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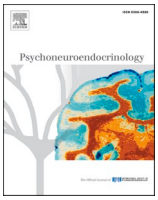

Early childhood multiple or persistent regulatory problems and diurnal salivary cortisol in young adulthood

Ayten Bilgin [a,*], Kati Heinonen [b,c], Polina Girchenko [b,d], Eero Kajantie [e,f,g,h], Dieter Wolke [i], Katri Räikkönen [b]

[a] Department of Psychology, University of Essex, Colchester, United Kingdom
[b] Department of Psychology & Logopedics, University of Helsinki, Helsinki, Finland
[c] Psychology/Welfare Sciences, Faculty of Social Sciences, Tampere University, Finland
[d] Research Unit of Clinical Medicine, University of Oulu, Finland
[e] Finnish Institute for Health and Welfare, Helsinki, Finland
[f] PEDEGO Research Unit, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland
[g] Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[h] Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[i] Department of Psychology, University of Warwick, Coventry, United Kingdom

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ABSTRACT

Background: Early childhood multiple or persistent regulatory problems (RPs; crying, sleeping, or feeding problems) have been associated with a risk of behavioural problems in young adulthood. It has been suggested that this may be due to the possible influence of early RPs on the functioning of the hypothalamic-pituitary-adrenal (HPA) axis. However, associations between early RPs and HPA-axis activity in young adulthood remain unexplored. Thus, the aim of the current study was to investigate whether early childhood multiple or persistent RPs are associated with diurnal salivary cortisol in young adulthood.
Methods: At the ages of 5, 20 and 56 months, RPs of 308 children from the Arvo Ylppö Longitudinal Study were assessed via standardized parental interviews and neurological assessments. Multiple RPs were defined as two or three RPs at the age of 5 months and persistent RPs as at least one RP at 5, 20 and 56 months. At the mean age of 25.4 years (SD= 0.6), the participants donated saliva samples for cortisol at awakening, 15 and 30 min thereafter, 10:30 am, at noon, 5:30 pm, and at bedtime during one day. We used mixed model regressions, and generalized linear models for testing the associations, controlling for important covariates.
Results: Of the 308 children, 61 (19.8%) had multiple or persistent RPs in early childhood: 38 had multiple, and 27 had persistent RPs. Persistent RPs were associated with significantly higher cortisol peak and output in the waking period, and cortisol awakening response. On the other hand, multiple RPs were not associated with salivary cortisol.
Conclusion: Children displaying persistent RPs throughout early childhood show, over two decades later, increased HPA axis activity in response to awakening stress. This may be one physiological mechanism linking early childhood RPs to adulthood behavioural outcomes.

1. Introduction

Regulatory problems (RPs), defined as excessive crying beyond 3 months of age and feeding and sleeping problems beyond 6 months of age, are common during early childhood (Bilgin et al., 2020; Cook et al., 2019a; Olsen et al., 2019). Approximately 20% of infants experience any RPs in the first year of life (Bilgin et al., 2020; Hemmi et al., 2011; Cook et al., 2019b), whereas a smaller group (i.e., 2 to 8%) have multiple RPs concurrently in infancy or persistently across more than one time point during early childhood (Bilgin et al., 2020; Cook et al., 2019a; Winsper et al., 2020). Early RPs are stressful and challenging for parents and can result in parental depression, stress, fatigue, and problems in parent-child relationships (Petzoldt et al., 2016). They are among the most common reasons for parents to seek help from health professionals

* Corresponding author.
E-mail address: a.bilgin@essex.ac.uk (A. Bilgin).

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regarding their children's health (St James-Roberts, 2008).

It has been suggested that early RPs may indicate emerging problems in self-regulation with a core feature of having difficulties inhibiting a current state such as self-soothing when crying, settling back to sleep at night, and overcoming neophobia to new food (Cook et al., 2019a; Hemmi et al., 2011). While most early RPs are transient with no long-term developmental consequences, increasing evidence suggests that multiple RPs in infancy or persistent RPs from infancy to toddlerhood are associated with an increased risk of dysregulation and behavioural and attention problems during childhood (Cook et al., 2019a; Hemmi et al., 2011; Winsper et al., 2020; Schmid et al., 2010; Hyde et al., 2012; Baumann et al., 2019; Bilgin and Wolke, 2020a; Galling et al., 2023). Further, emerging evidence suggests that the association between early childhood multiple or persistent RPs and behavioural, psychiatric, and attention problems may persist into young adulthood (Bilgin et al., 2020; Jaekel et al., 2020; Bäuml et al., 2019; Wolke et al., 2023).

One physiological mechanism that may link early childhood RPs with adult behavioural outcomes is the hypothalamic-pituitary-adrenal (HPA)-axis activity. Early childhood RPs can be highly stressful for the children experiencing them (Cook et al., 2019a). As the brain and the physiological feedback systems regulating stress, such as the HPA axis, undergo rapid developmental maturation during early life years, it is possible that the physiological stress induced by the early childhood RPs alter the set-points and functioning of the stress-regulatory systems in ways that persist into adulthood (Desantis et al., 2015; Doom and Gunnar, 2013). While empirical evidence supporting this hypothesis does not exist, ample evidence suggests that there is an association between exposure to stress early in life, such as separation from biological parents, physical or emotional abuse or neglect, parental death or divorce, socioeconomic disadvantage and altered HPA-axis activity in adulthood (Gunnar and Quevedo, 2007; McFarland and Hayward, 2014; Pesonen and Räikkönen, 2012). Moreover, it has been shown that altered HPA axis activity is associated with depressive and anxiety symptoms in children, adolescents and adults (Lopez-Duran et al., 2009; Adam et al., 2017; Doane et al., 2013; Boggero et al., 2017a), which also suggests that early childhood multiple or persistent RPs may be associated with cortisol levels in young adulthood.

Against this background, we examined whether multiple or persistent RPs, measured thrice throughout early childhood by parental interviews and neurological assessments, were associated with diurnal salivary cortisol, measured across one day in a follow-up, over two decades later. Although the literature is not entirely consistent (e.g., 22–25), we hypothesised that multiple or persistent RPs would be associated with flatter diurnal salivary cortisol slopes, but higher cortisol awakening response in young adulthood.

2. Methods

2.1. Participants

The current study included participants from the Arvo Ylppö Longitudinal Study (AYLS) (Heinonen et al., 2008a; Riegel et al., 1995; Wolke et al., 1998). They were recruited from a total of 15311 deliveries in the seven maternity hospitals in the county of Uusimaa, Finland between March 15, 1985 and March 14, 1986. The sample comprised 2194 infants (1000 girls). Of them 1535 (668 girls; 70% of the total sample) were admitted to the neonatal wards of the obstetric units, or to the Neonatal Intensive Care Unit (NICU) of the Children's Hospital within ten days after birth. The neonates ranged from severely ill preterm infants to infants requiring only brief inpatient observation. The majority of the admitted infants had no diagnosed illness and were on the ward for observation or because of common problems relating to neonatal adaptation (Heinonen et al., 2008a). An additional 658 (332 girls; 30% of the total sample) infants, not admitted to neonatal wards, were prospectively recruited from births occurring after every second hospitalized infant in the three largest maternity hospitals in the study area during the same period. Details of the study cohort are presented elsewhere (Heinonen et al., 2008a; Riegel et al., 1995).

In 2009–2012, of the initial sample (N = 2194), 1913 (87.2%) participants were invited for follow up assessments in young adulthood. Personal identification number was missing for 107 participants, and for 173 participants addresses were not traceable (i.e., they moved abroad) or they would have needed accommodation for an overnight stay. Of the participants, we were able to trace, 1136 (59.4%; 51.8% of the original cohort) participated in the follow-up assessments at young adulthood at a mean age of 24.5 years (SD=0.6). Among these participants, 846 (74.4%; 38.5% of the original cohort) provided salivary samples for cortisol assessment during one day.

Of the participants who provided salivary samples, 317 had data on multiple or persistent RPs (crying, sleeping, or feeding/eating problems) in follow-ups at ages 5, 20 and 56 months. We excluded nine participants based on the following criteria: night shift workers (N = 2), those who were pregnant during the study (N = 1), and those with rheumatoid arthritis (N = 1) or asthma diagnosis (N = 5). Thus, the final sample included in the current study comprised 308 participants, of whom 61 had multiple or persistent RPs in early childhood and 247 did not have multiple or persistent RPs in early childhood. The mean age of the current sample was 25.4 (0.61) years.

There were no significant differences between the participants who were invited into the adulthood follow-up but did not participate and the analytical sample of the current study. Further, the analytical sample of the current study (N = 308) did not differ from those who participated in the adulthood follow-up, but were not included in the analytic sample (n = 520 out of 828) in terms of weight (3325 vs 3341 g, p = .75) and gestational age (38.5 vs 38.5 weeks, p = .88) at birth, BMI in adulthood (24.1 vs 24.0, p = .90), age at assessment in adulthood (25.4 vs 25.4, p = .96), percentage of females (51.0% vs 51.9%, p = .76), and parents with upper tertiary education (17.2% vs 18.9%, p = .35).

2.2. Measures

2.2.1. Multiple or persistent RPs from 5 to 56 months

At 5 months of age, paediatricians asked parents about their infant's crying, feeding, and sleeping problems via a standardized interview as part of a neurodevelopmental assessment. At 20 and 56 months, sleeping and eating problems were assessed via standardized parental interview (Bilgin and Wolke, 2016) and neurological examination of oral motor function based on Prechtl's (1977) neurological examination method (Prechtl, 1977), which is a standard neurological assessment of fine and gross motor skills, oculomotor functioning, muscle tones and reflexes. Both assessments were conducted by paediatricians, who were trained to achieve an inter-rater reliability > 90% and received three-monthly booster workshops. The assessments at 5 and 20 months were carried out corrected for prematurity, and the assessment at 56 months was carried out according to chronological age. The definitions for crying, feeding, and sleeping problems at 5 months and sleeping and eating problems at 20 and 56 months have been described previously (Schmid et al., 2010) and are shown in Table 1.

Children with multiple RPs were those who had two or three RPs at 5 months. Persistent RPs were defined as having at least one RP at two or three of the following assessment points: 5, 20 and at 56 months of age. Subsequently, multiple and/or persistent RPs were combined into one binary variable: 0 = never RPs, 1 = multiple or persistent RPs.

2.2.2. Diurnal Salivary Cortisol in Young Adulthood

Participants collected seven saliva samples during a one-day period: at awakening (M=7:24AM hh:mm, SD=1:27 hh:mm), 15 min (M=7:39AM, SD=1:28) and 30 min (M=7:55AM, SD=1:28) thereafter, at 10:30AM (M=10:40 AM, SD=0:43), at noon (M=12:17, SD=0:52), at 5:30PM (M=5:45PM, SD=0:45) and at bedtime (M=11:44PM, SD=1:34). Participants were instructed to avoid brushing their teeth,

Table 1
Definition of crying, feeding, and sleeping problems at 5, 20 and 56 months and assessment mode.

Regulatory problems	Definition	Assessment Mode
5 months of age		
Crying problems: (diagnosed if ≥ 1 of 4 criteria were met)	1. Cry duration: ≥ 2 h per day. AND/OR	PI
	2. Cry amount: above average. AND/OR	PI
	3. Infant is usually difficult to soothe. AND/OR	PI
	4. Infant is constantly irritable.	PI
Feeding problems: (diagnosed if ≥ 1 of 3 criteria were met)	1. Infant does not eat and drink well. AND/OR	PI
	2. Formerly and currently problems with vomiting. AND/OR	PI
	3. Disordered oral-motor functioning, i.e., problems with sucking / swallowing, disordered mouth / tongue movement.	PI
Sleeping problems: (diagnosed if ≥ 1 of 2 criteria were met)	1. Infant wakes up ≥ 2 times per night. AND/OR	PI
	2. Infant wakes up for ≥ 15 min at night.	PI
20 months of age		
Eating problems: (diagnosed if ≥ 1 of 3 criteria were met)	1. Occurrence of eating problems. AND/OR	PI
	2. Problems with chewing, swallowing, or not accepting solid food. AND/OR	NE
	3. Oral-motor dysfunction, i.e., uncoordinated movements, not harmonic.	NE
Sleeping problems:	Occurrence of sleeping problems.	PI
56 months of age		
Eating problems: (diagnosed if ≥ 1 of 2 criteria were met)	1. Eating problems/problems with food intake. AND/OR	PI
	2. Neurological/behavioural dysfunction (motor problems, loss of appetite, refusal to eat, or other problems).	NE
Sleeping problems: (diagnosed if ≥ 2 of 4 criteria were met)	1. Sleeps through less than three nights per week.	PI
	2. Needs more than 30 min to fall asleep.	PI
	3. Only falls asleep when parents are around.	PI
	4. Regularly sleeps in parents' bed.	PI

Note. PI = Standardized parental interview; NE = Neurological examination by pediatrician.

drinking caffeinated products, and eating within 30 min after awakening. They were also asked to record the date and time at sample collection.

Samples were collected between November 2009 and May 2012. Samples were stored at −20 °C and analyzed in May-June 2012 at University of Trier, Germany. Salivary cortisol concentrations were determined by use of a competitive, solidphase, time-resolved fluorescence immunoassay with fluorometric end point detection (DELFIA; Wallac, Turku, Finland) (Dressendörfer et al., 1992). Cortisol concentrations were measured in duplicate and averaged. If the second measure was not available, the single concentration measured was used. The inter-assay coefficients of variation of the control samples were 6.53% for a mean concentration of 3.70 nmol/L, 7.69% for 7.73 nmol/L and 6.88% for 18.38 nmol/L. The intra-assay coefficients of variation ranged between 4.0% and 6.7%.

2.2.3. Diurnal salivary cortisol parameters

To study the diurnal cortisol slope, we used all seven cortisol values as wake-to-bedtime cortisol slope have shown relatively large effect sizes in relation to health outcomes (Adam et al., 2017). To study morning slope, we used the three morning values (from awakening to 30 min after awakening).

Furthermore, we studied separately all seven salivary cortisol values, the peak morning value (maximum of the three morning values), and the diurnal nadir (minimum of the seven cortisol values). Moreover we calculated integrated cortisol measures, namely time-weighted area under the curve with respect to ground (AUCg) of the seven cortisol values to study total diurnal cortisol output, total cortisol output in the morning (awakening time-weighted area under the curve with respect to ground, morningAUCg), and time-weighted AUC with respect to increase/change (AUCi) from the three morning values (Pruessner et al., 2003) to study the cortisol awakening response (CAR). All individual cortisol values and integrated measures were normalized due to skewed distributions using natural logarithm and standardized. We also truncated cortisol values at 100 if they were above the upper limit of assay range (>100 nmol/L), and if the values were ± 5 Standard Deviation (SD) units, they were coded as missing. This meant that one outlier was excluded from the analyses concerning the salivary cortisol values at 5:30 pm and bedtime. Further, we excluded one outlier in all analyses concerning the AUCi and two outliers in all analyses concerning the AUCg.

2.2.4. Covariates

According to the previous literature, we considered covariates that are related to early RPs and/or diurnal salivary cortisol. Wake-up time and cortisol sampling time were identified from the diurnal logs. Participant age (years) was calculated from the adulthood clinical visit date, and body-mass-index (BMI, kg/m^2) from weight and height measured at the clinical visit. Participant sex (male vs female), birth weight (grams) and gestational age (weeks) were identified from hospital birth records, and highest parental education level (upper secondary or less, lower tertiary, upper tertiary), was reported by the mothers in the childhood clinical visits.

2.3. Statistical Analysis

We first examined whether the diurnal cortisol slopes (from awakening to bedtime;) and the morning slope (from awakening to 30 min after awakening) in young adulthood varied according to early childhood multiple or persistent RPs by using random coefficients mixed model regressions. In these analyses, the seven cortisol values from awakening to bedtime, and the three values from awakening to 30 min thereafter were treated as outcome variables in two separate models. The models included multiple or persistent RPs in early childhood as a between-person predictor (multiple or persistent RPs, persistent RPs, multiple RPs tested in three separate models), salivary cortisol sampling time as a time-varying within-person predictor in models studying the average values, and additionally their interaction in models studying the slopes. We specified an unstructured (UN) covariance matrix and allowed random effects in the model to account for individual differences in the intercept and in the slope. Covariates were included in the models as fixed effects. We first considered participant age (Model 1), and then added participant BMI (Model 2), sex, weight and gestational age at birth and parental education (Model 3).

We then conducted generalized linear models (GLM) with Gaussian reference distribution to study whether participants with multiple or persistent RPs during early childhood differed in the individual diurnal salivary cortisol values, in the morning peak, in the diurnal nadir, or in the integrated cortisol measures, namely total diurnal cortisol output (time-weighted area under the curve with respect to ground, AUCg), total cortisol output in the waking period (awakening time-weighted area under the curve with respect to ground, morningAUCg) or cortisol awakening response (awakening time-weighted area under the curve with respect to increase/change, CAR, AUCi). Covariates were considered as in mixed model regressions.

As effect size, we present mean differences in standard deviation units and their 95% confidence intervals (95% CIs). All analyses were conducted with SAS version 9.4.

3. Results

Table 2 shows the characteristics of the study sample comparing participants who had multiple or persistent RPs in early childhood to those who did not. Those with early childhood multiple or persistent RPs did not differ from those who did not have RPs in early childhood in terms of age or BMI in young adulthood. Further, there were no significant differences between the two groups in the proportions of sex or parental education levels, as well as weight or gestational age at birth.

Fig. 1 shows the mean cortisol values in SD units per hour across all assessment points according to those who had early RPs (i.e., multiple or persistent RPs, persistent RPs, multiple RPs) and those who did not have any RPs in early childhood.

Table 2
Characteristics of the sample according to early childhood multiple or persistent regulatory problems (RPs).

	Early childhood multiple or persistent RPs		
	Yes (N = 61)	No (N = 247)	p
	N (%)/M (SD)	N (%)/M (SD)	
Sex (female), no. %	27 (44.3%)	134 (54.3%)	.16
Birth weight (grams)	3274.8 (747.5)	3347.1 (769.6)	.51
Gestational age (weeks)	38.4 (2.8)	38.4 (2.7)	.85
Age at assessment in adulthood (years)	24.8 (0.72)	24.8 (0.65)	.78
Body Mass Index in adulthood (kg/m^2)	24.03 (4.9)	24.0 (4.28)	.95
Highest education of either parent in childhood, no. %			
Upper secondary or less	23 (37.7%)	82 (33.2%)	.51
Lower tertiary	15 (24.6%)	81 (32.8%)	.21
Upper tertiary	22 (36.1%)	74 (30.0%)	.35
Cortisol (nmol/L), geometric means			
At awakening	9.69 (12.52)	8.04(6.61)	.15
15 min after awakening	11.04 (8.15)	9.76(6.05)	.17
30 min after awakening	12.95 (7.22)	11.88 (8.56)	.37
10:30 AM	4.81(3.29)	6.12(7.40)	.18
12:00 PM	3.75(2.59)	4.82(6.91)	.24
5:30 PM	2.89(2.21)	3.30(8.57)	.72
Bedtime	1.48(1.67)	1.97(7.13)	.60
Morning Peak	15.15 (13.06)	12.96 (8.57)	.11
Nadir	1.25 (1.18)	1.32 (3.05)	.86
Cortisol parameters (nmol/L)			
Total diurnal cortisol output (time-weighted area under the curve with respect to ground (diurnalAUCg))	63.70 (20.63)	60.65 (22.98)	.55
Total cortisol output in the waking period (awakening time-weighted area under the curve with respect to ground (morningAUCg))	6.10 (3.16)	5.02 (5.46)	.05
Cortisol awakening response (awakening time-weighted area under the curve with respect to increase/change (AUCi)	1.29 (1.96)	0.93 (1.57)	.14
Salivary sample collection time points (hh:mm)			
At awakening	7:19 (1:14)	7:22 (1:27)	.77
15 min after awakening	7:34 (1:14)	7:37 (1:27)	.76
30 min after awakening	7:50 (1:15)	7:53 (1:27)	.81
10:30 AM	10:39 (0:33)	12:15 (0:49)	.90
12:00 PM	12:20 (0:43)	12:15 (0:49)	.46
5:30 PM	17:50 (0:42)	17:45 (0:47)	.38
Bedtime	23:38 (1:06)	23:42 (1:33)	.71

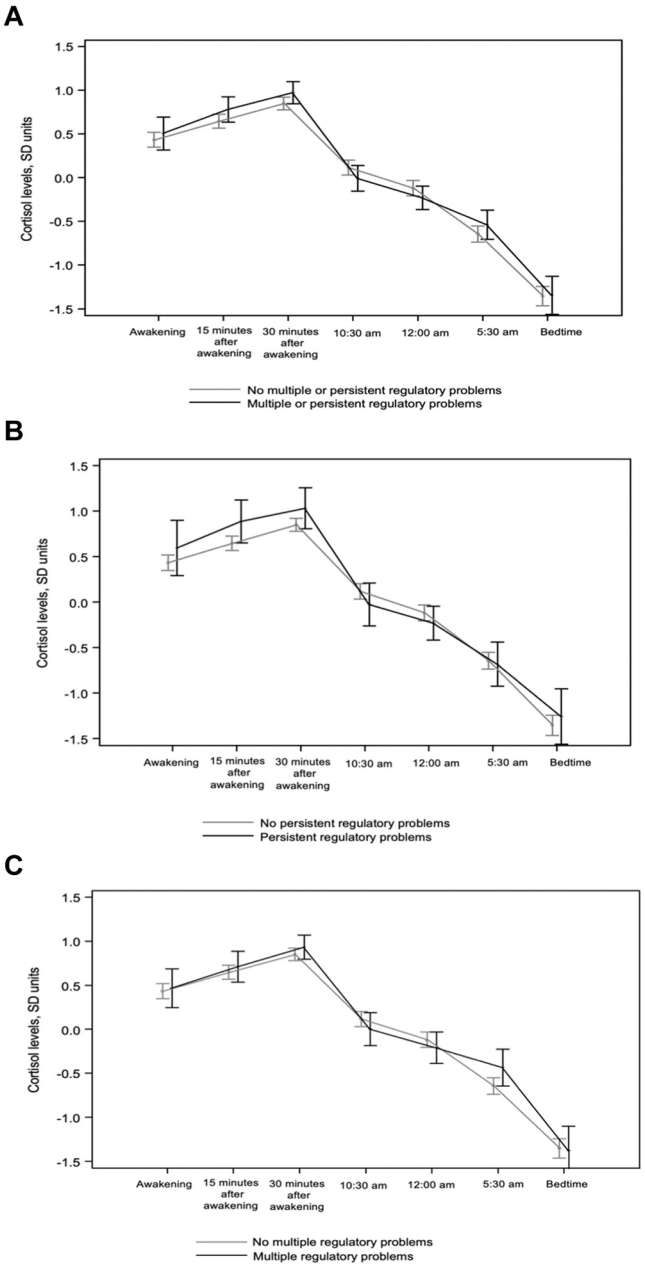

Fig. 1. Comparisons between adults who had and who did not have RPs in terms of the mean cortisol levels across the day **A**: Difference in diurnal cortisol slopes in standard deviation units per hour between adults with no multiple or persistent regulatory problems and multiple or persistent regulatory problems: from awakening to 30 min after awakening 0.13, (95% CI −0.36, 0.63), p = 0.59; from awakening to bedtime 0.00, (95% CI −0.02, 0.02), p = 0.79**B**: Difference in diurnal cortisol slopes in standard deviation units per hour between adults with no persistent regulatory problems and persistent regulatory problems: from awakening to 30 min after awakening − 0.01, (95% CI −0.69, 0.71), p = 0.98;from awakening to bedtime − 0.01, (95% CI −0.03, 0.01), p = 0.56 **C**: Difference in diurnal cortisol slopes in standard deviation units per hour between adults with no multiple regulatory problems and multiple regulatory problems: from awakening to 30 min after awakening 0.16, (95% CI −0.43, 0.75), p = 0.59; from awakening to bedtime 0.00, (95% CI −0.02, 0.02), p = 0.79.

3.1. Early childhood multiple or persistent RPs and diurnal and morning salivary cortisol slopes

Fig. 1 presents the findings of the mixed random coefficients regression models. There were no significant differences between adults who had early RPs (multiple or persistent RPs, multiple RPs, or persistent RPs) compared with those who never had RPs in cortisol slopes from awakening to bedtime, or across the three morning values.

3.2. Early multiple or persistent RPs and individual indices of diurnal salivary cortisol

Table 3 shows the findings of the GLMs. There were no significant differences between participants who had multiple or persistent RPs or multiple RPs compared with those who never had RPs in any of the studied individual cortisol indices (Table 3). However, those with persistent RPs had significantly higher levels of salivary cortisol morning peak compared with those who never had RPs (Table 3). Further, they also had significantly higher total cortisol output in the waking period and significantly higher cortisol awakening response compared with those who never had RPs. There were no other significant differences.

4. Discussion

To the best of our knowledge, this is the first study to investigate the

Table 3
Associations between early childhood regulatory problems and diurnal salivary cortisol parameters in young adulthood.

	Multiple or persistent RPs			Persistent RPs			Multiple RPs		
	B	95% CI	p	B	95% CI	p	B	95% CI	p
Cortisol at awakening									
Model 1	.11	(−.17;.38)	.45	.19	(−.20;.58)	.34	.06	(−.28;.39)	.74
Model 2	.11	(−.17;.39)	.45	.18	(−.21;.57)	.36	.05	(−.30;.37)	.78
Model 3	.15	(−.14;.43)	.31	.23	(−.17;.62)	.26	.06	(−.26;.40)	.71
Cortisol at 15 min after awakening									
Model 1	.22	(−.06;.50)	.12	.34	(−.07;.75)	.11	.13	(−.21;.47)	.44
Model 2	.22	(−.06;.50)	.13	.33	(−.09;.74)	.12	.13	(−.21;.48)	.45
Model 3	.26	(−.03;.55)	.08	.36	(−.07;.78)	.10	.16	(−.19;.51)	.37
Cortisol at 30 min after awakening									
Model 1	.24	(−.04;.51)	.09	.32	(−.09;.72)	.12	.14	(−.20;.47)	.42
Model 2	.23	(−.05;.51)	.10	.31	(−.10;.71)	.13	.13	(−.21;.47)	.45
Model 3	.27	(−.01;.56)	.06	.34	(−.08;.75)	.11	.17	(−.18;.51)	.34
Cortisol at 10:30 am									
Model 1	-.17	(−.43;.09)	.20	-.31	(−.68;.07)	.11	-.14	(−.46;.18)	.40
Model 2	-.16	(−.42;.10)	.23	-.31	(−.68;.07)	.11	-.11	(−.44; −22)	.51
Model 3	-.16	(−.43;.11)	.25	-.33	(−.72;.06)	.09	-.10	(−.43;.24)	.58
Cortisol at 12:00 PM									
Model 1	-.14	(−.42;.14)	.33	-.20	(−.60;.20)	.32	-.09	(−.44;.26)	.61
Model 2	-.12	(−.41;.16)	.39	-.19	(−.60;.21)	.34	-.07	(−.43;.29)	.69
Model 3	-.13	(−.42;.16)	.37	-.25	(−.67;.16)	.23	-.04	(−.41;.32)	.80
Cortisol at 5:30 pm									
Model 1	.17	(−.10;.43)	.22	-.08	(−.46;.30)	.68	.31	(−.02;.64)	.06
Model 2	.17	(−.10;.44)	.21	-.08	(−.46;.30)	.67	.33	(.00;.66)	.05
Model 3	.18	(−.09;.46)	.19	-.11	(−.50;.28)	.58	.35	(.01;.69)	.04
Bedtime cortisol									
Model 1	.02	(−.25;.30)	.87	.12	(−.27;.51)	.53	-.02	(−.35;.32)	.92
Model 2	.02	(−.26;.30)	.88	.12	(−.27;.52)	.53	-.01	(−.35;.33)	.94
Model 3	.07	(−.21;.34)	.63	.16	(−.24;.55)	.44	.03	(−.31;.38)	.84
Cortisol morning peak									
Model 1	.22	(−.06;.49)	.12	.43	(.03; 0.82)	.03	.03	(−.29;.35)	.84
Model 2	.22	(−.06;.49)	.13	.42	(.02; 0.82)	.04	.03	(−.30;.36)	.84
Model 3	.25	(−.03;.54)	.08	.43	(.02; 0.85)	.04	.07	(−.27;.41)	.69
Nadir cortisol									
Model 1	.07	(−.21;.35)	.63	.15	(−.25;.55)	.45	.01	(−.33;.36)	.93
Model 2	.06	(−.22;.35)	.65	.16	(−.24;.56)	.44	.01	(−.34;.36)	.96
Model 3	.11	(−.17;.39)	.44	.17	(−.23;.57)	.41	.06	(−.29;.41)	.73
Total diurnal cortisol output (time-weighted area under the curve with respect to ground (diurnalAUCg))									
Model 1	.12	(−.16;.42)	.41	.01	(−.42;.43)	.98	.18	(−.18;.55)	.32
Model 2	.13	(−.16;.43)	.38	.02	(−.41;.45)	.94	.20	(−.17;.57)	.29
Model 3	.15	(−.15;.45)	.33	-.02	(−.46;.43)	.94	.24	(−.14;.61)	.21
Total cortisol output in the waking period (awakening time-weighted area under the curve with respect to ground (morningAUCg))									
Model 1	.27	(−.01;.55)	.06	.48	(.08;.88)	.02	.10	(−.23;.44)	.55
Model 2	.27	(−.01;.55)	.06	.47	(.06;.87)	.02	.10	(−.24;.44)	.55
Model 3	.32	(.03;.61)	.03	.51	(.09;.93)	.02	.13	(−.21;.48)	.45
Cortisol awakening response (awakening time-weighted area under the curve with respect to increase/change (AUCi)									
Model 1	.15	(−.11;.41)	.26	.46	(.04;.88)	.03	-.04	(−.37;.30)	.85
Model 2	.14	(−.12;.41)	.28	.47	(.05;.89)	.03	-.04	(−.38;.30)	.82
Model 3	.15	(−.12;.42)	.28	.46	(.02;.90)	.04	-.03	(−.38;.32)	.88

RP: Regulatory Problems; B: unstandardized regression coefficient reflecting mean differences in standard deviation units between yes vs. no early childhood regulatory problems; CI: Confidence Intervals
Model 1: Adjusted for wake-up time, cortisol sampling time, age at salivary collection day
Model 2: Adjusted for wake-up time, cortisol sampling time, age at salivary collection day, BMI in young adulthood
Model 3: Adjusted for wake-up time, cortisol sampling time, age at salivary collection day, BMI in young adulthood, sex, parental education, gestational age, birth weight
Please note that B values reflect mean difference in SD units.

associations between early childhood multiple or persistent RPs and diurnal cortisol levels in young adulthood. In contrast to our expectations, there were no significant associations between multiple or persistent RPs and young adulthood salivary cortisol levels. However, when we investigated individuals who had persistent and multiple RPs separately, our findings revealed an association between persistent RPs in early childhood and higher morning cortisol values in young adulthood, namely higher peak and total cortisol output in the waking period, and higher cortisol awakening response.

The lack of association between multiple or persistent RPs in early childhood and cortisol level in young adulthood is in contrast to our expectations and the previous evidence showing an association between early multiple or persistent RPs in early childhood and later emotional and behavioural difficulties in young adulthood (Winsper et al., 2020; Jaekel et al., 2020; Wolke et al., 2023; Jaekel et al., 2023). However, the current findings indicate that persistent RPs in early childhood are associated with morning cortisol levels in young adulthood. This finding suggests that exposure to persistent RPs in early childhood may alter HPA axis activity in a way that it is more responsive to the awakening stress, which could explain how early RPs are linked with later emotional and behavioral problems (Winsper et al., 2020; Jaekel et al., 2020). Evidence from meta-analytical reviews suggest a link between elevated morning cortisol levels and general life stress and psychiatric disorders such as depression and anxiety (Adam et al., 2017; Boggero et al., 2017b; Chida and Steptoe, 2009). For example, a higher cortisol awakening response was observed among both participants with a current major depressive disorder diagnosis and remitted major depressive disorder diagnosis, as well as among those who have an anxiety disorder diagnosis (Vreeburg et al., 2009, 2010). Further, it was shown that elevated morning cortisol levels precede depression in adolescence (Zajkowska et al., 2022). Thus, persistent RPs might first influence cortisol levels during the morning, which could then increase the vulnerability of children to develop emotional and behavioral problems later on.

There could be several explanations for this finding. First, it is possible that persistent RPs in early childhood are indicators of chronic stress in early childhood (Skovgaard et al., 2007) or maternal stress during the fetal period (Bolten et al., 2013), which have been shown to have long-lasting influences on HPA axis dysregulation lasting into adulthood (McFarland and Hayward, 2014). The brain develops rapidly during infancy and toddlerhood and the experience of persistent stress during this period can influence the structural and functional development of the brain resulting in enduring influence on children's stress response (Gunnar and Quevedo, 2007). Relatedly, persistent RPs in infancy and toddlerhood could already be associated with alterations in HPA axis functioning in childhood. However, very little research has been done on this association in childhood with the existing studies mainly focusing on childhood sleep problems. In cross-sectional studies, it has been shown that there is an association between fragmented (Scher et al., 2010) and short sleep duration (Räikkönen et al., 2010) and higher awakening cortisol levels in children aged 12–36 months, and 8 years, respectively. However, longitudinal studies in infancy and mid-childhood have revealed mixed evidence regarding the link between sleep problems and alterations in HPA axis activity with one study showing an association between night-waking at 6 months of age and increased cortisol response at 12 months of age (Lucas-Thompson et al., 2009), while another study found no significant associations between sleep problems at 5 years of age and cortisol levels at 6 years of age (Hatzinger et al., 2013). These studies only assessed one symptom of RPs and had short follow-ups. Thus, further studies are required to investigate whether persistent RPs are associated with alterations in HPA axis functioning already in childhood.

Second, persistent RPs could be early characteristics that increase the risk for adverse outcomes in later life such as maladaptive coping skills, poor stress management and unhealthy lifestyles (e.g., smoking, alcohol consumption, reduced physical activity), which are associated with heightened cortisol concentrations in young adulthood (Shonkoff et al., 2012; De Weerth, 2018). Given the link between these outcomes and mental health problems (George et al., 2022), it is plausible that early persistent RPs are associated with these outcomes in young adulthood. However, this has never been investigated before and further research is needed to address this topic.

Third, it could be that persistent RPs reflect exposure to stressful environments such as overprotective or controlling parenting, which includes parenting behaviours that prevent children from engaging with the stimuli in their environment (Gunnar and Quevedo, 2007; Hutt et al., 2013). In addition to limiting children's ability to develop independent coping skills, there is suggestion that overprotective parenting could reflect parents' own stress levels which has an influence on the HPA axis functioning of their own children (Tu et al., 2007). In the context of early RPs, overprotective parenting may be contributing to the persistence of these problems (Samdan et al., 2020). For example, regarding sleeping problems, overprotective parenting may be reflected in immediate responding to infant's cry signals during the evening which might prevent the infant from developing skills to learn how to self-soothe, and thus contributing to the persistence of sleeping problems (Bilgin and Wolke, 2020b). This was investigated in one study focusing on the first 3 years of age which showed an association between higher morning cortisol levels and increased sleeping problems only for the group of toddlers who were exposed to overprotective parenting (Kiel et al., 2015). In addition, regarding feeding problems, it was shown that infants of mothers who were more controlling over feeding (i.e., pressure to eat) had food refusal more often than mothers who were not controlling (Fildes et al., 2015). Another explanation might be that persistent RPs could increase the likelihood of coercive parenting (Samdan et al., 2020; Smarius et al., 2017), which is associated with altered cortisol levels in children (van Bodegom et al., 2017). Thus, future studies are required to investigate whether overprotective or controlling or coercive parenting behaviours influence the long-lasting association between early persistent RPs and later cortisol levels.

The current study has several strengths, including the prospective design from infancy to adulthood, repeated measurement of early childhood RPs in infancy and toddlerhood and measurement of salivary cortisol across seven timepoints during one day. Furthermore, the assessment of RPs was made via both clinical parent interviews and neurological examinations. However, there are also limitations of the current study. First, RPs were not assessed via structured diaries. However, this was not feasible in this long-term prospective study due to the often-reported high attrition rates in diary studies. Thus, some aspects of our assessment of regulatory problems might reflect parental perception of regulatory problems. However, regulatory problems are commonly assessed using parental perception which has predictive validity given the link between parent-reported regulatory problems and later mental health problems in childhood and adulthood (Olsen et al., 2019; Wolke et al., 2023; Asmussen et al., 2023). Second, the definition of sleep problems in the current study was in line with previous research (St James-Roberts et al., 2015), however it is important to note the large variation in infant sleep patterns during the early years (Paavonen et al., 2020) which may had an influence on our findings. Third, the saliva sampling was performed during one day which does not allow to account for the role of change in cortisol levels across different days (Clow et al., 2010). Our findings may thus reflect the influence of state-related (situational) factors such as the demands of saliva collection and whether the collection was made during a weekday or a weekend (Stalder et al., 2022). However, it has been shown that more days of saliva collection does not appear to increase the size of association between diurnal cortisol slopes and health outcomes (Adam et al., 2017; Adam, 2006). Fourth, our sample included some participants who were admitted to a neonatal ward or NICU. However, the severity of reasons for hospitalization in Finland in mid-1980 s was lower than reasons for hospitalization nowadays. The majority of the admitted infants had no diagnosed illness and were on the ward for observation or they were

admitted because of common problems of neonatal adaptation (Heinonen et al., 2008b). Although the participants included in the current study did not differ from those lost to follow-up in terms of birth weight and gestational age, it may still influence the generalizability of the findings to all children born at term. Fifth, it is important to note that we cannot rule out the possible influence of unmeasured confounder variables such as unmeasured familial factors. Finally, it is important to note that the findings of the current study are correlational in nature precluding causal inferences.

4.1. Conclusions

To conclude, the current study showed that children who experience persistent RPs in early childhood show HPA axis hyperactivity in response to awakening stress over two decades later, which might be one physiological mechanism linking early childhood RPs to adult behavioral outcomes.

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CRediT authorship contribution statement

Drs Ayten Bilgin, Polina Girchenko, Katri Räikkönen, and Kati Heinonen had access to all the data and are responsible for the data, for accuracy of the data analysis, and for conducting the research. Drs Ayten Bilgin and Polina Girchenko analyzed and interpreted the data. Dr Ayten Bilgin drafted the initial manuscript, and revised the manuscript. Drs Kati Heinonen, Eero Kajantie, Dieter Wolke, and Katri Räikkönen contributed to study concept and design, acquisition of data, interpretation of data, and drafting and revising the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

Drs. Ayten Bilgin, Kati Heinonen, Polina Girchenko, Eero Kajantie, Dieter Wolke, and Katri Räikkönen have no conflict of interests to declare.

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