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The association between infant salivary cortisol and parental presence in the neonatal intensive care unit during and after COVID-19 visitation restrictions: A cross-sectional study

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ABSTRACT

Objectives: Parent-infant interaction in the neonatal intensive care unit (NICU) promotes health and reduces infant stress. During the COVID-19 pandemic, however, NICUs restricted parent-infant interaction to reduce viral transmission. This study examined the potential relationship between pandemic visitation restrictions, parental presence and infant stress as measured by salivary cortisol.

Methods: A two-NICU cross-sectional study of infants with gestational age (GA) 23–41 weeks, both during (n = 34) and after (n = 38) visitation restrictions. We analysed parental presence with and without visitation restrictions. The relationship between infant salivary cortisol and self-reported parental NICU presence in hours per day was analysed using Pearson's r. A linear regression analysis included potential confounders, including GA and proxies for infant morbidity. The unstandardised B coefficient described the expected change in log-transformed salivary cortisol per unit change in each predictor variable.

Results: Included infants had a mean (standard deviation) GA of 31(5) weeks. Both maternal and paternal NICU presence was lower with versus without visitation restrictions (both $p \leq 0.05$).

Log-transformed infant salivary cortisol correlated negatively with hours of parental presence ($r = -0.40$, $p = .01$). In the linear regression, GA (B = -0.03, $p = .02$) and central venous lines (B = 0.23, $p = .04$) contributed to the variance in salivary cortisol in addition to parental presence (B = -0.04 p = .04).

Conclusion: COVID-19–related visitation restrictions reduced NICU parent-infant interaction and may have increased infant stress. Low GA and central venous lines were associated with higher salivary cortisol. The interaction between immaturity, morbidity and parental presence was not within the scope of this study and merits further investigation.

1. Introduction

In the spring 2020, hospitals around the world implemented infection prevention and control (IPC) measures, including strict visitation restrictions, in response to the COVID-19 pandemic caused by the SARS-CoV2 virus. Facing an unprecedented public health crisis with a lack of a proper evidence base for decision-making, neonatal intensive care units (NICUs) also adopted visitation restrictions despite the known health-promoting effects of parent-infant interaction [1–3].

Infants in the NICU are daily exposed to harmful stress caused by separation from parents, care procedures, diagnostic examinations, painful procedures and mechanical ventilation [4,5]. Cortisol is one of several hormones produced by the adrenal glands in response to stress [6]. Although stress hormones may have short-term protective effects in infants [7], including the maintenance of blood pressure and blood sugar levels, a prolonged stress response may result in altered organ

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functions. An increased stress response with elevated levels of circulating cortisol may cause hyperglycaemia, tachycardia, hypertension and insulin resistance [8,9]. Furthermore, chronic stress in early life may cause structural and functional changes to an infant's brain, including dysregulation of the hypothalamic-pituitary-adrenal axis, leading to long-term neurodevelopmental changes [6,9,10]. Studies have shown a correlation between infant salivary cortisol and clinical stress scores [11] and that the amount of stress experienced by an infant may affect neurological outcomes [4,5,12].

Parents play an important role in alleviating infants' stress, and state-of-the-art neonatal intensive care nursing involves close collaboration with parents, actively engaging them in the care of their infants [13]. Thus, both parents normally have unrestricted access to our two university hospital NICUs. At implementation of pandemic IPC measures in March 2020, only one parent/caregiver was allowed access to the NICUs, and the other was restricted from seeing their sick or premature infant(s) for weeks or even months. The objective of this study was to examine the potential relationship between these COVID-19 related visitation restrictions and infant stress as measured by salivary cortisol, subdivided into 1) the relationship between visitation restrictions and parental presence, and (2) the relationship between parental presence and salivary cortisol. We hypothesised that reduced parental presence in the NICU during the pandemic would be associated with higher salivary cortisol in sick and premature infants. The knowledge gained from the study may be used in future epidemic and pandemic situations.

2. Design and method

2.1. Design

This was a cross-sectional study, a design appropriate for describing the status of phenomena or describing relationships at a fixed point in time [14]. The study is reported according to the STROBE guidelines [15].

2.2. Setting

The setting was two level-4 NICU sections at a university hospital in Norway that has approximately 9800 deliveries and 1500 admissions to the NICUs annually. The two sections have a total of 47 beds: 20 in one and 27 in the other. Both sections treat critically ill premature and term infants from gestational age (GA) 23 to ≥37. One section is the national referral centre for congenital heart defects and have a national responsibility for neonatal surgery, this section is also the main referral centre for inborn errors of metabolism. The other section is the main regional referral centre for therapeutic hypothermia treatment of hypoxic-ischemic encephalopathy and has the higher volume of very preterm infants. Both sections have a predominantly open-bay unit design. One section has 10 intensive care beds and 10 intermediate care beds (including four single rooms); the other has two intensive care bays (each with four beds), two intermediate care bays (with a total of 12 beds) and three nurseries for infants soon to be discharged.

2.3. Visitation restrictions (Fig. 1)

Beginning in March 2020, only one parent/caregiver (almost always the mother) was granted visitation in the two NICU sections. As in other NICUs, fathers/co-mothers/partners/other caregivers (henceforth referred to as the 'father') were restricted from seeing their sick or premature infants [3]. Exceptions were made only in cases in which the infant's condition was life threatening [16]. After two months of these very strict initial visitation restrictions, the two NICU sections gradually opened up to the father over the course of the pandemic. From June 2020–June 2021, the parents could visit one at a time, with the parents being able exchange visitation rights at their own discretion. Multiples (twins and triplets) were allowed to have both parents present beginning June 2020. Throughout the whole restriction period, no parents were allowed in the NICUs during rounds and handovers.

2.4. Inclusion and exclusion criteria

The inclusion criteria embraced infants born at GA 23 to term who were admitted to the one NICU section from June 2020 through January 2022 (817 total admissions) or to the other NICU section from December 2021 through March 2022 (218 total admissions). We included premature as well as sick term born infants who were expected to have a NICU stay lasting at least three days. No exclusions based on GA, sex or birth weight were made. The exclusion criteria included head and neck malformations that precluded saliva sampling, treatment with systemic steroids within the past week, and immediate life-threatening conditions and terminal illness.

2.5. Enrolment and data collection

Fig. 2 presents the enrolment of study participants. The study commenced in June 2020; from June 2021, both parents were allowed unrestricted joint visitation with their infant in the NICUs. We continued study enrolment and data collection until March 2022 to include families admitted to the NICUs without any visitation restrictions.

Information about the pregnancy and delivery concerning the

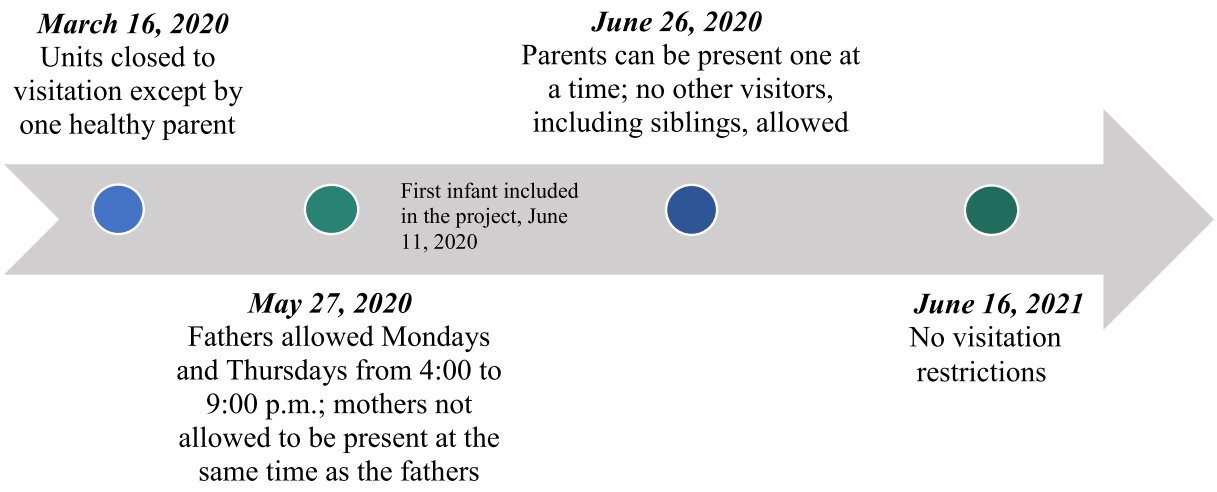

Fig. 1. Timeline of the period with visitation restrictions at the two university hospital neonatal intensive care units.

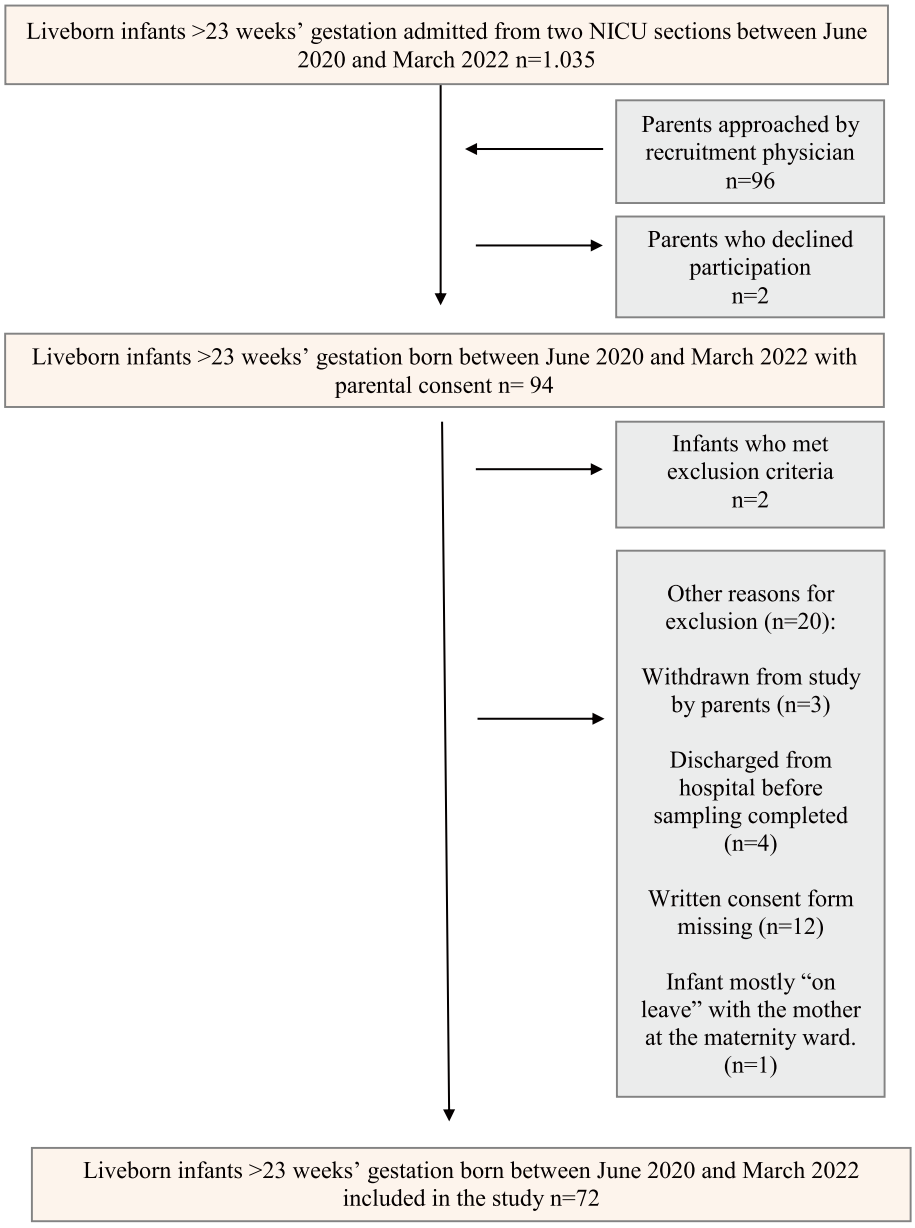

Fig. 2. The included participants and the reasons for exclusion of 22 infants.

included infants, as well as their demographic data, diagnoses and treatment were obtained from the electronic patient record (DIPS, Bodø, Norway) and the Norwegian Neonatal Network's electronic database. For preterm infants, we collected information about the antenatal administration of steroids. A complete course of antenatal steroids was defined as delivery >48 h after the first of two doses of betamethasone [17]. Postnatal steroids in our NICUs comprise mainly oral or intravenous hydrocortisone and dexamethasone. Infants treated with postnatal steroids within the past week were excluded.

2.6. Salivary cortisol sampling and analysis

Saliva collection is less stressful than blood sampling and does not itself increase stress hormones [18]. We therefore adopted salivary cortisol as the main outcome of our study. Analysis of salivary cortisol was performed by an in-house method at the Hormone Laboratory, Oslo University Hospital using liquid chromatography tandem mass spectrometry (LC-MS/MS). A detailed description of the method and its validation is under publication.

All the NICU nurses received verbal and written information about the study and how the saliva should be collected and handled. The bedside nurse collected the saliva using a MicroSal wick device (Oasis Diagnostics, Vancouver, WA, USA). The sponge of the device was left in the infant's mouth for a minimum of two but preferably for 4 min. If the infant showed signs of discomfort, saliva collection was interrupted. Saliva collection was mainly performed between 7:00 and 9:00 a.m. and between 6:00 and 9:00 p.m. on three consecutive days for each included infant. The collected saliva was immediately expressed from the wick using the manufacturer's compression device, transferred to a sterile matrix tube (Thermo Scientific, MA USA) and immediately frozen at −20 °C for a maximum of a week before storage at −80 °C until analysis.

2.7. Recording of parental presence

The study employed a slightly modified and translated paper parental presence form [20,21] that recorded information about when the parents were present with their newborn infant(s) in the NICU and that distinguished between being present bedside and providing skin-to-

skin care (SSC) to the infant. The form consisted of six rows, three for the mother (coloured red) and three for the father (coloured blue). Each row represented eight hours and was subdivided into squares, each representing five minutes [21]. Each parent was responsible for filling out the form individually. The two parents completed the same form, one form for each of the three days of saliva sampling in the infant.

2.8. Statistical analysis

The continuous variables are presented as means with standard deviations (SDs) if normally distributed, otherwise as medians with 25th and 75th percentiles. Differences in parental presence with versus without visitation restrictions were analysed using the independent samples *t*-test [22]. Each infant's salivary cortisol was calculated as an average concentration from all available samples. The resulting variable was not normally distributed and therefore log transformed before further analyses. The categorical variables are presented as numerals (%). The correlations between variables were analysed by calculating Pearson's correlation coefficient (r) [22]. Linear regression analysis was performed using log-transformed averaged salivary cortisol as the dependent variable [22] while parental presence and potential confounders constituted the independent variables. Variables such as bronchopulmonary dysplasia (BPD – requirement for supplemental oxygen and/or respiratory support at 28 postnatal days or 36 weeks postmenstrual age), intraventricular haemorrhage (IVH – all grades) and necrotizing enterocolitis (NEC) (Table 1) were considered to be strongly associated with GA and were left out of the regression [23]. Intravenous lines, treatment with inotropes and days on mechanical ventilation were considered markers of/proxies for infant disease severity/morbidity and were included in the regression analysis together with GA. The unstandardised B coefficient was used to describe the expected change in the log-transformed dependent variable (salivary cortisol) per unit change in the predictor variable [22]. The analyses used the average value of log-transformed salivary cortisol and parental presence across the three included days. Total parental presence included bedside presence and SSC and was defined as the infant's time with one or both parents present, i.e., the hours of the mother and father's presence were not combined but were mutually exclusive. A p-value of <0.05 was considered significant [24]. Statistical analyses were performed with IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

Subgroup analyses were performed for:

- Infants admitted during and after (without) visitation restrictions; multiples (twins or triplets) were included in the group without restrictions.
- Extremely premature (GA <28 weeks), very premature (GA 28–33 weeks), moderate to late premature (GA 33–36 + 6 weeks) and term infants (GA ≥37 weeks) [25].

2.9. Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics Southeast Norway (reference 145224) and the data protection officer at the university hospital (reference 20/12787). Infants in both NICUs were included after written informed consent was obtained from both parents. Participation in the study was voluntary, and the families could withdraw from the study at any time without any explanation or consequences. Participants could also request that their data and samples be destroyed or excluded from analysis.

All the study information, including parental presence, was

Table 1
Background characteristics of the included infants.

Gestational age (at birth), n (%)	23–28 weeks	29–32 weeks	33–36 weeks	≥37 weeks	Total
	20 (28)	26 (36)	13 (18)	13 (18)	72 (100)
Post-menstrual age at sampling, weeks, mean (±SD)	31 (4)	34 (4)	36 (2)	41 (1)	35 (5)
Female, n (%)	12 (60)	12 (46)	8 (62)	3 (23)	35 (49)
Weight at birth, gram, Median (25th–75th percentile)	810 (642–970)	1445 (1304–1676)	2174 (1980–2446)	3660 (2823–3914)	1557 (1008–2269)
Weight at sampling, gram, Median (25th–75th percentile)	1121 (845–2148)	1709 (1520–2652)	2472 (2111–2746)	3634 (2845–4007)	2111 (1432–2925)
Antenatal steroids, one dose, n (%)	13 (65)	7 (27)	-	-	20 (28)
complete course, n (%)	6 (30)	13 (50)	-	-	19 (26)
Apgar 1 min, median (25th–75th percentile)	5 (4–7)	7 (5–8)	9 (6–9)	9 (6–9)	7 (5–9)
Apgar 5 min, median (25th–75th percentile)	8 (6–9)	8 (7–9)	9 (8–10)	9 (8–10)	8 (7–9)
Small for gestational age, n (%)	4 (20)	8 (31)	5 (39)	4 (31)	21 (29)
Large for gestational age, n (%)	-	1 (4)	-	2 (15)	3 (4)
Diagnosis					
Bronchopulmonary dysplasia[a], n (%)	14 (70)	2 (8)	-	-	16 (22)
Retinopathy of prematurity[b], n (%)	4 (20)	3 (12)	-	-	7 (10)
Intraventricular haemorrhage[b], n (%)	6 (30)	4 (15)	1 (8)	-	11 (15)
Periventricular leukomalacia[b], n (%)	1 (5)	2 (8)	-	-	3 (4)
Necrotizing enterocolitis, n (%)	2 (10)	4 (15)	1 (8)	-	7 (10)
Drugs					
Caffeine citrate, n (%)	15 (75)	16 (62)	-	1 (8)	32 (44)
Inotropes, n (%)	-	-	-	1 (8)	1 (1)
Insulin, n (%)	1 (5)	-	-	-	1 (1)
Intravenous lines					
No lines, n (%)	8 (40)	13 (50)	7 (54)	2 (15)	23 (32)
Peripheral intravenous lines, n (%)	10 (50)	8 (31)	4 (31)	11 (85)	33 (46)
Central venous lines, n (%)	5 (25)	7 (27)	3 (23)	2 (15)	17 (24)
Days on MV, median (25th–75th percentile)	11 (1–37)	1 (0–4)	0 (0–2)	0 (0–4)	1 (0–7)
Days on NIV, median (25th–75th percentile)	14 (9–33)	4 (2–12)	0 (0–6)	1 (0–2)	5 (1–13)
Positive blood culture at sampling, n (%)	3 (15)	–	–	–	3 (4)

MV: mechanical ventilation; NIV: non-invasive ventilation.
[a] Extra oxygen requirement on postnatal day 28 or postmenstrual age 36 + 0 weeks.
[b] Any grade.

registered, stored and analysed de-identified. The code key linking the study information to the individual participants was stored electronically in MedInsight (MedInsight, Seattle, WA, USA) in line with the procedures and recommendations of the data protection officer at the university hospital.

3. Results

The study included a total of 72 infants, 62 from one section and 10 from the other. Background characteristics of the included infants are presented in Table 1. The infants had a mean (SD) GA at birth of 31 (5) weeks and a mean (SD) postmenstrual age at inclusion of 35 (5) weeks.

Being in the critical stage immediately after birth was not an exclusion criterion, but the physicians responsible for inclusion did not approach the parents of infants in this stage for reasons of sensitivity to the families' needs in the first few days after birth. The flowchart in Fig. 2 shows the included participants and the reasons for exclusion of 22 infants. Twelve signed consent forms were missing due to non-compliance (e.g., consent forms were discarded by unit personnel), which resulted in exclusion of 14 % of included infants.

3.1. Salivary cortisol

The parental presence forms were missing for five infants, but their salivary cortisol samples were included in the total of 450 saliva samples. An adequate saliva volume for analysis of cortisol was achieved in 380 samples, and analysis of salivary cortisol could thus not be performed in 70 samples. The mean (SD) cortisol value was 0.5 (0.4) nmol/l. The scatter plot in Fig. 3 illustrates the distribution of salivary cortisol values in various GA groups. The summary statistics of salivary cortisol are presented in a supplementary table. The salivary cortisol values of the lower GA groups are distributed predominantly in the upper part of the diagram.

3.2. Parental presence

3.2.1. The relationship between visitor restrictions and presence

The mother ($p < .02$) and father ($p < .001$) both spent less time with their infant during versus after visitation restrictions. Total hours of parent-infant interaction did not differ during versus after visitation restrictions ($p = .54$). In the period without visitation restrictions, the parents visited the NICU mostly together at the same time, as illustrated by the difference in the blue and green boxes of Fig. 4, panel B.

Total mean (SD) parental presence was 7.4 (2.8) hours per day, with a very high consistency across the three registered days in individual families. Fig. 3 also illustrates the distribution of parental presence in various GA groups. The summary statistics of parental presence and SSC are presented in a supplementary table. Parental presence in hours in the lower GA groups is distributed predominantly in the lower left of the diagram. Mothers provided SSC to their infants for a mean (SD) of 3.8 (2.2) hours daily while fathers provided SSC for 2.5 (1.2) hours daily. Fig. 4 shows total (bedside and SSC) maternal and paternal presence during and after visitation restrictions.

3.2.2. The relationship between presence and salivary cortisol

Total parental presence and salivary cortisol correlated negatively ($r = -0.35$, $p < .01$) for the entire cohort, but only significantly for the GA subgroup 33–36 + 6 weeks: GA <28 weeks ($r = -0.33$, $p = .18$), GA 28–33 weeks (r = −0–29, p = .18), GA 33–36 + 6 weeks ($r = -0.72$, $p = .009$) and GA ≥37 weeks ($r = -0.56$, $p = .07$). There was a negative correlation between the mother's SSC and cortisol ($r = -0.40$, $p < .01$) and the father's SSC and cortisol ($r = -0.41$, $p < .01$).

3.3. Potential confounders

A linear regression model was applied to identify potential causes of variation in salivary cortisol using the independent variables GA, peripheral intravenous lines, central venous lines and days of mechanical or non-invasive ventilation in addition to total parental presence. The

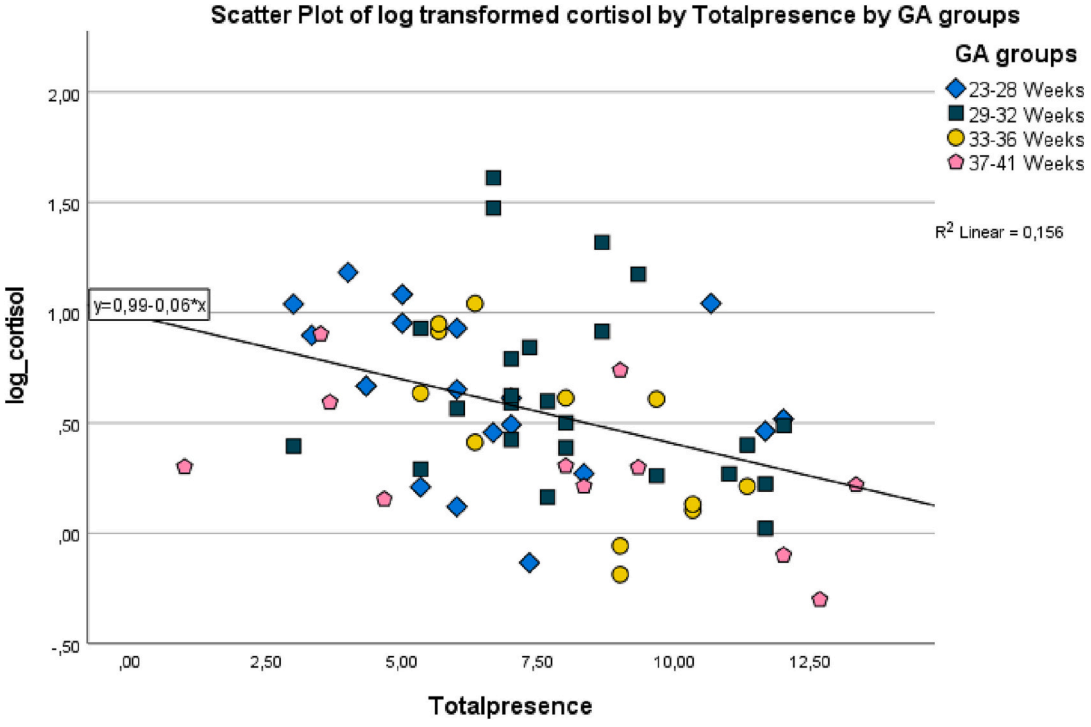

Fig. 3. Scatter diagram of the distribution of salivary cortisol values and parental presence in 72 infants. Each individual infant is marked by a coloured gestational age groups. The x-axis represents total parental presence (both during and after visitation restrictions) in hours average over three days in the neonatal intensive care unit. The y-axis represents log-transformed infant salivary cortisol in nmol/l.

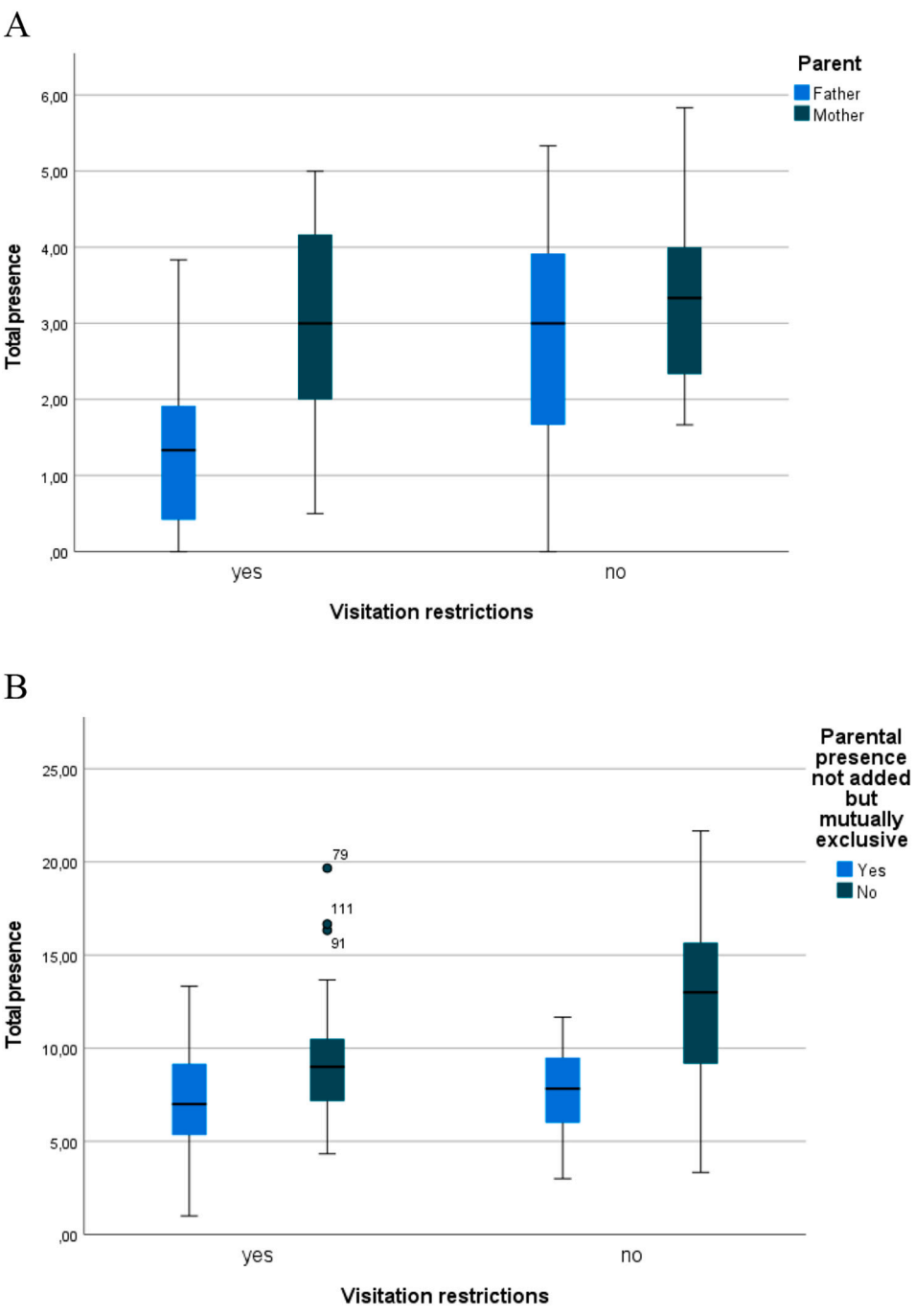

Fig. 4. Panel A shows maternal and paternal presence in hours per day during ("yes") and after ("no") visitation restrictions. Panel B shows that when maternal and paternal presence in hours were added (green boxes), there was a difference during ("yes") versus after ("no") visitation restrictions. After the visitation restrictions ("no"), the two parents visited mostly together/at the same time, resulting in the time the infant had one *or* both parents present (blue boxes) was unchanged compared with the period with restrictions.
Within each box, the horizontal black line represents the median value; boxes extend from the 25th to the 75th percentile; while the whiskers represent the minimum and maximum values, respectively.

use of inotropes and a positive blood culture were also considered markers of morbidity but were left out of the model, as only one infant received inotropes during saliva sampling (Table 1).

Table 2 shows the result from the linear regression analysis. The model explained 23 % of the variation in salivary cortisol ($R^2 = 0.23$). Total parental presence, GA and central venous lines all explained the variance in salivary cortisol significantly, with a *p*-value <.05. Salivary cortisol was expected to increase as GA decreased and as the use of central venous lines increased.

4. Discussion

This cross-sectional study aimed to examine the effect on infant stress (as measured by salivary cortisol) of reduced parental presence resulting from restrictions on NICU visitation during the COVID-19 pandemic. We found that the restrictions negatively influenced the quantity of parent-infant interaction during NICU hospitalization. Less parental presence, including SSC, in the NICU during the pandemic was associated with higher levels of infant salivary cortisol when all sick and premature infants were analysed as a group. This is in agreement with Vittner et al. [26] who found that salivary cortisol decreased during SSC. Stress experienced during the neonatal period is reported to be associated with long term neurological morbidity [6]. Additionally, stress may have long-term metabolic consequences, which may result in later diabetes and/or obesity [4]. Our study contributes to the literature by demonstrating the inverse relationship of salivary cortisol to total parent-infant interaction.

Our linear regression model explained only 23 % of the variance in infant salivary cortisol, and there are many potential reasons for elevated infant salivary cortisol and stress that our study did not

Table 2
Linear regression model including potential confounders in addition to parental presence (independent/predictor variables); log-transformed salivary cortisol is the dependent variable.

	Unstandardised B coefficient	Standard error	Standardised B coefficient	P-value
Average total presence	−0.04	0.018	−0.26	0.04
Gestational age (at birth)	−0.03	0.012	−0.36	0.02
Intravenous lines				
Peripheral intravenous line	0.04	0.10	0.053	0.66
Central venous catheter	0.23	0.11	0.23	0.04
Days on MV	−0.01	0.003	−0.04	0.73
Days on NIV	−0.01	0.004	−0.23	0.11

The unstandardised B coefficient is used to describe the expected change in the log-transformed dependent variable (salivary cortisol) per unit change in the predictor variable.
MV: mechanical ventilation; NIV: noninvasive ventilation.

measure. In general, the NICU environment is characterised by a high noise level, and this noise negatively affects infants' cardiovascular, respiratory, neurological and endocrine systems [27]. In addition, infants admitted to the NICU are exposed to 10–14 painful and stressful procedures every day [6].

Surprisingly, the number of days of mechanical ventilation did not have a significant impact on infant salivary cortisol ($p = .73$). Procedures associated with mechanical ventilation may be painful procedures, such as endotracheal suctioning, central line insertions and venipunctures [28], yet, in our linear regression analysis, only central venous lines explained some of the variance in salivary cortisol ($p = .04$). We speculate that the low median (25th–75th percentile) days of mechanical ventilation, which was 1 (0–7) days, may explain why mechanical ventilation did not have a significant impact on salivary cortisol in the included infants.

When the first wave of the pandemic hit in 2020, there was no scientific evidence to guide hospitals in handling the situation with regards to intra-hospital IPC measures. NICU staff, including nurses, worked in unknown territory under restrictions that felt unreasonable and difficult to justify to parents. The SSC provided to infants by parents is important for optimal development by reducing stress and pain [4,7,28,29]. The benefits of SSC include reduced infant salivary cortisol [26], with consequent greater cardiorespiratory stability, less infection and increased breastfeeding rates [6,10,30]. This is confirmed by our study, which found that SSC with both mother and father was associated with lower infant salivary cortisol. In the two-month period with the strictest restrictions, only the mother was able to perform SSC with her infant, since the father was not allowed access to the unit. Limiting parent-infant interaction, including SSC, during the pandemic was thus both counterintuitive and contradicted by existing evidence.

Our results indicate that lower GA is associated with higher salivary cortisol. In particular extreme prematurity is associated with significant morbidity and a need for mechanical ventilation, central lines and inotropes [23,31]. This is partially supported by the background characteristics of our infants (Table 1), which include more mechanical ventilation and diagnoses such as IVH and BPD in the lower GA groups. However, the lower GA group infants also had less parental presence (Fig. 3), the reason for which was beyond the scope of this study. Regardless of this, there was a negative correlation between parental presence and salivary cortisol when all the infants were analysed collectively.

Total parental presence, i.e., the infant's time with one or both parents present, did not differ significantly between the period with restrictions and the period without restrictions. This may be because, during the period with restrictions, the parents could visit their infant only one at a time while, after the restrictions, they could visit the infant together (Fig. 4). In the variable 'total parental presence', the mother and father's presence were not added but were mutually exclusive. Fig. 4 illustrates that when maternal and paternal presence were added, there was in fact a difference during vs. after visitation restrictions. This is supported by the fact that the fathers' interaction with the infants almost doubled from the period with restrictions to the period without restrictions. The mothers' interactions with the infants were also higher in the period without restrictions (Fig. 4). According to Kynø et al. [16], the parents prefer being present in the NICU together and this can explain why, in our study, both the mother and the father's interaction with the infant increased when they could visit the NICU together. It is unknown whether the parent-infant interaction is qualitatively different when one or both parents are present with their infant at any given time. However, our findings are similar to those of Mahoney et al. [32], who found that the COVID-19 pandemic negatively affected parental presence in the NICU. Similar to our findings, Mahoney et al. [32] reported less parental presence during the visitation restrictions, especially in units with open-bay design. Interestingly, the restrictions were associated with families interacting with their infant in a different way, i.e., less shared decision making, less parental participation in NICU rounds and changes in breast feeding rates, or that they did not interact at all [32].

4.1. Strengths and limitations

The main strength of this study is the recruitment of participants during a period with severe restrictions on parental presence in the NICU. This period also placed significant strain on NICU staff due to constantly changing policies and procedures related to IPC. Our broad study population of hospitalised newborn infants with a GA of 23 weeks to full term may be representative of patients in other NICU settings. Although the setting was two level-4 NICUs, there was a selection bias towards more stable infants because our participants were included only after the most critical initial phase. This selection bias towards more stable infants could be interpreted as a limitation, but also represents a strength, as it may have reduced confounding by various disease severities and treatment complexities. Also, as the hypothalamic–pituitary–adrenal axis (HPA) axis' responses to stress are highly variable in preterm infants and change with maturation of the HPA axis over time, the more homogenous population in our study might be an advantage. Another strength is that the LC/MS-MS method to measure cortisol in saliva in newborns gives measurable values in smaller volumes compared with previously used methods, such as radioimmunoassays, that have been unsuccessful in neonatal medical research [18]. Thus, we managed to analyse a large number of saliva samples collected from our participants and to achieve significant results in regard to our research question. In addition, LC/MS-MS methodology provides superior specificity allowing detection of closely related substances, such as other natural and synthetic steroids, that show considerable interreference in the antibody-based assays [19].

We also acknowledge some limitations. There was a small number of families included due to a high workload during the pandemic with associated noncompliance and missing data. Moreover, some infants had unplanned transfers to other hospitals before they could complete the three days of sampling and registration. Despite the use of the LC-MS/MS method, some saliva samples had insufficient volume to be analysed, mainly those of the smallest and sickest infants. Finally, parental presence without restrictions may have been negatively impacted compared to pre-pandemic times, as the pandemic may have caused lasting changes in the unit culture and practice regarding parental involvement. The fact that the total parental presence did not increase in the period after restrictions may reflect this.

5. Conclusion

COVID-19–related visitation restrictions resulted in less NICU parent-infant interaction and may have increased infant stress, as fewer hours of parent-infant interaction were associated with higher infant salivary cortisol. Low GA and central venous lines were also associated with higher salivary cortisol. The interaction between immaturity, morbidity and parental presence was not within the scope of this study and should be a focus of future studies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2023.105788.

Declaration of competing interest

"The association between infant salivary cortisol and parental presence in the neonatal intensive care unit during and after COVID-19 visitation restrictions: A cross-sectional study" by Stine Marie Brekke and colleagues

Stine Marie Brekke has no conflicts of interest relevant to this article to disclose

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CRediT authorship contribution statement

"The association between infant salivary cortisol and parental presence in the neonatal intensive care unit during and after COVID-19 visitation restrictions: A cross-sectional study".

Stine Marie Brekke: Included participating families and collected data, analysed and interpreted data, wrote the manuscript.

Silje Torp Halvorsen: Included participating families and collected data, analysed and interpreted data, wrote the manuscript.

Julie Bjørkvoll: Included participating families and collected data, analysed and interpreted data, wrote the manuscript.

Per Medbøe Thorsby: Conceptualized and designed the study, contributed to sample analysis, data interpretation and writing of the manuscript.

Arild Rønnestad: Conceptualized and designed the study, contributed to data interpretation and writing of the manuscript.

Svetlana N. Zykova: Conceptualized the idea of and contributed to method development, contributed to data analysis, data interpretation and writing of the manuscript.

Liv Hanne Bakke: Method development and sample analysis, contributed to data interpretation and writing of the manuscript.

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Kirsti Haaland: Included participating families and collected data, contributed to data interpretation and writing of the manuscript.

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Marianne Trygg Solberg: Supervision, contributed to data interpretation and writing of the manuscript.

Anne Lee Solevåg: Conceptualized and designed the study, included participating families and collected data, contributed to the data analysis and interpretation.

All authors participated in critical revision of the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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