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REGULAR ARTICLE

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Self-reported mental health and cortisol activity at 27-28 years of age in individuals born with very low birthweight

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Abstract

Aim: To assess mental health outcomes of very low birthweight (VLBW, <1500 g) subjects to adulthood and to examine salivary cortisol and hair cortisol levels and their relation to birth characteristics and mental health.

Methods: A Swedish regional cohort of 56 VLBW subjects and 55 full-term controls were assessed at the ages 27-28 with adult self-reported scales and the mean of 2 days diurnal salivary cortisol and hair cortisol. The cohorts had been assessed at 15 years of age with youth self-reported scales.

Results: There were no differences between the groups in youth self-reported scales and adult self-reported scores. The 24 participating VLBW girls scored lower on youth self-reported scales externalising and total problem scores than the control girls. In adulthood, the 21 participating VLBW women had significantly higher morning concentrations of salivary cortisol than control women, $P = .014$. No significant associations were found between cortisol concentrations and adult self-reported scales internalising, externalising and total scores.

Conclusion: Self-reported mental health in VLBW subjects was comparable with normal birthweight controls indicating a satisfying transition from adolescence to adulthood. VLBW females had higher morning salivary cortisol concentrations, suggesting a gender difference. We found no correlations between cortisol and mental health.

KEYWORDS

adults, cortisol, longitudinal, low birthweight, mental health

1 | INTRODUCTION

It is known that adolescents and young adults born preterm at very low birthweight (VLBW), that is, a birthweight <1500 g, or extremely low birthweight (ELBW) defined as birthweight <1000 g are at increased risk of poorer general health, cognitive impairments, attention deficit hyperactive disorder and internalising problems.[1-3] Preterm birth and intrauterine growth restriction are specifically associated with psychiatric morbidity in adolescence and young adulthood.[4-6]

Preterm birth and being born with VLBW imply a neonatal period with daily invasive and stressful medical procedures at a time

Abbreviations: VLBW, very low birthweight; ELBW, extremely low birthweight; SGA, small for gestational age; HPA axis, hypothalamic-pituitary-adrenal axis; AGA, appropriate for gestational age.

of rapid and vulnerable brain development.[7] A functioning hypothalamic-pituitary-adrenal (HPA) axis activity is already present in the human foetus from the second trimester. It is plausible that the plasticity of the infant brain is even more vulnerable to the exposure to illness and the environment in neonatal intensive care. Neonatal pain-related stress in very preterm infants is associated with altered brain cortical thickness at school age[8] and has been shown to contribute to slower growth of thalamus associated with poorer cognitive and motor outcome at 3 years of age.[9] An association has been found between neonatal pain-related stress and hair cortisol in preterm boys at school age, suggesting the early programming effect downregulating the HPA axis response to psychosocial stress in preterm children several years after prenatal and postnatal stressors had been terminated.[10] It is possible that an altered HPA axis activity programmed by unfavourable foetal life conditions is a key factor mediating associations with mental symptoms later in life.[11] However, the picture of early life stress and later HPA activity is complicated and results showing both increased and decreased levels have been reported. Children with increased cortisol levels had more behavioural problems at 2-5 years of age, based on maternal reports, than children with decreased levels following a stressor.[12] A regional study of children at 7 and 9 years of age who were born with a VLBW found a downregulated HPA function without significant associations with behavioural problems.[13]

We have previously reported a long-term follow-up study of the same cohort of VLBW children and controls regarding the morbidity, neurodevelopmental outcome, health, academic achievement and social functioning from birth to 20 years of age.[14,15] In mental health at 15 years of age, we found that the VLBW girls reported less externalising and total problems than their controls.[14] Little is known of mental health into adulthood, especially associations between subjective mental health and neuroendocrine function of VLBW individuals. The primary aim was to investigate the association between very low birthweight and self-reported mental health at 27-28 years of age in comparison with matched controls and with results at 15 years of age. The secondary aim was to assess stress hormone cortisol levels in relation to birth characteristics as well as self-perceived mental health.

Key notes

- Adolescents and adults of very low birthweight (VLBW, <1500 g) are known to be at increased risks of mental health problems, but it is not known about possible links to neuroendocrine functioning.
- Self-reported mental health assessments and cortisol levels did not differ in adulthood at age 27-28 between the VLBW individuals and their controls.
- The cortisol levels showed no significant associations with mental health problems.

2 | MATERIAL AND METHODS

2.1 | Study populations

The VLBW participants were born in the Southeast region of Sweden between February 1, 1987 and April 30, 1988. All pregnancies were dated by early ultrasound examinations. An infant was classified as small for gestational age (SGA) if the birthweight was ≤2 SD from the mean according to the Swedish standard based on sex and gestational age. Antenatal steroids were given to 21% of the mothers. The majority of the regional birth cohort (63/107) were born at the University Hospital in Linköping, and nine infants were transferred to the hospital after birth. The other infants were cared for in neonatal units at the other hospitals in the region. Surfactant treatment was not in use at that time.

The original cohort of VLBW children included 107 children to 97 mothers and represented 1% of the total births during this period. A total of 86 (80%) children survived the neonatal period (47 boys and 39 girls) and were recruited to the follow-up studies at 4, 9, 12, 15 and 20 years of age. One child with Down syndrome was excluded at follow-up, and one child had emigrated.

For each VLBW child who survived the first 2 days, a control child of the same sex and parity of the mother was selected. The control child was born at term, without malformations and born at the hospital where the VLBW infant was born, or would have been born if the mother had not been referred before birth, and next in order of the VLBW child. In the final control group, 45 boys and 41 girls were included.

A total of 56/84 (67%) VLBW and 55/86 (64%) controls participated in the present follow-up study at 27-28 years of age. There were 38 (68%) VLBW individuals born SGA (VLBW and SGA), and 18 (32%) categorised as appropriate for gestational age (VLBW and AGA, birthweight > −2 SD from the mean and gestational age). In the study population, seven VLBW cases had neurosensory impairments vs one control, see Table 1.

There were no statistically significant differences between participating and non-participating VLBW individuals in the variables birthweight, gestational age, sex, ELBW and mechanical ventilation (data not shown). Among the 28 non-participants, 18 (64%) were classified as SGA.

2.2 | Data collection

Information about the study and a consent form was sent by postal mail in 2014 and 2015 to VLBW and control individuals of the original birth cohort. Those who agreed to participate in the present study were sent questionnaires to be answered at home and asked to visit either one of two hospitals in the catchment area in order to have hair samples taken. Non-responders were reminded twice. Neurological diagnoses were collected from the child habilitation centres at the 15-year follow-up.

TABLE 1 Socio-demographic background and diagnoses of the study cohort

	VLBW n = 56 n (%)	Controls n = 55 n (%)	*P*-value
Perinatal data			
Maternal age at birth			
Median/(min-max)	28.0 (16.0-40.0)	27.0 (19.0-37.0)	.596
Maternal level of education at birth			
Primary school	21 (42.0)	12 (24.5)	.140
Secondary school	19 (38.0)	21 (42.9)	
College/University	10 (20.0)	16 (32.7)	
Paternal level of education at birth			
Primary school	20 (44.4)	12 (24.5)	.132
Secondary school	15 (33.3)	18 (38.3)	
College/University	10 (22.2)	17 (36.2)	
Birthweight			
Median/ Interquartile range	1185 (685-1500)	3550 (2230-4860)	<.001
Gestational age			
Days, median (min-max)	217 (179-263)	282 (258-297)	<.001
Weeks, median (min-max)	31 (25-37)	40 (36-42)	<.001
Extremely low birthweight			
Yes	9 (16.1)	-	
No	47 (83.9)	-	
Small for gestational age			
Yes	38 (67.9)	0	<.001
No	18 (32.1)	55	
Apgar score, 5 min			
Median/ Interquartile range	9 (4-10)	10 (9-10)	<.001
7>	43 (79.6)	48 (100.0)	<.001
≤7	11 (20.4)	0 (0.0)	
Neonatal data			
Mechanical ventilation[a]			
Yes	24 (42.9)	-	
No	32 (57.1)	-	
Bronchopulmonary dysplasia[b]			
Yes	3 (5.4)	-	
No	53 (94.6)	-	
Intraventricular haemorrhage[c]			
Yes	8[e](14.3)	-	
No	48 (85.7)	-	
Sepsis[d]			
Yes	5 (8.9)	-	
No	51 (91.1)	-	
Data from 15 y of age			
Cerebral palsy[e]			
Yes	4 (7.7)	0 (0.0)	.118
No	52 (92.3)	55 (100.0)	
ADHD[e]			
Yes	1 (1.8)	1 (1.8)	1.000
No	55 (98.2)	54 (98.2)	
IQ[f]			
Median (min-max)	87 (51-123)	99.0 (65-129)	<.001
Cerebral MRI abnormality[g]			
Yes	14 (30.0)	-	
No	32 (70)	-	

[a]>24 h.
[b]Based on clinical and radiographic findings.
[c]Cranial ultrasonography: d 1-3, d 6-10 and at discharge.
[d]Based on clinical symptoms and positive blood culture.
[e]Based on diagnoses from child habilitation centres.
[f]IQ < 70:2 VLBW subjects, 1 control.
[g]White matter damage.

Saliva samples were collected at home in a calm environment during a weekend after the subjects had been thoroughly informed by a specially trained nurse about the sampling procedure at a visit to the hospital. Saliva samples were collected three times a day, morning, mid-day and evening, on two consecutive days. The samples were sent back to the hospital by mail. A commercial salivette tube containing a cotton swab was used to collect the saliva. Hair samples were obtained by a nurse at the hospital visit.

2.3 | Study-specific questionnaire

In order to get socio-economic background data, a study-specific questionnaire consisting of 28 questions for the men and 31 for the women was used. Information was collected about lifestyle factors, including marital status, education, employment, family, health, use of tobacco and alcohol and medical data.

2.4 | Youth self-report and adult self-report

The Youth Self-Report[16] was used for adolescents at 15 years of age, and the corresponding instrument Adult Self-Report[17] was used at 27-28 years of age. Both were standardised for a Swedish population. A high problem score indicates more emotional and behavioural problems. The Adult self-report questionnaire for ages 18-59 consists of 126 items that are self-rated with the following options: 'not true', 'somewhat or sometimes true' and 'very true or often true'.

The instrument was developed by Achenbach System of Empirically Based Assessment, and it provides scores from adaptive functioning scales; friends, spouse or partner, family, work, education and personal strengths. A total problem score reflects overall psychosocial adjustment and is thus the sum of all problem scales. In addition to the total problem scores, scores on the subscale internalising, which is based on the syndrome scales anxious or depressed behaviour, withdrawn behaviour and somatic complaints, and the subscale externalising, which is based on the syndrome scales aggressive behaviour, rule-breaking behaviour and intrusive behaviour. However, the present study only uses the total problem score and the scores of the two subscales internalising and externalising. The internalising, externalising and total scale scores were divided at the 90th percentile to identify individuals at elevated risk for clinical disorder[1] and in comparisons with cortisol levels.

2.5 | Cortisol

The mean salivary cortisol for each sampling time for the 2 days was calculated for each individual and was analysed using a cortisol enzyme immunoassay kit #1-3002 from Salimetrics (Salimetrics LLC.), according to the instructions of the manufacturer. All samples were stored frozen until assayed.

Concentrations of cortisol in saliva and in hair both reflect the activity of the HPA axis, but in a different time scale. The concentrations of cortisol in saliva reflect the concentrations at the moment, but the concentrations of cortisol in hair extracts reflect the average activity during recent months. Hair was obtained from the posterior vertex area of the participants' heads in accordance with guidelines published by the Society of Hair Testing.[18] Hair samples were stored at room temperature until weighing, extraction and analysis. Each sample of between 5 and 10 mg was put into a 2-mL QiaGenRB sample tube (Qiagen Inc) with a 0.5-mm QiaGen stainless steel bead (Qiagen Inc). The samples were weighed on a Sartorius MC 210p microscale (Sartorius Corp.) and homogenised using a Retsch Tissue Lyser II, 20 HZ, (Retsch Gmbh.). The sample tubes were placed in aluminium cylinders and frozen in liquid nitrogen for 2 minutes. The hair samples were homogenised for 2 minutes, producing fine hair powder which was extracted in 1 mL of methanol for 24 hours on a moving board to keep the steel pellets in constant soft motion within the tubes. Then 0.8 mL of the methanol supernatant was pipetted off and lyophilised using a Savant Speed Vac Plus SC210A (Thermo Fisher Scientific Inc). The samples were dissolved in radioimmunoassay buffer before radioimmunoassay.

Cortisol was analysed using rabbit antiserum MBS535414 (MyBioSource Inc) using ^{125}I- labelled and reverse-phase HPLC-purified cortisol 3-CMO-Histamine as radioligand (MyBioSource Inc). Taking the binding of cortisol as 100%, the antiserum cross-reacts 36.8% with prednisolone, 5.1% with 11-deoxycortisol, 3.3% with corticosterone and <0.7% with cortisone hair samples. Between three and 10 mg were required to maintain a total inter-assay coefficient of variation below 8% for hair extraction and measurement of cortisol. The intra-assay coefficient of variation for the radioimmunoassay itself was 7% at 10 nmol/L.

2.6 | Ethics

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was received from the regional ethical review board, Linköping, Sweden, No 2013/394-31. Informed written consent was received from all participants.

2.7 | Statistics

The statistical analyses were performed using the Statistical Package for the Social Sciences version 24 (IBM Inc). Non-parametric tests were suitable due to the skewed distribution of results. Pearson's chi-square test was used to analyse differences between the VLBW group and the control group. Fisher's exact test was, however, used in those cases where cell counts were below five. Hormone concentrations are presented as median, minimum and maximum values. Continuous variables were evaluated using Mann-Whitney's *U* test, and this includes evaluation of the hormone levels on several different group levels, including gender, VLBW and controls, and size for gestational age. Wilcoxon's signed-rank test was used to test for differences between the Youth Self-Report and Adult Self-Report questionnaires. Statistical significance was set as a *P* value below .05. Stratified analyses for men and women were carried out separately. A median split was used to make high and low cortisol groups.

3 | RESULTS

3.1 | Group characteristics

Parental background information regarding educational level and maternal age at birth is presented in Table 1, together with information on birth data, neonatal care and complications. As expected, perinatal differences were found between the groups for birthweight, gestational age, Apgar score at 5 minutes and being born SGA.

The results of socio-demographic self-reported data at 27-28 years of age in educational level, alcohol and tobacco use, the subjective general health and medical prescription are presented in Table 2. More individuals in the VLBW group, especially those who were born SGA, were unemployed or studied than in the control group, while other background facts did not differ significantly between the groups.

Among the participants, two VLBW children and two controls were diagnosed with ADHD, while 10 VLBW children and 10 controls were diagnosed with allergy, and 11 VLBW children and three

TABLE 2 Social data and subjective health data at 27-28 y of age in VLBW (n = 56) and control groups (n = 55) and according to gender for VLBW/AGA and VLBW/SGA subgroups

	VLBW	Controls	VLBW		Controls		VLBW/ AGA	VLBW/ SGA					
	(n = 56) n (%)	(n = 55) n (%)	Female (n = 27) n (%)	Male (n = 29) n (%)	Female (n = 32) n (%)	Male (n = 23) n (%)	(n = 18) n (%)	(n = 38) n (%)	*P*-value[a,*]	*P*-value[b]	*P*-value[c]	*P*-value[d,*]	*P*-value[e,*]
Gender													
Female	27 (48.2)	32 (58.2)					7 (38.9)	20 (52.7)	.293	.142	.600	-	-
Male	29 (51.8)	23 (41.8)					11 (61.1)	18 (47.4)					
Occupation													
Other[f]	32 (57.1)	21 (38.2)	14 (51.9)	18 (62.1)	11 (34.4)	10 (43.5)	8 (44.4)	24 (63.2)	.118	.864	.036	.279	.099
College/University required employment	13 (23.2)	16 (29.1)	5 (18.5)	8 (27.6)	11 (34.4)	5 (21.7)	4 (22.2)	9 (23.7)					
Employment with no university claim	11 (19.6)	18 (32.7)	8 (29.6)	3 (10.3)	10 (31.3)	8 (34.8)	6 (33.3)	5 (13.2)					
Education													
Primary school	4 (7.1)	3 (5.6)	1 (3.7)	3 (10.3)	3 (9.7)	0 (0.0)	0 (0.0)	4 (10.5)	.111	.191	.131	.168	.130
Secondary school	34 (60.7)	23 (42.6)	17 (63.0)	17 (58.6)	12 (18.7)	11 (47.8)	12 (66.7)	22 (57.9)					
College/University	18 (32.1)	28 (51.9)	9 (33.3)	9 (31.0)	16 (51.6)	12 (52.2)	6 (33.3)	12 (31.6)					
Marital status													
Married/cohabiting	31 (55.4)	34 (61.8)	17 (63.0)	14 (48.3)	25 (78.1)	9 (39.1)	9 (50.0)	22 (57.9)	.490	.782	.704	.254	.581
Single	25 (44.6)	21 (38.2)	10 (37.0)	15 (51.7)	7 (21.9)	14 (60.9)	9 (50.0)	16 (42.1)					
Tobacco													
No	34 (63.0)	37 (67.3)	18 (69.2)	16 (57.1)	22 (68.8)	15 (65.2)	13 (76.5)	21 (56.8)	.662	.769	.568	.533	.698
Cigarettes	9 (16.7)	7 (12.7)	5 (19.2)	4 (14.3)	6 (18.8)	1 (4.3)	1 (5.9)	8 (21.6)					
Snus[g]	10 (18.5)	8 (14.5)	3 (11.5)	7 (25.0)	2 (6.3)	6 (26.1)	3 (17.6)	7 (18.9)					
Both	1 (1.9)	3 (5.5)	0 (0.0)	1 (3.6)	2 (6.3)	1 (4.3)	0 (0.0)	1 (2.7)					
Alcohol													
Never	6 (11.1)	6 (10.9)	5 (19.2)	1 (3.6)	4 (12.5)	2 (8.7)	2 (11.8)	4 (10.8)	.883	.889	.930	.480	.739
1-2 times per week	22 (40.7)	20 (36.4)	12 (46.2)	10 (35.7)	12 (37.5)	8 (34.8)	7 (41.2)	15 (40.5)					
2+ times per week	26 (48.1)	29 (52.7)	9 (34.6)	17 (60.7)	16 (50.0)	13 (56.5)	8 (47.1)	18 (48.6)					
Prescribed medication													
Yes	42 (75.0)	39 (70.9)	19 (70.4)	23 (79.3)	20 (62.5)	19 (82.6)	14 (77.8)	28 (73.7)	.628	.657	.769	.589	1.000
No	14 (25.0)	16 (29.1)	8 (29.6)	6 (20.7)	12 (37.5)	4 (17.4)	4 (22.2)	10 (26.3)					

(Continues)

TABLE 2 (Continued)

	VLBW (n = 56) n (%)	Controls (n = 55) n (%)	VLBW Female (n = 27) n (%)	VLBW Male (n = 29) n (%)	Controls Female (n = 32) n (%)	Controls Male (n = 23) n (%)	VLBW/AGA (n = 18) n (%)	VLBW/SGA (n = 38) n (%)	P-value[a,*]	P-value[b]	P-value[c]	P-value[d,*]	P-value[g,*]
Good health													
Yes	51 (92.7)	48 (88.9)	25 (92.6)	26 (92.9)	27 (87.1)	21 (91.3)	17 (100.0)	34 (89.5)	.488	.234	.868	.675	1.000
No	4 (7.3)	6 (11.1)	2 (7.4)	2 (7.1)	4 (12.9)	2 (8.7)	0 (0.0)	4 (10.5)					

[a]VLBW vs controls.
[b]VLBW/AGA vs controls.
[c]VLBW/SGA vs controls.
[d]Female VLBW vs female controls.
[e]Male VLBW vs male controls.
[f]Unemployed, studying, parental leave, sick-leave.
[g]wet tobacco usually placed under the lip.
*Pearson's chi-square statistics if cell counts are above 5, otherwise Fisher's exact test has been used.

controls were diagnosed with asthma. Furthermore, two VLBW and five controls were diagnosed with depression, one VLBW and three controls with social phobia, and one VLBW and seven controls with panic disorder.

Among the controls only, two participants were diagnosed with bipolar disease, four with anxiety, one with cardiac arrhythmia and one with obsessive-compulsive disorder. Among the VLBW children, one participant was diagnosed with epilepsy.

3.2 | Mental health according to youth self-report and adult self-report measures

The results of the Youth Self-Report and Adult Self-Report scores are shown for VLBW and control groups in Table 3. There were no significant differences between VLBW and control groups at both ages. Subgroup analyses showed that VLBW females demonstrated significantly lower externalising scores (P = .017) and lower total scores (P = .036) than the control females at 15 years of age, but there were no significant differences at 27-28 years of age. VLBW females demonstrated significantly higher internalising scores than VLBW males at both 15 years of age (P = .027) and at 27-28 years of age (P = .012). VLBW/AGA adolescents had significantly lower internalising scores (P = .049), lower externalising scores (P = .027) and lower total scores (P = .020) than control adolescents, and no significant differences were found in adulthood.

3.3 | Cortisol values

Salivary cortisol levels across the day had a decline, reflecting the known diurnal rhythm in cortisol excretion. Results of mean salivary cortisol and hair cortisol values in groups and subgroups are shown in Table 4. VLBW women had significantly higher values in morning saliva cortisol than control women (P = .014). In the VLBW group, women born SGA (n = 16) showed significantly higher morning values than control women (n = 24), 23.0 nmol/L, min-max 6.3-86.2 vs 9.9 nmol/L, min-max 3.7-40.0 (P = .029). Hair cortisol did not differ between the VLBW and control groups or between the subgroups and controls.

Categorising each cortisol measurement into high and low using the median value for each measurement and analysing the distribution across the three Adult Self-Report scales (internalising, externalising and total score), no statistical differences were detected (Tables S1 and S2) between those scoring ≤90 and >90 percentile in the combined group of VLBW and control adults. Since these analyses are associated with a low statistical power, additional analyses where the three Adult Self-Report scales were treated as continuous variables were performed. These analyses did not alter the findings presented in Tables S1 and S2. The individuals with high points in respective scale (>90th percentile) were few, so further stratifying of the data according to gender or AGA and SGA could not be done.

4 | DISCUSSION

There are few longitudinal studies of mental health in young people with low birthweight when they have entered adult life. Our VLBW group had similar background characteristics as the controls regarding educational level, substance use and being married or cohabitating, similarities also found by others.[19,20] Individuals in the VLBW group, especially those born SGA, were more often unemployed or were studying, as has been shown in other studies of participants assessed at young adulthood.[21,22] In general, the differences in outcomes between different preterm or low birthweight cohorts are probably related to differences in background factors such as birth characteristics, national school systems or socio-economic conditions. The ADHD diagnosis did not differ between the groups, which is consistent with Boyle et al[1] Notably, two additional individuals, one in each group compared with the 15-year study, were diagnosed with ADHD, probably because over time it has become easier to get the diagnosis.

At the group level, we found similar internalising and externalising behaviours among the VLBW and control groups. These findings are consistent with our previous report at the age of 20 of self-perceived mental health.[15] At the age of 15, the girls in the VLBW group reported fewer externalising and total problems than the control girls, results which we published earlier[14] and also others have reported.[2,23] There were no differences between the VLBW females and their controls in adulthood, which could indicate a normalisation of the behaviour of the VLBW women from a more passive-acting behaviour in adolescence. We found gender differences within the VLBW group at both examinations in the internalising scale with higher problem scores in females. Thus, the differences between the sexes in the VLBW group persisted to adulthood, which is to be observed and need to be explored further.

Our outcomes in Adult Self-Report differ from a recently published meta-analysis of pooled data of six study cohorts from five countries, which described a higher risk of internalising problems and lower risk of externalising problems in both sexes in adult VLBW individuals.[24] The proportion of ELBW participants was 39% and the age of participants 19-26 years, which differs from our study. A high proportion of ELBW individuals means increased risk of complications and diseases in the perinatal period and the risk of poorer physical and mental health at follow-up.[15] Behavioural studies of children using parental or teacher reports have found an increasing risk of problems in VLBW children, results directly correlated with their degree of immaturity at birth.[25,26]

Increasing risks of mental problems assessed by psychiatric interviews and diagnoses were found at 14 and 20 years of age in preterm VLBW and term SGA individuals with an unexpected increase between time points of term SGA individuals.[6] However, the results in the present study demonstrated decreasing or unaltered self-reported mental and behavioural problems between adolescence and adulthood. This is in agreement with the results in studies of health-related quality of life.[27] Thus, the trajectory of self-reported mental health problems and the health-related quality of life findings gave corresponding results from adolescence to young adulthood. Brain maturation or favourable social factors might explain the results. VLBW subjects in the present study were comparable to the controls in major family and socio-economic factors. Resiliency factors are likely to contribute towards a neutralisation of unfavourable biological factors associated with preterm birth.[28] In addition, a study published in 2018 has shown that grey matter alterations between adolescence and adulthood were suggested to be related to a maturation of the brain.[29] This could also support studies that have shown diminishing mental health problems from adolescence.

The activity in the HPA axis allows the individual to handle stress in such a way that it can maintain the physical and mental balance. Only a few studies have studied the long-term effects of preterm birth on cortisol profiles, although a modified HPA axis function due to preterm birth is likely to influence future health. We found that VLBW women, especially those born SGA, had higher morning salivary cortisol concentrations than control females but there were no differences in the hair measurements. It is conceivable that persons in the VLBW group can have higher concentrations of cortisol in saliva in the morning than the control group, whereas their concentrations of cortisol in extracts of hair are not different, since it reflects the average concentrations over day and night and a long period of time.

The association between SGA and salivary cortisol is interesting and demonstrates a higher reactivity in the HPA system, but the findings should be interpreted with caution. The analyses in the current study were carried out in a pooled sample of both preterm and term individuals and may have diluted the association. Thus, it would have been interesting to analyse the association between prematurity and salivary cortisol levels separately. However, separating the VLBW group into preterm/term would produce very small groups and thus very unprecise estimates.

We found no significant associations between cortisol levels and behaviours. A few earlier studies have reported a moderating effect of neuroendocrine responses on the behaviour among individuals born premature. Bagner et al[12] found a correlation between cortisol reactivity and internalised behaviour and attention problems in premature children 18-60 months old. Waxman et al[30] studied neuroendocrine regulation by salivary cortisol measurements and internalising problems in surviving ELBW individuals born 1977-1982 in Canada at 30-35 years of age and found that higher afternoon values were correlated with internalising-related behaviours. The authors suggested that different patterns of regulation of the neuroendocrine system in ELBW individuals might affect the development of psychopathology and contributed to the higher levels of anxiety and depressive symptoms seen in adulthood. It is conceivable that early dysregulation in the HPA axis may have long-lasting effects on the neurodevelopment and behaviour in VLBW individuals with different vulnerability, for example, being born after intrauterine growth disorder. However, no such associations were found in our present study.

As in many other longitudinal studies, there were a moderate number of participants in the study. We could not rule out that some

TABLE 3 Behavioural and emotional problem scores in YSR at 15 y of age and ASR at 27-28 y of age in VLBW and control groups, gender in the respective groups, VLBW/AGA and VLBW/SGA subgroups. Data are limited to those who participated at the 27-28 y follow-up

			VLBW		Controls								
	VLBW n = 46-52	Controls n = 39-51	Female n = 24-25	Male n = 22-27	Female n = 20-31	Male n = 19-20	VLBW/AGA n = 16-17	VLBW/SGA n = 30-35	*P*-value[a]	*P*-value[b]	*P*-value[c]	*P*-value[d]	*P*-value[e]
YSR, 15 y													
Internalising													
Median (min-max)	5 (0-25)	7 (0-36)	6.5 (0-25)[f]	4 (0-22)	9 (2-36)	4 (0-13)	3.5 (0-25)	6 (0-22)	.807	.202	.627	**.049**	.693
Externalising													
Median (min-max)	9 (1-28)	10 (1-32)	10 (2-19)	8.5 (1-28)	13 (4-32)	6 (1-26)	6.5 (1-19)	11 (3-28)	.084	**.017**	.763	**.027**	.593
Total score													
Median (min-max)	18.5 (1-68)	24 (3-82)	21.5 (5-50)	17 (1-68)	32.5 (8-82)	14 (3-53)	14.5 (1-50)	20.5 (5-68)	.084	**.036**	.834	**.020**	.577
ASR, 27-28 y													
Internalising													
Median (min-max)	8 (0-33)	9 (0-45)	12 (1-33)[g]	5 (0-24)	9 (0-45)	9 (0-30)	8 (0-24)	10 (0-33)	.721	.692	.511	.573	.898
Externalising													
Median (min-max)	5.5 (0-38)	6 (1-32)	4 (0-29)	6 (1-38)	7.5 (1-31)	5 (1-32)	4 (1-22)	6 (0-38)	.452	.129	.603	.352	.691
Total score													
Median (min-max)	28.5 (5-80)	26.5 (3-131)	39 (6-80)	25 (5-76)	30.5 (3-131)	26 (5-98)	29 (7-80)	28 (5-76)	.997	.739	.906	.917	.948

P-values <.05 are in bold.

[a]VLBW vs controls.

[b]Female VLBW vs female controls.

[c]Male VLBW vs male controls.

[d]VLBW/AGA vs controls.

[e]VLBW/SGA vs controls.

[f]Female VLBW vs male VLBW, *P* = .027.

[g]Female VLBW vs male VLBW, *P* = .012.

TABLE 4 Saliva cortisol and hair cortisol among VLBW and control groups, gender in the respective groups and VLBW/AGA and VLBW/SGA subgroups cont'd, *P*-values pertaining to group comparisons in given below

	Group		VLBW		Controls			
	VLBW	Control	Female	Male	Female	Male	VLBW/AGA	VLBW/SGA
Saliva cortisol[a]	n = 48	n = 39	n = 21	n = 27	n = 24	n = 15	n = 18	n = 30
Morning, median (min-max)	10.7 (4.0-93.6)	10.2 (3.7-65.2)	22.2 (6.3-86.2)	9.2 (4.0-93.6)	9.9 (3.7-7.8)	10.4 (5.6-65.2)	12.8 (4.0-93.6)	10.0 (4.5-88.9)
Afternoon, median (min-max)	4.7 (0.6-147.8)	5.4 (1.4-74.6)	4.0 (1.7-147.8)	5.4 (0.6-117.0)	5.4 (1.4-61.8)	5.4 (1.6-74.6)	4.5 (1.3-117.0)	5.4 (1.5-147.8)
Evening, median (min-max)	2.6 (0.5-20.8)	2.4 (0.6-174.8)	2.8 (0.7-20.8)	2.5 (0.5-20.6)	2.2 (0.6-174.8)	2.4 (0.6-16.9)	4.4 (0.8-20.0)	2.2 (0.5-20.8)
Hair cortisol	n = 39	n = 32	n = 22	n = 17	n = 22	n = 10	n = 13	n = 26
Nmol/L, median (min-max)	0.3 (0.2-3.8)	0.3 (0.2-26.6)	0.3 (0.2-1.0)	0.4 (0.2-3.8)	0.3 (0.2-26.6)	0.3 (0.2-0.7)	0.6 (0.2-1.0)	0.3 (0.2-3.8)
Pmol/g, median (min-max)	27.6 (16.0-326.8)	25.8 (14.8-91.9)	24.7 (16.0-85.2)	31.3 (17.3-325.8)	25.3 (14.8-91.9)	27.9 (17.8-60.2)	30.9 (16.2-85.2)	25.3 (16.0-325.8)
Pg/mg, median (min-max)	10.0 (5.8-118.1)	9.4 (5.4-860.7)	9.0 (5.8-30.9)	11.4 (6.3-118.1)	9.2 (5.4-860.7)	10.1 (6.4-21.8)	11.2 (5.9-30.9)	9.2 (5.8-118.1)

	P-value[b]	*P*-value[c]	*P*-value[d]	*P*-value[e]	*P*-value[f]
Saliva cortisol[a]					
Morning, median (min-max)	.363	**.014**	.401	.138	.809
Afternoon, median (min-max)	.938	.783	.758	.970	.895
Evening, median (min-max)	.574	.644	.752	.127	.814
Hair cortisol					
Nmol/L, median (min-max)	.808	.716	.421	.401	.845
Pmol/g, median (min-max)	.624	.903	.422	.322	.962
Pg/mg, median (min-max)	.804	.699	.422	.423	.870

P-value <.05 is in bold.

[a]nmol/L.

[b]VLBW vs controls.

[c]Female VLBW vs female controls.

[d]male VLBW vs male controls.

[e]VLBW/AGA vs controls.

[f]VLBW/SGA vs controls.

individuals in our cohort were bothered by serious mental and social problems, and we were not able to detect deviant behaviour at the individual level. We could not control for lifetime stressful events and current perceived stress affecting the HPA axis function. We lacked the ability to use physical characteristics such as menstrual data or adiposity for statistical adjustments. In addition, we did not introduce any stressor or control over the awakening during the sampling.

Some strengths of the study may be mentioned. We used validated and well-accepted instruments to measure the participant's mental health. The diurnal salivary cortisol samples were taken at home environment to avoid stress moments linked with hospital visits. We also have information on hair cortisol, a validated biomarker that monitors stress intensity and changes over time. The follow-up period to 27-28 years is rather long. The data are continuous from the pre- and neonatal period and onwards and with subjects from a geographically defined cohort of surviving VLBW infants. The control group was selected in the new-born period and was matched for date of birth, parity of the mother, place of birth and sex.

5 | CONCLUSION

Self-perceived mental health did not differ in young adulthood between individuals born at VLBW and controls in this prospective regional study from birth to the age of 27-28. Adolescent girls born VLBW reported fewer externalising behaviours than the controls, and these differences decreased at young adulthood, indicating a satisfactory transition of mental health into adulthood. The results regarding neuroendocrine regulation were not pronounced, but the salivary cortisol activity in the morning was higher in VLBW women, especially those who were SGA at birth. There were no significant associations between cortisol and self-reported mental health in a pooled sample of VLBW and control adults. Further research should aim to understand in detail the impact of perinatal stress, gender and socio-economic factors on preterm children's mental health to adulthood.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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