a possible interpretation rather than an established mechanism. Second, and independently of this pattern, preterm children showed higher heart rate during maternal than during stranger interactions, whereas full-term children did not. This should be considered alongside the main effect of group, whereby preterm children exhibited consistently elevated heart rate across conditions relative to full-term peers. Comparable elevations have been reported in other low-birthweight cohorts at school age, in one case accompanied by elevated urinary catecholamines (Johansson

et al. 2007; Zamecznik et al. 2017; Abe et al. 2007). One possible interpretation of this pattern is that preterm birth is associated with a higher physiological operating point of arousal, consistent with accounts proposing that early stress exposure may have lasting effects on autonomic development (Buchhorn et al. 2016; Shonkoff et al. 2012; Waterland and Garza 1999). This interpretation is also broadly consistent with the behavioral profile of the present cohort, in which preterm children showed elevated levels of internalizing problems and autism-related scores (Van den Broeck et al. 2026), as well as with literature linking elevated heart rate to internalizing tendencies and heightened arousal (Dietrich et al. 2007; Ortiz and Raine 2004; Portnoy and Farrington 2015). However, these links remain speculative in the present study, as heart rate and behavioral scores were not significantly correlated.

Conversely, high HR variability with strangers suggests children actively modulate physiological responses to meet changing social demands in unfamiliar contexts. These fluctuations may represent adaptive self-regulatory strategies: parasympathetic withdrawal and reduced arousal during passive conditions (eyes closed/open), followed by heightened engagement during interaction. A potential consideration is whether prior experience with non-parental adults and group settings may influence children's responses during interactions with an unfamiliar adult. Although we did not collect detailed information on daycare attendance or prior exposure to such environments, all children were attending the final year of preschool (third year of kindergarten in the Flemish educational system) at the time of assessment and had therefore experienced regular contact with teachers and peers. While individual differences in these experiences cannot be excluded, the relatively standardized educational trajectory in Flanders (Belgium) makes it unlikely that school-based exposure to non-parental adults differed systematically between the preterm and full-term groups. However, this does not rule out differences in earlier life experiences, as children born preterm may have had more extensive contact with a range of healthcare professionals during neonatal hospitalization and follow-up care.

Lastly, we found no significant correlations between the physiological parameters (HR, RMSSD-HRV, HF-HRV) and either the neonatal variables (GA, BW, kangaroo care, skin-breaking procedures) or the measures of socio-affective functioning (SRS-2, CBCL) in either group. These are two distinct null findings and warrant separate consideration. The absence of associations with neonatal variables may in part reflect the composition of the sample: children with major cerebral complications were excluded, which restricts the range of neonatal morbidity. It is also consistent with evidence that autonomic development in preterm infants may be more related to prematurity morbidity than gestational age itself (Mulkey and du Plessis 2019; Schlatterer and du Plessis 2021). The absence of associations with socio-affective functioning may warrant a different consideration. Behavioral difficulties in this cohort are predominantly subclinical, with the great majority of preterm children scoring within normative ranges (Van den Broeck et al. 2026), which restricts variance on these measures and may attenuate any correlation. These analyses were moreover exploratory, conducted with a threshold of $p < 0.01$. Physiological and questionnaire-based indices of related constructs are also known to correlate only modestly and should not be treated as interchangeable (Mauss et al. 2005; Mauss and Robinson 2009). Taken together, the present findings establish group differences in cardiac functioning without establishing their early determinants or their concurrent behavioral correlates. Future studies, with greater variability in behavioral outcomes and repeated physiological assessment, will be needed to determine whether the elevated heart rate observed here carries consequences for later socio-emotional development.

Clinically, the persistent elevation in basic HR alongside preserved regulatory flexibility suggests that preterm children possess the fundamental mechanisms for healthy socio-emotional development, though routine cardiovascular monitoring remains warranted. Early identification during developmental transitions such as adolescence, when autonomic regulation may deteriorate, could guide targeted interventions.

5 | Limitations

This study has several limitations. First, the cross-sectional design limits conclusions about developmental trajectories of autonomic regulation following preterm birth. Although we incorporated NICU data, longitudinal assessments at multiple developmental time points are needed for a comprehensive picture. Second, while HR and HRV provide meaningful autonomic indices, additional parameters such as gaze behavior could offer a more nuanced understanding of social interaction dynamics. Third, as attachment was not directly assessed, interpretations invoking attachment-related processes (e.g., the "secure base" framing) remain speculative. Future studies combining autonomic assessments with direct measures of attachment security would allow these mechanisms to be tested more explicitly. Fourth, although the content of the negative conversation was verified through experimenter observation and audio recordings, we did not include an independent assessment of the emotional valence or arousal elicited by the interaction. Consequently, variation in affective intensity across dyads cannot be ruled out. Future work would benefit from incorporating observational coding or observer-based affect ratings to validate the emotional characteristics of the interaction independent of autonomic measures. Fifth, the composition of the sample constrains generalizability. Children with major cerebral complications and diagnosed neurological conditions were excluded, in order to distinguish the effects of preterm birth itself from those of overt brain injury. Our findings therefore apply to preterm children without major neurological sequelae rather than to the full clinical population. The sample was also ethnically homogeneous, reflecting the population served by the NICU centre, and replication in more diverse cohorts is needed. Relatedly, the full-term comparison group was smaller than the preterm group ($n = 32$ versus $n = 70$), which reduces statistical power for detecting group differences. Our non-significant findings should therefore be interpreted as an absence of evidence rather than as evidence of equivalence. Finally, future research should include fathers and other primary caregivers to examine effect specificity and enhance ecological validity.

6 | Conclusion

This study demonstrates that 5-year-old preterm children exhibit elevated cardiac activity during social interactions, particularly with their mothers, while preserving fundamental regulatory flexibility comparable to full-term peers. The observed pattern of stable autonomic responses with mothers versus greater variability with strangers suggests adaptive developmental compensation rather than dysregulation. These findings highlight resilience mechanisms that may inform the design of targeted interventions to support optimal socio-emotional and physiological outcomes in this vulnerable population.

Author Contributions

Lisa Gistelinck: conceptualization, investigation, writing – original draft, methodology, validation, visualization, writing – review and editing, project administration, formal analysis, supervision, data curation. **Rowena Van den Broeck:** writing – review and editing, project administration, supervision. **Maarten De Vos:** funding acquisition, writing – review and editing. **Els Ortibus:** funding acquisition. **Bart Boets:** conceptualization, funding acquisition, writing – review and editing, resources, supervision. **Bieke Bollen:** funding acquisition, writing – review and editing. **Sam Wass:** funding acquisition, writing – review and editing. **Gunnar Naulaers:** funding acquisition, writing – review and editing.

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Ethics Statement

Approved by the UZ/KU Leuven Medical Ethical Committee (S58807).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Descriptive statistics for heart rate, RMSSD and HF by gestational age subgroup across interaction conditions. **Table S2:** Overview of correlations between individual physiological parameters (mean HR, RMMSD and HF), NICU measures (GA, BW and SBP) and socio-emotional functioning outcomes (SRS-2, CBCL (I), CBCL (E)) for the preterm group. **Table S3:** Overview of correlations between individual physiological parameters (mean HR, RMMSD and HF) and socio-emotional functioning outcomes (SRS-2, CBCL (I), CBCL (E)) for the full term group.