Příloha 1

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Cognitive and Socioemotional Development at 5 and 9 Years of Age of Children Born with Very Low Birth Weight and Extremely Low Birth Weight in the Czech Republic

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Background: There is a high prevalence of cognitive and socioemotional dysfunction in very low birth weight (VLBW <1500 g) and extremely low birth weight (ELBW <1000 g) children. This study from the Czech Republic aimed to compare the cognitive and socioemotional development at 5 and 9 years of age of children born with VLBW/ELBW with children born with normal birth weight (NBW ≥2500 g).

Material/Methods: The clinical group consisted of 118 VLBW/ELBW children and the control group consisted of 101 children with NBW at ages 5 to 9 years. The research battery included selected subscales from the Intelligence and Development Scales (IDS), A Developmental Neuropsychological Assessment – second edition (NEPSY-II), and the Behavior Rating Inventory of Executive Function (BRIEF). Data were analyzed using STATA IC v. 15 software and G*Power (descriptive statistic, analysis of variance (ANOVA), correlations, multivariate analysis of variance – MANOVA, post hoc power analysis).

Results: We found a statistically significant difference in cognitive and socioemotional development between children with VLBW/ELBW and those with NBW. The average intelligence quotient (IQ) of VLBW/ELBW children was 96.38, while that of NBW children was 12.98 points higher ($P<0.001$). NBW children achieved better results on all subtests of the IDS ($P<0.001$) as well as in affect recognition ($P<0.001$). All results for both groups were within normal range. Parents of VLBW/ELBW children did not recognize impaired executive functioning ($P=0.494$).

Conclusions: This study has shown significant cognitive and socioemotional deficit in children born with VLBW and ELBW when evaluated at 5 and 9 years of age.

Keywords: Child Development • Cognitive Dysfunction • Infant, Extremely Low Birth Weight • Infant, Very Low Birth Weight

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Background

All citizens, residents, and employees in the Czech Republic have access to healthcare via compulsory general healthcare insurance [1]. However, current medical and psychological care provided for premature children and their families remains inadequate, as it is largely unsystematic and is directly dependent on the varying capacities of the local perinatal centers [2]. Furthermore, continuous monitoring of mental development is mandated only from infancy through 2 years of age [2]. This is not sufficient for the care of low-birth-weight children and children, as it is often impossible to generate an accurate prognosis of their developmental trajectory at this young age [2,3]. Birth weight is the first weight of the fetus or neonate obtained after birth. According to the World Health Organization (WHO), birth weight is divided into low birth weight (LBW <2500 g), very low birth weight (VLBW <1500 g), and extremely low birth weight (ELBW <1000 g) [4]. Premature birth before the 37th week of pregnancy and/or growth faltering in the womb increase the risk of low birth weight [5]. The number of LBW children born in the Czech Republic has been increasing in recent years. In 2018, 6.9% of all live children born in the Czech Republic were identified as LBW [6]. Along with efforts to reduce child mortality, experts have also focused on treatment options that might be used to reduce morbidity both in the neonatal period and later on in life [2]. Children with ELBW are the group that is most at risk for these complications [7-9].

There is strong evidence indicating that children born with VLBW and ELBW have a greater predisposition to develop cognitive deficits and/or delayed cognitive development [11,13-18]. Impaired attention, memory, perceptual-motor skills, and visual-motor skills are among the deficits that are most frequently reported in studies of cognitive development of VLBW/ELBW children [9,11,18-20]. Speech and language disabilities or delays (both receptive and expressive) have also been reported [12,21-25]. Impairment has also been reported in the areas that include executive functions [7,26-28]. The aforementioned deficits are detected most often at school age, when children are facing increasing demands, notably in mathematics, reading, and spelling [25,29-34]. Although studies that address measurements of intelligence quotient (IQ) in VLBW and ELBW children show great variability [35-37], it is clear that VLBW/ELBW children may have a limited capacity for intellectual and overall cognitive development compared to children born at term at the normal birth weight (NBW ≥2500 g) [37,38]. Some of the deficits observed among VLBW/ELBW children relate to the development of socioemotional competencies [7,8,39-42]. Johnson and Marlow described the "preterm behavioral phenotype", which is characterized by an increased risk of developing symptoms and disorders associated with inattention/hyperactivity, emotional, and social difficulties. Individuals with this phenotype are also at an increased risk for internalizing rather than externalizing problems [43]. Children born with VLBW or ELBW are also more vulnerable to attention deficit hyperactivity disorder (ADHD) and impulsivity, with symptoms more likely to persist into adulthood [39,44,45]. Other studies report an increased risk of pervasive developmental disorders; the incidence of autism spectrum disorders (ASDs) has been reported to range from 3.65% to 8% among VLBW/ELBW children [44,46]. These children also experience a higher incidence of depressive symptoms, low self-esteem, and anxiety disorders [8,47]. However, a whole population longitudinal study from birth to adulthood found that VLBW children were not at persistently increased risk for anxiety and mood disorders [48]. Other studies have reported difficulties in affect recognition among VLBW/ELBW children at preschool age [42,49]; some of these deficits may persist into middle childhood, notably with those involving the recognition of anger [50,51]. Problems with affect recognition and facial expressions result in an overall impairment in social skills and social adaptation [50], and can also lead to problems with the regulation of emotions [52,53], with a significant impact on relationships with peers, parents, and teachers [54,55]. Difficulties with social adaptation tend to appear early and persist into adolescence [56]. Although a number of the above studies demonstrate that these impairments can have a major long-term impact on children and their families and require long-term support and interventions, in the Czech Republic these children are not given the long-term attention they need [2].

To the best of our knowledge, there are no published studies that explore the relationship between birth weight and cognitive and socioemotional development at 5 and 9 years of age of children residing in the Czech Republic. The development of these children has not yet been mapped. In 2015/2016, we conducted a research project entitled "New Methods in the Follow-Up Care for Children with Perinatal Stress" at the Center for Follow-up Care of Ex-preterm Babies within the Department of Pediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital in Prague. Most often, babies born in one of Prague's maternity hospitals with a perinatal burden come under the care of the center. This was a large-scale project focused on the development of multidisciplinary care for children with specific perinatal burdens. Over the course of a given day, each child underwent a comprehensive evaluation that included pneumatological, routine pediatric, rehabilitative, psychological, and psychiatric assessments. One goal of the study was to evaluate the mental development of VLBW/ELBW children who were then between 5 and 9 years of age. Socioemotional and cognitive development was measured by subtests selected from the Intelligence and Development Scales (IDS) [57] and Developmental Neuropsychological Assessment, second version (NEPSY-II) [58,59]. Executive functions were examined using the Behavior Rating Inventory of Executive Function

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(BRIEF) [60]. This project was followed by the present study, which aimed to compare the cognitive and socioemotional development at 5 and 9 years of age of 118 children born with VLBW/ELBW with 101 children born with NBW. Based on our review of the literature, we proposed 4 hypotheses. H1 0: There is no statistically significant difference between the cognitive development of children with VLBW/ELBW and children with normal birth weight. H1: Children with normal birth weight have statistically significantly better cognitive development than children with VLBW/ELBW. H2 0: There is no statistically significant difference in socioemotional development between children with VLBW/ELBW and children with normal birth weight. H2: Children with normal birth weight have statistically significantly better socioemotional development than children with VLBW/ELBW.

Material and Methods

Ethics Statement

The research project has been carefully considered in all aspects of its research and ethical content by the institutional review board for "Medical Psychology and Psychopathology" at the First Faculty of Medicine, Charles University. The parents of the children in both groups were informed of the goals and the procedures involved in this research project, and all signed a written informed consent form. An emphasis was placed on the current well-being of the child throughout the evaluation period.

Procedure and Participants

One hundred and eighteen children aged 5 to 9 years were selected for participation in this study. Inclusion criteria were: age 5 to 9 years who were VLBW or ELBW. All children were monitored and treated at the Center for Follow-up Care of Expreterm Babies. This was a non-probability sampling method as the children and parents were selected from among those who were already receiving care in this center. Children with severe sensory impairments, mutism, and severe ASD were excluded from the study. The research studies took place primarily during the morning hours at the Center for Follow-up Care of Ex-preterm Babies within the Department of Pediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic. The duration of the assessment of the child was about 1 hour, plus an interview with the parent for about 15 minutes.

A control group recruited in 2017-2019, included NBW children who were 5 to 9 years of age who were not receiving mental health care. The participants were selected from a voluntary response sample from Prague and its close surroundings. The control group included 101 children who underwent the psychological examination only. The examination took place at the Institute of Psychology, Prague, Czech Republic.

Children came for the assessment with their parent (mostly with their mother). Subsequently, the child and the parents were told what the assessment entailed. The child underwent the assessment without the presence of the parent. During testing, an emphasis was placed on the current well-being of the child. If the test situation was too stressful for the child or caused any distress or anxiety, the child was given some time to familiarize him/herself with the situation, take a break from the test, or go back to the parent. An alternative testing date could have been arranged, but in neither case was it necessary.

Measures

IDS is appropriate for children at 5-10 years of age. The administration of the entire battery of tests typically requires 1.5-2 hours. For this reason, we administered selected subtests only, including those focused on visual perception, selective attention, phonological memory, visual-spatial memory, auditory memory, visual-motor skills, and receptive and expressive language, using validated Czech language standards [57].

NEPSY-II is a comprehensive battery of neuropsychological tests designed to evaluate neurocognitive development in preschoolers, children, and adolescents (ie, 3-16 years of age) [58,59]. We used only the subtest designed to evaluate affect recognition.

BRIEF is a questionnaire for parents or teachers that allows them to assess executive function in children aged 5 to 18 years. The BRIEF has 3 main indices: (1) Metacognition Index (MI) assesses the ability to initiate, organize, plan, and remember the steps needed to achieve a specific goal; (2) Behavior Regulation Index (BRI) evaluates the ability to manage and control behavior and emotional responses; and (3) Global Executive Composite (GEC – a composite of the 2 aforementioned indices) [60].

Statistical Analysis

Data were analyzed using STATA IC v. 15 software. Post hoc statistical power was calculated in G*Power. Birth weight was coded as a discrete dichotomous variable (0 – control, 1 – VLBW/ELBW) and was used as the predictor (independent) variable in all of our analyses. IQ, IDS subscales, as well as the NEPSY-II and BRIEF subscales were linear continuous variables that were included as outcome (dependent) variables.

The overall IQ score as determined by the IDS was used as the single-outcome variable, and analysis of variance (ANOVA)

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was performed with the control group was used as a reference. ANOVA is a statistical method used to compare means of multiple groups to find out if the differences between them are statistically significant.

However, because the total IQ score is calculated from IDS subscales, our second analysis included the simultaneous use of visual perception, selective attention, phonological memory, visual-spatial memory, auditory memory, visual-motor skills, and receptive and expressive language as dependent variables and birth weight as the independent variable. A multivariate analysis of variance (MANOVA) was performed to accommodate the co-existence of multiple outcome variables. MANOVA is similar to ANOVA in that it is a mean comparison test with multiple dependent variables. Correlations were performed in conjunction with this process because the dependent variables evaluated in the MANOVA should be correlated with one another.

Socioemotional development was also evaluated using ANOVA. In this case, the birth weight group was the independent variable, and the results of the affect recognition subtest of NEPSY-II were the dependent variables.

Responses from parents were evaluated in a separate MANOVA in which the BRIEF BRI and MI subscales were included as the dependent variables and birth weight as the independent variable.

The effect size was calculated using the ^{2} value obtained from the ANOVAs together with a post hoc power analysis.

Results

Descriptive Statistics

One hundred and eighteen LBW children were enrolled in our study, including 59 boys (50%) and 59 girls (50%). Forty-one (34.8%) of the participants were VLBW children and 77 (65.3%) were ELBW (65.3%) children. The mean age was 76.5 months (range, 60-115 months). The average birth weight was 918.07 g (range 405-1470 g). The control group of 101 children included 53 boys (52.5%) and 48 girls (47.5%) girls. The mean age was 81.2 months (range 60-107 months). The average birth weight was 3363.55 g (range 2600-4800 g). Quantitative analysis revealed no correlation between gender or age (preschool or young school-age) and the overall IQ. Likewise, our analysis revealed no significant differences between the groups of VLBW and ELBW children (t [71]=0.37, *P*=0.71). Therefore, we divided the participants into 2 groups according to birth weight (ie, NBW and VLBW/ELBW cohorts) for all subsequent statistical analyses.

Analyses of IDS

ANOVA revealed significant differences in cognitive development (F [1.217]=41.49, *P*<0.001). Overall, birth weight explained only ~16% of the variance in IQ. The average IQ of VLBW/ELBW children was 96.38, while the average IQ of NBW children was 12.98 points higher (**Table 1**). The individual scores are presented in **Figure 1**. A post hoc power analysis of the IQ data revealed a statistical power of 0.99 (**Table 2**). Before computing the MANOVA for cognitive development, we evaluated the results from the IDS subscales in a correlation matrix (**Table 3**). The results revealed a moderate correlation between the results from the IDS subscales (**Table 4**). The Wilks' lambda value was significant (F [8.210]=7.73, *P*<0.001) as were all the IDS subscales. Furthermore, our findings revealed that NBW children as a group performed better than VLBW/ELBW children on all subscales evaluated. The strongest associations (as per the R^2 value) were observed for subscales of visual perception, phonological memory, and selective attention. The partial η^2 (=0.22) was used to calculate the effect size, ie, $f^2(V)=0.22/(1-0.22)=0.29$. A post hoc power analysis of overall cognitive development revealed a high statistical power (0.99; **Table 5**). Collectively, our findings revealed that NBW children performed better than VLBW/ELBW children on all cognitive domains measured by the IDS scale when evaluated at 5-9 years of age.

Analysis of NEPSY-II

ANOVA revealed significant differences in socioemotional development (F [1.217]=11.79, *P*<0.001). Birth weight explained ~4.7% of the total variance in affect recognition (**Table 6**). VLBW/ELBW children achieved an average score of 9 on this evaluation, while NBW children achieved significantly higher scores. The individual scores on this subtest are shown in **Figure 2**. A post hoc power analysis revealed a high statistical power for this evaluation (**Table 7**). Collectively, our results revealed that NBW children (5-9 years of age) performed significantly better on subtests of affect recognition than children born with VLBW/ELBW.

Analysis of BRIEF

Finally, results from the BRI and MI BRIEF subscales were evaluated by MANOVA. The results from tests using these subscales were based on responses to questionnaires completed by the parents of the study participants. The differences observed in this case did not reach statistical significance (F [2.216]=0.71, *P*=0.494).

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Table 1. Analysis of Variance (ANOVA) comparison of intelligence quotient (IQ) and birth weight. The mean (M) IQ score was 100 with a standard deviation (SD) of 15. ANOVA revealed significant differences (F [1.217]=41.49, *P*<0.001). Overall, birth weight explained only ~16% of the variance in IQ. The average IQ of children with very low birth weight (VLBW <1500 g) or extremely low birth weight (ELBW <1000 g) was 96.38, while the average IQ of children with normal birth weight (NBW ≥2500 g) was 12.98 points higher.

Means for each group			
	Mean IQ	SD	N
VLBW/ELBW	96.38	15.95	118
NBW	109.36	13.49	101
Total	102.36	16.193	219

ANOVA					
	SS	df	MS	F	Prob >F
Between groups	9175.75	1	9175.75	41.49	0.000
Within groups	47987.28	217	221.13		
Total	57163.04	218	262.21		

Post-Hoc Bonferroni test	
	VLBW/ELBW
NBW	12.98*

* *p*<0.001.

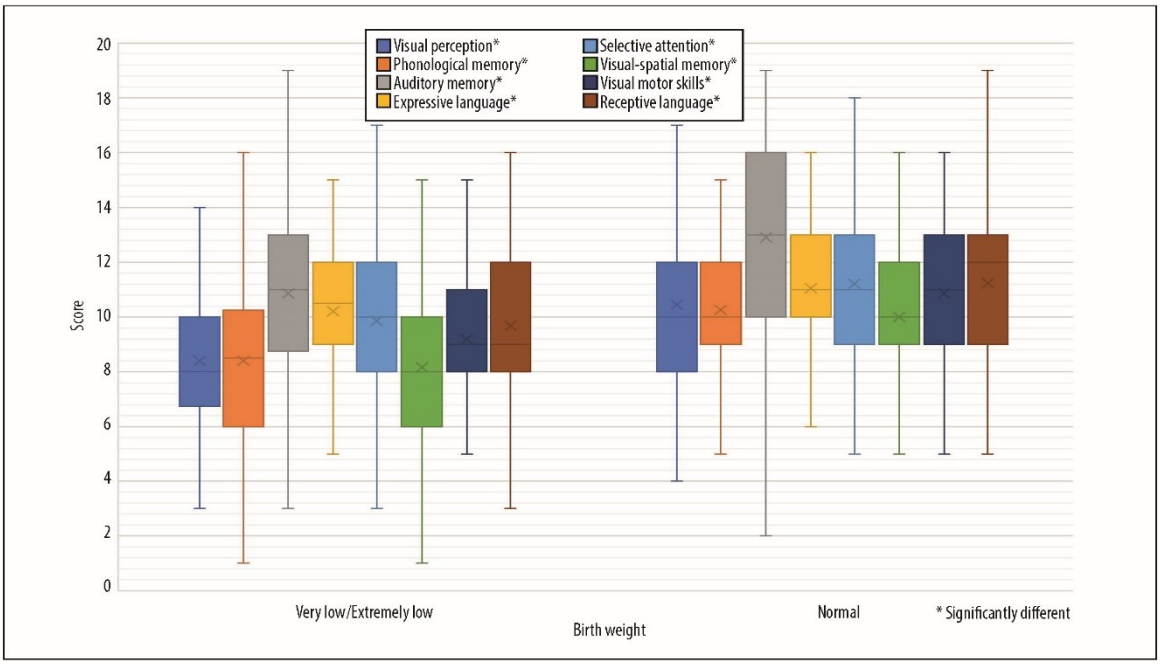

Figure 1. Scores on subscales of Intelligence and Development Scales (IDS). IDS subscale scores have a mean (M) of 10 with a standard deviation (SD) of 3. The test scores of children with very low birth weight (VLBW <1500 g) or extremely low birth weight (ELBW <1000 g) and with normal birth weight (NBW ≥2500 g) were not below the standardized average. NBW children performed significantly better than their VLBW/ELBW counterparts on all IDS subtests evaluated. The figure was prepared in Microsoft Excel, version 2112, Microsoft 365.

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Table 2. Post hoc power analysis of intelligence quotient (IQ). A post-hoc power analysis revealed a statistical power of 0.99.

Input: Effect size f2(V)	0.44	Output: Noncentrality parameter λ	42.39
α err prob	0.05	Critical F	3.88
Total sample size	219	Numerator df	1
Number of groups	2	Denominator df	217
		Power (1-β err prob)	**0.99**

Table 3. Correlation matrix of subscales of Intelligence and Development Scales (IDS). The results revealed a moderate correlation between the results from the IDS subscales.

	Visual perception	Selective attention	Phonological memory	Visual-spatial memory	Auditory memory	Visual-motor skills	Expressive language	Receptive language
Visual perception	1							
Selective attention	0.34	1						
Phonological memory	0.24	0.28	1					
Visual-spatial memory	0.28	0.30	0.22	1				
Auditory memory	0.24	0.33	0.32	0.38	1			
Visual-motor skills	0.37	0.32	0.25	0.35	0.28	1		
Expressive language	0.38	0.21	0.26	0.33	0.41	0.33	1	
Receptive language	0.40	0.22	0.33	0.33	0.31	0.24	0.40	1

Table 4. Multivariate analysis of variance (MANOVA) for subscales of Intelligence and Development Scales (IDS) and birth weight. Number of observations (N)=219. The Wilks' lambda value was significant (F [8.210]=7.73, *P*<0.001) as were all the IDS subscales. The strongest associations (as per the R^2 value) were observed for subscales of visual perception, phonological memory, and selective attention. Children with normal birth weight (NBW ≥2500 g) as a group perform better than children with very low birth weight (VLBW <1500 g) or extremely low birth weight (ELBW <1000 g) on all subscales evaluated.

Source	Statistic		df	F(df1)	F(df2)	F	Prob >F	
Birth weight	W	0.77	1	8.0	210.0	7.73	0.000	e
	P	0.22		8.0	210.0	7.73	0.000	e
	L	0.29		8.0	210.0	7.73	0.000	e
	R	0.29		8.0	210.0	7.73	0.000	e
	Residual		217					
	Total		218					

W – Wilks' lambda; P – Pillai's trace; L – Lawley-Hotelling trace; R – Roy's largest root; e – exact bound on F.

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Table 4 continued. Multivariate analysis of variance (MANOVA) for subscales of Intelligence and Development Scales (IDS) and birth weight. Number of observations (N)=219. The Wilks' lambda value was significant (F [8.210]=7.73, *P*<0.001) as were all the IDS subscales. The strongest associations (as per the R^2 value) were observed for subscales of visual perception, phonological memory, and selective attention. Children with normal birth weight (NBW ≥2500 g) as a group perform better than children with very low birth weight (VLBW <1500 g) or extremely low birth weight (ELBW <1000 g) on all subscales evaluated.

Equation	Observations	Parameters	RMSE	R^2	F	p
Visual perception	219	2	2.73	0.12	30.56	<0.001
Selective attention	219	2	2.77	0.10	24.19	<0.001
Phonological memory	219	2	3.69	0.07	16.50	<0.001
Visual-spatial memory	219	2	2.66	0.02	5.39	0.021
Auditory memory	219	2	2.92	0.05	11.82	<0.001
Visual motor skills	219	2	2.61	0.11	26.94	<0.001
Expressive language	219	2	2.94	0.07	17.78	<0.001
Receptive language	219	2	2.86	0.06	16.13	<0.001
	Coefficient	**SEM**	**t**	**P>t**	**95% Confidence interval [CI])**	
Visual perception						
Birth weight	2.04	0.37	5.53	<0.001	1.31-2.77	
Constant	8.39	0.25	33.40	<0.001	7.90-8.89	
Selective attention						
Birth weight	1.85	0.37	4.92	<0.001	1.10-2.59	
Constant	8.40	0.25	32.90	<0.001	7.90-8.91	
Phonological memory						
Birth weight	2.03	0.50	4.06	<0.001	1.04-3.02	
Constant	10.86	0.34	31.92	<0.001	10.19-11.53	
Visual-spatial memory						
Birth weight	0.83	0.36	2.32	0.021	0.12-1.54	
Constant	10.21	0.24	41.69	<0.001	9.72-10.69	
Auditory memory						
Birth weight	1.36	0.39	3.44	<0.001	0.58-2.14	
Constant	9.85	0.26	36.65	<0.001	9.32-10.38	
Visual-motor skills						
Birth weight	1.83	0.35	5.19	<0.001	1.14-2.53	
Constant	8.16	0.24	33.92	<0.001	7.68-8.63	
Expressive language						
Birth weight	1.68	0.39	4.22	<0.001	0.89-2.47	
Constant	9.18	0.27	33.86	<0.001	8.65-9.72	
Receptive language						
Birth weight	1.55	0.38	4.02	<0.001	0.79-2.32	
Constant	9.67	0.26	36.71	<0.001	9.15-10.19	

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Table 5. Post hoc power analysis of subscales of Intelligence and Development Scales (IDS). A post-hoc power analysis of overall cognitive development revealed a high statistical power (0.99).

Input: Effect size $f^2(V)$	0.29	Output: Noncentrality parameter λ	64.16
α err prob	0.01	Critical F	2.59
Total sample size	219	Numerator df	8
Number of groups	2	Denominator df	210
Response variables	8	**Power (1-β err prob)**	0.99
		Pillai V	0.05

η^2 ((8×7.73)/(8×7.73+210)=0.22)) was used to calculate the effect size, i.e., $f^2(V)$=0.22/(1-0.22)=0.29.

Table 6. Analysis of variance (ANOVA) for Affect recognition subtest of Developmental Neuropsychological Assessment, second version (NEPSY-II) and birth weight. The ANOVA revealed significant differences in socioemotional development (F [1.217]=11.79, *P*<0.001). Birth weight explained ~4.7% of the total variance in affect recognition.

Means for each group					
	Mean IQ		SD		N
VLBW/ELBW	9		2.89		118
NBW	10.30		2.70		101
Total	9.60		2.87		219
ANOVA					
	SS	df	MS	F	Prob >F
Between groups	92.95	1	92.95	11.79	0.000
Within groups	1711.48	217	7.88		
Total	1804.43	218	8.27		
Post-Hoc Bonferroni test					
			VLBW/ELBW		
NBW			1.30*		

* *p*<0.001.

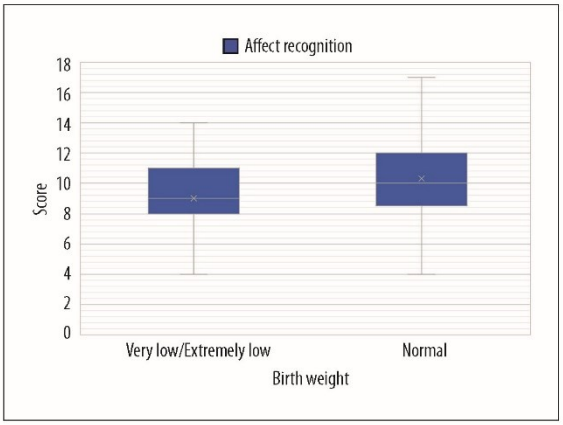

Figure 2. Scores on the affect recognition subtest of Developmental Neuropsychological Assessment, second version (NEPSY-II). Age-adjusted scaled scores include mean (M) 10 with a standard deviation (SD) 3. Children with very low birth weight (VLBW <1500 g) or extremely low birth weight (ELBW <1000 g) achieved an average score of 9 on this evaluation, while children with normal birth weight (NBW ≥2500 g) achieved significantly higher scores. The figure was prepared in Microsoft Excel, version 2112, Microsoft 365.

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Table 7. Post hoc power analysis of Affect recognition subtest of Developmental Neuropsychological Assessment, second version (NEPSY-II). A post hoc power analysis revealed a high statistical power for this evaluation (0.89).

Input: Effect size $f^2(V)$	0.22	Output: Noncentrality parameter λ	10.59
α err prob	0.05	Critical F	3.88
Total sample size	219	Numerator df	1
Number of groups	2	Denominator df	217
		Power (1-β err prob)	0.89

Discussion

The results of this study revealed that VLBW/ELBW children have diminished levels of cognitive and socioemotional development compared to their NBW peers at 5-9 years of age. The average intelligence quotient (IQ) of children with NBW was higher. NBW children achieved better results on all subtests of the IDS as well as in affect recognition. All the results for both groups were within normal range. Parents of VLBW/ELBW children or children with NBW did not recognize impaired executive functioning.

While the average IQ of NBW children in our study was 109.36, ELBW/VLBW children had an average score of 96.38, representing a 12.98-point difference. These findings are consistent with the results of a meta-analysis published by Gu et al that reported lower (albeit normal) IQs among VLBW/ELBW children compared to those born at NBW [37]. Recently published systematic reviews document individuals with LBW to have around 5-12 points lower IQ scores [10,37,61]. These authors also reported a gradient relationship between different levels of LBW and IQ score [37]; interestingly, our results did not confirm this finding. However, we recognize that only 5 of 7 subscales used to determine IQ were performed in the study. The scores of the omitted subtests were included as weighted averages. Therefore, these results should be interpreted with caution. Our results revealed that NBW children performed significantly better than their VLBW/ELBW counterparts on all IDS subtests evaluated. These findings are consistent with those previously reported in the medical literature and include differences in selective attention, perceptual-motor skills, visual motor skills [9,11,19,20], memory (phonology, auditory, visual-spatial) [21,45], and language development [12,21,22,24]. We also found that NBW children performed significantly better than VLBW/ELBW children on subtests of affect recognition. These results are also in agreement with those reported in previously published studies [42,49-51]. Interestingly, parents did not report impaired executive function on the BRIEF questionnaire. This implies that the parents believe that their children are all able to manage and control behavior and emotional responses and also can initiate, organize, plan, and remember the steps needed to achieve a specific goal. We recognize that this is a fully subjective evaluation. We cannot rule out the possibility of a bias based on social desirability. Several studies reported that VLBW/ELBW children have impairments in executive functions, predominantly those involving planning and organization, cognitive flexibility, working memory, attention, inhibition processes, verbal fluency, and behavioral and emotional control [7,26-28]. Overall, our results are in general agreement with findings reported in the literature [7,8,40,44]. Our quantitative analysis revealed significant differences in cognitive and socioemotional development when comparing the VLBW/ELBW group to the NBW controls. However, it is important to recognize that the results of all the psychological evaluations of children (including those in the VLBW/ELBW group) were within the normal range. In other words, while the test scores of the VLBW/ELBW children were statistically different from those of NBW children, the results as a whole were not below the standardized average.

The comparatively strong results achieved by the children in our VLBW/ELBW cohort may relate directly to the individualized, long-term, and comprehensive care provided by a multidisciplinary team at our hospital. We recognize that this level of comprehensive care does not reach all VLBW/ELBW children in the Czech Republic. The review by Spittle et al (2015) suggests that early developmental interventions improve cognitive outcomes up to preschool age. Little evidence was found of an effect on long-term cognitive outcomes (up to school age). Were included 25 randomized or quasi-randomized controlled trials of early developmental interventions for preterm children. Variability among these early developmental intervention programs limits the conclusions that can be drawn about their effectiveness [62].

Going forward, it is important to focus on several steps. In the Czech Republic there are currently significant shortcomings in follow-up psychological care both for the premature baby and the parents and family. The availability of high-quality psychological services might be expanded together with efforts to provide standardized methods for screening, assessing, and increasing the awareness of the need to monitor the behavior of these children and their families [2]. Further insight into the potential mechanisms associated with the socioemotional and

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cognitive development of LBW/preterm children could be provided by neuroscience, such as further study of changes in the structural and functional architecture of brain networks involved in emotion regulation and other parts of the brain. To better understand the whole issue, it is desirable to perform further research, not only in young children, but also in adolescents and adults born with low birth weight. The consequences of low birth weight are not yet sufficiently mapped for these periods.

This study had several limitations. As noted above, all VLBW/ELBW children enrolled in this study have undergone extensive long-term monitoring at the Center for Follow-up Care of Ex-preterm Babies. This level of care far exceeds the current standards in the Czech Republic. Also, we recognize that all our participants were active volunteers. Thus, the participants may have included only children with particularly motivated parents who also provided their children with superior attention and care. We also recognize that our study lacked socio-economic demographic data. Parental education, employment, and income, as well as the number of siblings in the family, have all been identified as predictors of cognitive development [63-66].

As noted above, there is no standard Czech language version of the NEPSY-II. We had only limited decision-making capacity in this regard, as the instruments to be used for this study were selected by an outside expert commission. Furthermore, the omission of the structural and conceptual thinking subscales of the IDS limited our overall analysis of cognition. Other limitations relate to the testing conditions. During the course of one day, the children underwent a comprehensive psychological and physical examination. Although we all agreed that the psychological examination would be performed first to avoid possible bias caused by fatigue, this plan was not followed in all cases.

Conclusions

This study has shown significant cognitive and socioemotional deficits in children born with VLBW and ELBW when evaluated at 5 and 9 years of age. Although the study had several limitations, our results confirm that LBW remains a major risk factor for delayed mental development. We hope that the results of the study will raise awareness of the effects of perinatal stress and its impact on mental development. Our results highlight the need to improve the availability of systematic follow-up focused on both medical and psychological care of VLBW/ELBW children even after their discharge from perinatal centers.

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Declaration of Figures' authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have been previously published in whole or in part.

References:

1. Alexa J, Rečka L, Votápková J, et al. Czech Republic: Health system review. Health Syst Transit. 2015;17(1):1-165
2. Marková D, Weberová-Chvílová M, Raušová P, et al. Péče o předčasně narozené dítě: Kdy začíná a kdy končí. Čes-slov Pediat. 2014;69(1):53-62 [in Czech]
3. Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics. 2005;116(2):333-41
4. World Health Organization. International statistical classification of diseases and related health problems, 10th revision, Fifth edition, 2016. World Health Organization; 2015. Available from: https://apps.who.int/iris/handle/10665/246208
5. United Nations Children's Fund, World Health Organization. Low birthweight estimates: Levels and trends 2000-2015. Geneva: World Health Organization; 2019. Available from: https://www.unicef.org/media/96976/file/UNICEF-WHO-Low-Birthweight-estimates-2000-2015.pdf
6. ÚZIS ČR. Narození a zemřelí do 1 roku 2018. Prague: ÚZIS ČR; 2019. Available from: https://www.uzis.cz/res/f/008279/narzem2018.pdf [in Czech]
7. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcome in very preterm and/or very low birth weight children. Pediatrics. 2009;124:717-28
8. Mathewson KJ, Chow CH, Dobson KG, et al. Mental health of extremely low birth weight survivors: A systematic review and meta-analysis. Psychol Bull. 2017;143:347-83
9. Bhutta AT, Cleves MA, Casey PH, et al. Cognitive and behavioral outcomes of school-aged children who were born preterm: A meta-analysis. JAMA. 2002;288:728-37
10. Upadhyay RP, Naik G, Choudhary TS, et al. Cognitive and motor outcomes in children born low birth weight: A systematic review and meta-analysis of studies from South Asia. BMC Pediatr. 2019;19(1):1-15
11. Orchinik LJ, Taylor HG, Espy KA, et al. Cognitive outcomes for extremely preterm/extremely low birth weight children in kindergarten. J Int Neuropsychol Soc. 2011;17:1067-79
12. Stolt S, Matomäki J, Lind A, et al. The prevalence and predictive value of weak language skills in children with very low birth weight – a longitudinal study. Acta Paediatr. 2014;103:651-58
13. Doyle LW, Anderson PJ. Stability of general cognition in children born extremely preterm as they grow older: Good or bad news? Arch Dis Child Fetal Neonatal Educ. 2018;103(4):F299-300
14. Stålnacke J, Lundequist A, Bohm B, et al. Individual cognitive patterns and developmental trajectories after preterm birth. Child Neuropsychol. 2015;21(5):648-67
15. Mangin KS, Horwood LJ, Woodward LJ. Cognitive development trajectories of very preterm and typically developing children. Child Dev. 2017;88(1):282-98
16. Linsell L, Johnson S, Wolke D, et al. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: A prospective, population-based cohort study. Arch Dis Child. 2018;103(4):363-70

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17. Wong HS, Santhakumaran S, Cowan FM, Modi N, Medicines for Neonates Investigator Group. Developmental assessments in preterm children: A meta-analysis. Pediatrics. 2016;138(2):e20160251
18. Anderson PJ. Neuropsychological outcomes of children born very preterm. Semin Fetal Neonatal Med. 2014;19(2):90-96
19. Kulseng S, Jennekens-Schinkel A, Naess P, et al. Very-low-birthweight and term small-for-gestational-age adolescents: Attention revisited. Acta Paediatr. 2006;95:224-30
20. Gidley Larson G, Baron IS, et al. Neuromotor outcomes at school age after extremely low birth weight: Early detection of subtle signs. Neuropsychol. 2011;25:66-75
21. Debata P, Kumar J, Mukhopadhyay K. Screening for language delay between 6 months and 3 years of corrected age in very low birth weight children. Indian Pediatr. 2019;56(6):481-84
22. Barre N, Morgan A, Doyle LW, Anderson PJ. Language abilities in children who were very preterm and/or very low birth weight: A meta-analysis. J Pediatr. 2011;158:766-74
23. Guarini A, Marini A, Savini S, et al. Linguistics features in children born very preterm at preschool age. Dev Med Child Neurol. 2016;58(9):949-56
24. Ortiz-Mantilla S, Choudhury N, Leevers H, Benasich AA. Understanding language and cognitive deficits in very low birth weight children. Dev Psychobiol. 2008;50(2):107-26
25. Vohr BR. Normal and Abnormal Neurodevelopmental and Behavioral Outcomes of Very Low-Birth Weight (VLBW) Infants. In: Buonocore G, Bracci R, Weindling M., editors. Neonatology: A Practical Approach to Neonatal Diseases. Springer, 2016;1-19
26. Ritter BC, Perrig W, Steinlin M, Everts R. Cognitive and behavioral aspects of executive functions in children born very preterm. Child Neuropsychol. 2014;20(2):129-44
27. Luu TM, Ment L, Allan W, et al. Executive and memory function in adolescents born very preterm. Pediatrics. 2011;127:e639-46
28. van Houdt CA, Oosterlaan J, van Wassenaer-Leemhuis AG, et al. Executive function deficits in children born preterm or at low birthweight: A meta-analysis. Dev Med Child Neurol. 2019;61(9):1015-24
29. Leijon I, Ingemansson F, Nelson N, et al. Reading deficits in very low birthweight children are associated with vocabulary and attention issues at the age of seven. Acta Paediatr. 2016;105(1):60-68
30. Feder KP, Majnemer A, Bourbonnais D, et al. Handwriting performance in preterm children compared with term peers at age 6 to 7 years. Dev Med Child Neurol. 2005;47(3):163-70
31. Allotey J, Zamora J, Cheong-See F, et al. Cognitive, motor, behavioural and academic performances of children born preterm: A meta-analysis and systematic review involving 64061 children. BJOG. 2017;125(1):16-25
32. Takeuchi A, Ogino T, Koeda T, et al. Intelligence test at preschool-age predicts reading difficulty among school-aged very low birth weight infants in Japan. Brain Dev. 2018;40(9):735-42
33. Akshoomoff N, Joseph RM, Taylor HG, et al. Academic achievement deficits and their neuropsychological correlates in children born extremely preterm. J Dev Behav Pediatr. 2017;38(8):627-37
34. Johnson S, Strauss V, Gilmore C, et al. Learning disabilities among extremely preterm children without neurosensory impairment: Comorbidity, neuropsychological profiles and scholastic outcomes. Early Hum Dev. 2016;103:69-75
35. Méio MD, Lopes CS, Morsch DS. Prognostic factors for cognitive development of very low birth weight premature children. Rev Saude Publica. 2003;37(3):311-18
36. Cooke RW, Foulder-Hughes L. Growth impairment in the very preterm and cognitive and motor performance at 7 years. Arch Dis Child. 2003;88(6):482-87
37. Gu H, Wang L, Liu L, et al. A gradient relationship between low birth weight and IQ: A meta-analysis. Sci Rep. 2017;7(1):18035
38. Martinez-Cruz CF, Poblano A, Fernandez-Carrocera LA, et al. Association between intelligence quotient scores and extremely low birth weight in school-age children. Arch Med Res. 2006;37(5):639-45
39. Franz AP, Bolat GU, Bolat H, et al. Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: A meta-analysis. Pediatrics. 2018;141:e20171645
40. Spittle AJ, Treyvaud K, Doyle LW, et al. Early emergence of behavior and social-emotional problems in very preterm infants. J Am Acad Child Adolesc Psychiatry. 2009;48:909-18
41. Moore PS, Mokrova I, Frazier JA, et al. Anxiety and depression correlates at age 10 in children born extremely preterm. J Pediatr Psychol. 2021;46(4):422-32
42. Marleau I, Vona M, Gagner Ch, et al. Social cognition, adaptive functioning, and behavior problems in preschoolers born extremely preterm. Child Neuropsychol. 2020;27(1):96-108
43. Johnson S, Marlow N. Preterm birth and childhood psychiatric disorders. Pediatr Res. 2011;69(5 pt 2):11R-18R
44. Indredavik MS, Vik T, Evensen KAI, et al. Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age. J Dev Behav Pediatr. 2010;31:286-94
45. Anderson PJ, De Luca CR, Hutchinson E, et al. Attention problems in a representative sample of extremely preterm/extremely low birth weight children. Dev Neuropsychol. 2011;36:57-73
46. Matheis M, Matson JL, Burns CO. Premature birth, low birth weight, and positive screening for autism spectrum disorder in an early intervention sample. J Dev Phys Disabil. 2018;30:689-705
47. Treyvaud K, Ure A, Doyle LW, et al. Psychiatric outcomes at age seven for very preterm children: rates and predictors. J Child Psychol Psychiatry. 2013;54:772-79
48. Jaekel J, Baumann N, Bartmann P, Wolke D. Mood and anxiety disorders in very preterm/very low-birth weight individuals from 6 to 26 years. J Child Psychol Psychiatry. 2017;59(1):88-95
49. Witt A, Theurel A, Tolsa CB, et al. Emotional and effortful control abilities in 42-month-old very preterm and full-term children. Early Hum Dev. 2014;90(10):565-69
50. Wocadlo C, Rieger I. Social skills and nonverbal decoding of emotions in very preterm children at early school age. Eur J Dev Psychol. 2006;3(1):48-70
51. Mossad SI, Muscat C, Pang EW, Taylor M. Emerging atypical connectivity networks for processing angry and fearful faces in very preterm born children. Hum Brain Mapp 2020;41(13):3794-806
52. Jones KM, Champion PR, Woodward LJ. Social competence of preschool children born very preterm. Early Hum Dev. 2013;89(10):795-802
53. Boyd LAC, Msall ME, O'Shea TM, et al. Social-emotional delays at 2 years in extremely low gestational age survivors: Correlates of impaired orientation/engagement and emotional regulation. Early Hum Dev. 2013;89(12):925-30
54. Potjik MR, de Winter AF, Bos AF, et al. Higher rates of behavioral and emotional problems at preschool age in children born moderately preterm. Arch Dis Child. 2012;97(2):112-17
55. Nosarti C. Social relationships, preterm birth or low birth weight, and the brain. JAMA Netw Open. 2019;2(7):e196960
56. Ritchie K, Bora S, Woodward LJ. Social development of children born very preterm: A systematic review. Dev Med Child Neurol. 2015;57(10):899-918
57. Grob A, Meyer CS, Hagmann-von Arx P. Intelligence and development scales. Bern, Switzerland: Hogrefe, 2009
58. Brooks BL, Sherman EM, Strauss E. NEPSY-II: A developmental neuropsychological assessment. Child Neuropsychol. 2009;16:80-101
59. Korkman M, Kirk U, Kemp S. NEPSY-II: Clinical and interpretive manual. San Antonio, TX: The Psychological Corporation, 2007
60. Gioia GA, Guy SC, Isquith PK, Kenworthy L. Behavior rating inventory of executive function. Psychological Assessment Resources, 1996
61. Kormos CE, Wilkinson AJ, Davey CJ, Cunningham AJ. Low birth weight and intelligence in adolescence and early adulthood: A meta-analysis. J Public Health (Oxf). 2014;36(2):213-24
62. Spittle A, Orton J, Anderson PJ, et al. Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. Cochrane database Syst Rev. 2015;24(11):CD005495
63. Breeman LD, Jaekel J, Baumann N, et al. Neonatal predictors of cognitive ability in adults born very preterm: A prospective cohort study. Dev Med Child Neurol. 2017;59:477-83
64. Stålnacke SR, Tessma M, Böhm B, Herlenius E. Cognitive development trajectories in preterm children with very low birth weight longitudinally followed until 11 years of age. Front Physiol. 2019;10:307
65. Beauregard JL, Drews-Botsch C, Sales JM, et al. Does socioeconomic status modify the association between preterm birth and children's early cognitive ability and kindergarten academic achievement in the United States? Am J Epidemiol. 2018;187:1704-13
66. Manley BJ, Roberts RS, Doyle LW, et al. Social variables predict gains in cognitive scores across the preschool years in children with birth weights 500 to 1250 grams. J Pediatr. 2015;166:870-76

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Příloha 2

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DUŠEVNÍ VÝVOJ DĚTÍ S NÍZKOU PORODNÍ HMOTNOSTÍ

souborný článek

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SOUHRN

Švandová L, Ptáček R, Goetz M, Marková D, Vňuková M, Raboch J. Duševní vývoj dětí s nízkou porodní hmotností

Spolu se zdokonalujícími se medicínskými postupy roste počet přežívajících dětí se stále nižší porodní hmotností. Tím stoupá také potřeba zmapování duševního vývoje těchto dětí pro komplexní uchopení problematiky této populace. Stále více se u dětí s nízkou porodní hmotností ukazuje dopad nezralosti v oblastech neurokognitivního a psychosociálního zrání. Vzhledem k perinatální zátěži, mnohočetnosti a různorodosti působících faktorů jsou děti s nízkou porodní hmotností rizikovou skupinou, která je ohrožena širokým spektrem neurovývojové psychopatologie, emočně-kognitivních deficitů, behaviorálních problémů a narušení adaptivních funkcí, ve srovnání s dětmi narozenými s normální porodní hmotností. Nejčastěji jsou uváděny lehké odchylky v řečovém vývoji, problémy s učením, pracovní pamětí, poruchy pozornosti, oslabení exekutivních funkcí. Prevalence psychiatrických poruch se u dětí s nízkou porodní hmotností ve školním věku pohybuje v rozmezí 22–28 %, s nejvyšším rizikem pro úzkostné poruchy, ADHD, pervazivní vývojové poruchy a poruchy chování. Odchylky jsou pozorovány taktéž v socioemočním a motorickém vývoji. Ukazuje se tak narůstající potřeba následné dlouhodobé a kvalitní péče a nezbytnost lepšího porozumění specifikům vývoje dětí s extrémně nízkou porodní hmotností (ENPH) a velmi nízkou porodní hmotností (VNPH). V současné době je však následná dlouhodobá psychologická péče o tyto děti zcela nedostatečná, nesystematická,

SUMMARY

Švandová L, Ptáček R, Goetz M, Marková D, Vňuková M, Raboch J. Mental development of children with low birth weight

Due to improving medical practices a growing number of children born with low birth weight survive. This raises the need to map the mental development of these children in order to improve our understanding of this phenomenon. It is increasingly observed that children with low birth weight show immaturity in areas of neurocognitive and psychosocial maturation. The perinatal burden as well as the multitude and variability of influencing factors, places children with low birth weight in a risk group for a wide range of neurodevelopmental psychopathologies, emotional-cognitive deficits, behavioural problems and disruption of adaptive functions, compared to children born with normal birth weight. Frequently are reported slight variations in speech development, learning difficulties, working memory, attention disorders and weakening of executive functions. The prevalence of psychiatric disorders is 22-28% in children with low birth weight in school age, with the highest risk for anxiety disorders, ADHD, pervasive developmental disorders and behavioural disorders. Deficits are also observed in socioemotional and motor development. This raises the need for subsequent long-term and high-quality care for these children and the need to understand the specifics of the development of extremely low birth weight (ELBW, < 1000g) and very low birth weight (VLBW, < 1500g) children. However, at present the long-term psychological support of these children is highly inadequate, unsystematic

a je proto nezbytné její rozvoj podporovat. V závěru jsou shrnuty výsledky studie „Nové metody v následné péči o děti s perinatální zátěží v Centru komplexní péče pro děti s perinatální zátěží na Klinice dětského a dorostového lékařství Všeobecné fakultní nemocnice a 1. lékařské fakulty Univerzity Karlovy", v rámci které byly vyšetřeny děti ve věku od 5 do 9 let s velmi nízkou a extrémně nízkou porodní hmotností. Zjištěny byly jemné odchylky ve vývoji, kdy největší obtíže byly shledány v oblastech zrakového vnímání a selektivní pozornosti, oslabení exekutivních funkcí – obtíže především v oblasti plánování a organizace, pracovní paměti a kontrole chování. Kvantitativní analýza neprokázala statisticky významný rozdíl v kognitivním ani socioemočním vývoji mezi dětmi s ENPH a VNPH.

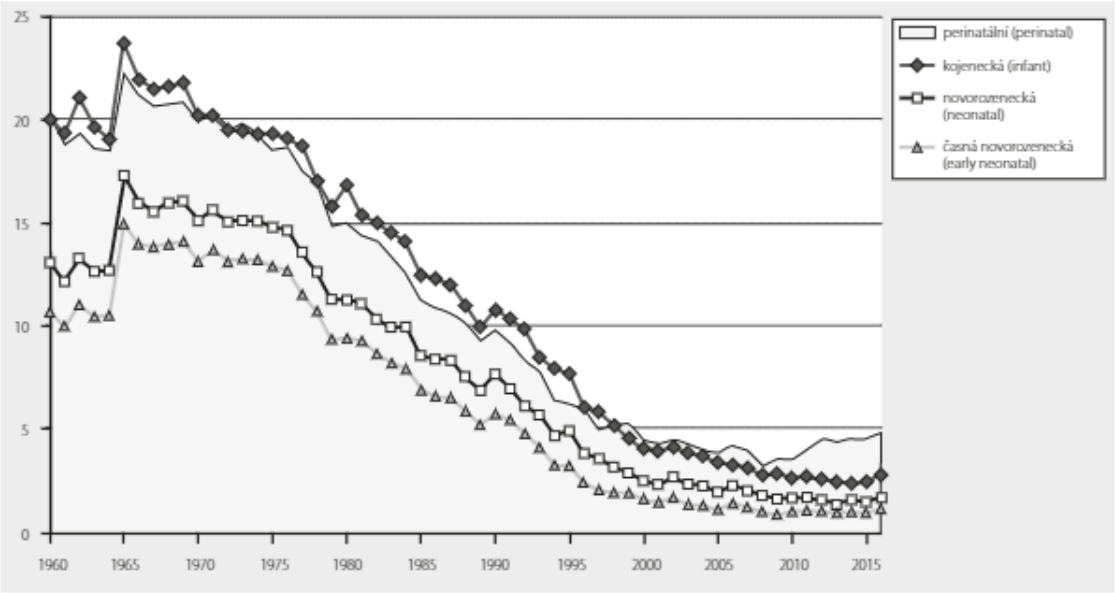
Klíčová slova: duševní vývoj, velmi nízká porodní hmotnost, extrémně nízká porodní hmotnost, morbidita, komplexní péče.

and calls for further development. In conclusion of this article we summarise the results of the study "New methods in the follow-up care for children with perinatal stress in the Centre for Complex Care of newborn at risk at the Clinic of Child and Adolescent Medicine of the General Faculty Hospital and the 1st Faculty of Medicine of Charles University", in which they assessed children aged 5 to 9 with very low and extremely low birth weight. Small deviations in development have been identified, with the greatest difficulty observed in areas of visual perception and selective attention, weakening of executive functions – difficulties in planning and organising, working memory and behavioural control. Quantitative analysis did not show a statistically significant difference in cognitive or socioemotional development among children with ELBW and VLBW.

Key words: mental development, very low birth weight, extremely low birth weight, morbidity, complex care.

ÚVOD

V poslední době se do popředí zájmu odborníků dostává duševní vývoj dětí s nízkou porodní hmotností (NPH; < 2500 g), neboť se především díky pokrokům v medicíně počty živě narozených dětí s NPH neustále zvyšují. V roce 2018 dosáhl počet dětí s nízkou porodní hmotností 6,9 %



Graf 1. **Vývoj novorozenecké, kojenecké a perinatální mortality[2]**

ze všech živě narozených dětí v ČR.[1] Z pohledu duševního vývoje je v rámci výzkumů věnována pozornost především dětem s velmi nízkou (VNPH, < 1500 g) a extrémně nízkou porodní hmotností (ENPH, < 1000 g).

Aktuálně se řadíme mezi země s nejnižší novorozeneckou mortalitou na světě. Časná novorozenecká mortalita (do 7 dní od narození) dosahovala v roce 2016 hodnoty 1,18 ‰ a pozdní novorozenecká mortalita (od 8 do 28 dní) 0,52 ‰.[2]

Hranice viability se nyní pohybuje mezi 22. a 24. týdnem těhotenství a kolem 500 g porodní hmotnosti. Mezi odborníky se však vedou diskuse, zda tuto hranici nadále posouvat, neboť se ukazuje, že riziko následných zdravotních komplikací, závažné morbidity či mortality dítěte stoupá s nižším gestačním týdnem a porodní hmotností.[1,3]

Zpočátku byla pozornost věnována především záchraně života, tedy snižování mortality, dále možnostem léčby a neonatální morbiditě, i proto se dnes Česká republika řadí mezi státy s nejnižší novorozeneckou mortalitou stejně jako s nejlepší péčí o předčasně narozené a rizikové novorozence.[2] Pořád je však co zlepšovat. Stále více se ukazuje, že je nezbytné věnovat těmto dětem péči také v pozdějším věku, snažit se zajistit jim co nejvyšší kvalitu života, což znamená mimo jiné zaměřit se nejen na časnou, ale i pozdní morbiditu. Prevalence pozdní morbidity roste dle mnohých studií s klesající porodní hmotností, tedy skupina dětí s ENPH bývá nejrizikovější skupinou.[3–6] Je ale nezbytné si uvědomit, že porodní hmotnost není jediným faktorem, který pozdní morbiditu ovlivňuje. Je jich nepřeberné množství – od genetických predispozic, zralosti CNS, okolností těhotenství a porodu až po časnou morbiditu a kvalitu následné lékařské, odborné či rodičovské péče.[7]

NEUROPSYCHICKÁ MORBIDITA DĚTÍ S NPH

V oblasti psychického vývoje dětí s NPH zůstává stále řada nezodpovězených otázek, například kdy se odchylky ve vývoji objeví, jakou budou mít intenzitu, jak nejlépe jim předcházet, jaké intervence jsou vhodné atd. Psychický vývoj každého z nás je zcela individuální. Jsou určité mezníky, kterými by měl zdravý jedinec projít, nicméně pásmo normy je široké, a to, co některé děti zvládnou již v 10 měsících, mohou jiné zvládnout například ve 12 měsících či déle, a stále je to hodnoceno v rámci normy. Dále přichází do úvahy vliv nespočetného množství dalších faktorů, které zdárný vývoj jedince ovlivňují. I vzhledem k tomu je odhalení případných odchylek v psychickém vývoji dítěte, a to zejména v raném věku, obtížné.

V současné době poukazují odborníci u dětí s NPH čím dál častěji na zvýšené ohrožení širokým spektrem neurovývojové psychopatologie, na deficity v kognitivní, emoční, sociální a behaviorální oblasti.[8–11] Ve většině případů se nejedná o závažné poruchy, spíše o mírné odchylky, které se však u jednotlivých dětí mohou lišit svou intenzitou i načasováním. Symptomy se mohou překrývat, potencovat, mít přechodný charakter, ale také přetrvávat dlouhodobě či do konce života. Ačkoliv se zpočátku nemusejí žádné odchylky v psychickém vývoji projevit, neznamená to, že se nemohou objevit později, například v době, kdy jsou na dítě kladeny vyšší nároky (např. v souvislosti se školní docházkou) nebo díky dozrávání centrální nervové soustavy.[3,6,11,12]

Kognitivní vývoj

V kognitivní oblasti jsou uváděny převážně lehké odchylky v rozvoji řeči, pracovní paměti, oslabení exekutivních funkcí, problémy s učením a také poruchy pozornosti, a to jak u dětí s extrémně nízkou porodní hmotností (ENPH; < 1000 g), tak i u dětí s velmi nízkou porodní hmotností (VNPH; < 1500 g).[4,13,14] Některé studie upozorňují na nižší či výrazně nevyvážený intelekt.[3,5] Dané odchylky v kognitivním vývoji mohou přetrvávat od dětství do adolescence až do dospělosti.[3,5]

Oslabení kognitivního vývoje bývá nejvíce patrné ve školním věku, kdy jsou na děti kladeny stále vyšší nároky. Mohou se objevit problémy s učením. Některé studie dokládají horší studijní výsledky u dětí s VNPH/ENPH, a to především v oblastech čtení, pravopisu, psaní a matematiky.[3,5,15,16] K horším studijním výkonům pak často přispívají právě daná oslabení v kognitivním vývoji, která nebývají včas odhalena, a nejsou tak zahájena potřebná opatření, intervenční programy. Z mírné odchylky se tak mohou vyvinout závažnější obtíže či poruchy, jako jsou specifické poruchy učení, které jsou u dětí s VNPH/ENPH častější nežli u dětí s normální porodní hmotností. Jedná se především o dysgrafii, dyskalkulii a dyslexii.[3,5,6]

Dále je u dětí s VNPH a ENPH poukazováno na opožděný řečový vývoj. V roce 2010 provedli Barre et al. metaanalýzu dostupných studií a výzkumů, zabývajících se řečovým vývojem u dětí s VNPH. Obtíže se objevují jak v receptivní, tak i v expresivní složce řeči, a to nejčastěji ve školním věku.[17] K podobným zjištěním došli i Stolt et al., kteří analyzovali prevalenci oslabení řečového vývoje u dětí s VNPH ve věku dvou a pěti let.[18] V průběhu tříletého sledovacího období se prevalence řečového oslabení zvýšila a dosáhla statistické významnosti v porovnání s kontrolní skupinou. Zatímco u dvouletých dětí s VNPH se prevalence oslabení řečového vývoje pohybovala mezi 16 a 18 %, v kontrolní skupině mezi 8 a 10 %. Po vyloučení dětí s neurologickými problémy nebyl již rozdíl statisticky významný. Ve věku 5 let však byla u dětí s VNPH prevalence mezi 20 a 27 %, v kontrolní skupině 10 %, kdy i po vyloučení dětí s neurologickými problémy byl rozdíl statisticky významný.[18] I zde se znovu ukazuje, jak je důležité průběžné sledování dětí s nízkou porodní hmotností, a to nejen z hlediska řečového vývoje. Čím dříve se podaří jednotlivé vývojové odchylky odhalit, tím dříve mohou být zahájena potřebná opatření, intervenční programy, a lze tak leckdy předejít mnohem závažnějším problémům.

Kognitivní funkce a jejich efektivní uplatnění souvisí také s funkcemi exekutivními. Stále častěji jsou studovány z důvodu jejich zásadní role při problémech s chováním a učením.[19] Hlavní deficity u dětí s VNPH/ENPH jsou zmiňovány převážně v oblastech plánování a organizace, pracovní paměti, pozornosti, kognitivní flexibilitě, v inhibičních procesech a kontrole chování a emocí.[3,19–22] Scott et al. upozorňují u dětí s VNPH především na poruchy pracovní paměti, se kterými souvisí poruchy pozornosti

a problémy se seberegulací.[22] Některé studie se přednostně zaměřují na oslabení pracovní paměti u dětí s nízkou porodní hmotností, jelikož pracovní paměť, schopnost udržení informací v paměti za účelem splnění určitého úkolů, je klíčem například k řešení problémů, následování instrukcí apod.[8] Oslabení pracovní paměti tedy může vést nejen k horším studijním výsledkům, ale i dalším problémům v oblasti kognitivní i behaviorální.[3,20]

Mezi nejsilnější prediktory pozdějšího kognitivního výkonu u dětí s nízkou porodní hmotností patří nejen úroveň poskytnuté somatické péče, vzdělávání rodičů, ale také včasné zachycení odchylek ve vývoji a naplánování podpůrných opatření a intervencí.

Socioemoční vývoj

V socioemočním vývoji se nejčastěji jedná o odchylky v oblasti sociálně-emočních kompetencí, narušení adaptivních funkcí, problémy v regulaci chování a emocí, internalizované obtíže (vyhýbavost, somatizace, úzkost a deprese) a externalizované obtíže (impulzivita a hyperaktivita, opoziční a vzdorovité chování, agrese), poruchy autistického spektra.[5,23] Jelikož mají děti s VNPH a ENPH větší vulnerabilitu k obtížím s pozorností, hyperaktivitou i impulzivitou, mají ve srovnání s dětmi s normální porodní hmotností zvýšené riziko diagnózy ADHD.[4–5,9,24] Ve skupině s ENPH tato pravděpodobnost stoupá. Taktéž u dětí s VNPH a ENPH častěji přetrvávají symptomy ADHD až do adolescence.[25] Prevalence duševních poruch u dětí s VNPH v období školního věku je v rozmezí 22 až 28 %. Nejvyšší riziko je právě pro ADHD, dále pak poruchy chování, pervazivní vývojové poruchy a úzkostné poruchy.[4,9,25]

U dětí s VNPH a ENPH je výskyt poruch autistického spektra v rozmezí 3,65 % až 8 %.[8–9] Hrdlička et al. v roce 2012 přinesli přehled dosavadních zahraničních studií, které hypotézu o zvýšeném výskytu poruch autistického spektra u dětí s nízkou porodní hmotností podporují.[26] V běžné populaci se hovoří o 1 %. Ačkoliv se jednotlivé studie zaměřené na výskyt PAS u dětí s NPH liší ve své kvalitě i metodologii, je zřejmé, že děti s VNPH/ENPH jsou rizikovou skupinou a měly by být prospektivně klinicky sledovány.[26] Dle českého výzkumu Dudové et al. z roku 2014 vyplynula prevalence poruch autistického spektra u předčasně narozených dětí/dětí s nízkou porodní hmotností 12,9 %.[27]

V rámci socioemočního vývoje poukazují některé studie také na vyšší výskyt depresivní symptomatiky, nižší sebehodnocení, úzkostné poruchy (např. specifické fobie a separační úzkostná porucha).[5,28] Dle výzkumu Nomury et al. mají dospělí jedinci, kteří se narodili s VNPH, zvýšené riziko pro depresivní a úzkostné poruchy zvláště v případě, že jejich rodiče také trpí depresí nebo úzkostí.[29] To poukazuje na interakci genetických a environmentálních faktorů a zároveň na význam programů mírnících dopady duševního onemocnění rodičů na vývoj jejich dětí.

Taktéž obtíže v socioemočním vývoji mohou přetrvávat nejen během předškolního a školního období, ale v některých případech až do adolescence či dospělosti. I zde je proto velmi důležité zachytit tyto obtíže co nejdříve a zahájit vhodnou intervenci.

Motorický vývoj

Motorický vývoj je jedním z významných základních kamenů pro zdárný psychický vývoj, ať již na úrovni kognitivní, emoční, sociální, či motivačně volní. Harmonický motorický vývoj umožňuje dítěti samostatně prozkoumávat své okolí, zapojovat se do společenského dění a vnímat nové podněty, které napomáhají správnému psychickému vývoji.[30] Také zde je u dětí s nízkou porodní hmotností pozorováno oslabení. Znovu se jedná spíše o mírné odchylky, a to především v oblastech jemné motoriky, vizuomotorické koordinace a integrace.[13,16,31–33]

Například dle studie Feder et al. dosáhly děti s VNPH, oproti dětem s normální porodní hmotností, v průběhu prvního roku školní docházky slabších výsledků v oblasti zrakové percepce, koordinace oko–ruka, manipulace prstů.[16] Oslabení vizuo-motorických schopností u dětí s NPH dokládá také studie Pietz et al., kdy byly porovnávány výkony sedmiletých dětí s nízkou porodní hmotností (< 2500 g) a dětí s normální porodní hmotností.[31] Méně často jsou zmiňovány poruchy koordinace pohybů. Například ve studii Davis et al. byly obtíže s koordinací pohybů shledány u 9,5 % dětí s ENPH ve věku 8–9 let, u dětí s normální porodní hmotností jen u 2 %. Jak již bylo zmíněno výše, motorický vývoj je jedním ze základních kamenů pro kognitivní vývoj a v rámci této studie bylo oslabení koordinace pohybů velmi často spojeno také s oslabenými kognitivními funkcemi, nižšími akademickými výkony a problémy v chování.[32]

Podobně jako u kognitivního a socioemočního vývoje se mohou oslabení v motorickém vývoji objevit v dětském věku a přetrvávat do období adolescence či dospělosti.[5,33] I zde je nezbytné odhalit oslabení v motorickém vývoji co nejdříve a zahájit vhodnou intervenci.[30]

PSYCHOLOGICKÁ PÉČE O DĚTI S NÍZKOU PORODNÍ HMOTNOSTÍ V ČR

Je zřejmé, že adekvátní a optimální vývoj dětí nezáleží pouze na genetice, zdravotní péči, průběhu zrání ani rizikových faktorech typu nízké porodní hmotnosti. Významný je také vliv prostředí, ve kterém dítě vyrůstá, péče a výchova rodičů/pečovatelů, důležitost informování a vzdělávání rodičů, možnosti terapie, podpůrných programů apod. Svůj nezastupitelný podíl má také psychologická péče, především v podobě kontinuálního sledování vývoje dítěte, díky čemuž je možné včas zachytit odchylky v psychickém vývoji a zahájit intervenci.

Nyní je psychický vývoj dítěte sledován pouze do 2 let, avšak v takto raném věku není možné stanovit přesnou prognózu psychického vývoje. Teprve v souvislosti s postupným dozráváním centrální nervové soustavy, se zvyšujícími se nároky kladenými na dítě, zejména pak v období školní docházky, případně v časné dospělosti, se teprve mohou některé poruchy či odchylky psychického vývoje objevit nebo se průběžně měnit.[3,12] Ve studii Saigal et al. byl psychický vývoj u 52 % dětí s ENPH hodnocen ve 4 letech v normě, při druhém hodnocení v 8 letech to bylo již jen 31 % dětí.[34]

Dosavadní následná psychologická péče o děti s nízkou porodní hmotností a jejich rodiny je však bohužel prozatím nesystematická, nedostatečná, není všude dostupná a liší se svou úrovní. V České republice je průběžné sledování duševního a psychomotorického vývoje psychologem stále bohužel spíše výjimkou. Stejně tak následná péče a odborná pomoc pro rodinu dítěte s perinatální zátěží je nedostatečná.

Je nezbytné si uvědomit, že perinatální zátěž je problematikou nejen zdravotnickou, ale i psychologickou, společenskou, sociální a pedagogickou. Vztahuje se nejen k dítěti, ale i k jeho rodině a širšímu okolí. Péče a odborná pomoc pro rodinu dítěte by tak zcela jistě měla být nedílnou součástí péče o dítě s perinatální zátěží. Například u matek nedonošených dětí se častěji objevují pocity viny a selhání, které mohou negativně ovlivnit chování matky, její schopnost správně reagovat na dítě, což může vést k narušení optimálního interakčního chování mezi matkou a dítětem, které je jedním z významných faktorů ovlivňujících další vývoj dítěte.[6,12,35]

V ideálním případě by měla být péče o děti s perinatální zátěží zajištěna týmem, který by zahrnoval specialisty z různých oborů lékařství (např. pediatrie, oftalmologie, kardiologie, neurologie, rehabilitace), dále logopedy, psychology a psychiatry, speciální pedagogy, sociální pracovníky apod.[6,12] Pro řešení specifických problémů a především pro zdárný nejen psychický vývoj dítěte s perinatální zátěží, ale celkové prospívání, by měla být dětem a rodinám poskytována komplexní péče, což bude možné pouze v případě, že budou vznikat nová vývojová centra, intervenční programy, rizikové poradny a bude podporována dlouhodobá multioborová spolupráce.

VÝZKUMNÝ PROJEKT V ČR

V letech 2015/2016 proběhl výzkumný projekt „Nové metody v následné péči o děti s perinatální zátěží v Centru komplexní péče pro děti s perinatální zátěží na Klinice dětského a dorostového lékařství Všeobecné fakultní nemocnice a 1. lékařské fakulty Univerzity Karlovy“, který byl podpořen norskými fondy. Jednalo se o rozsáhlý projekt, který byl zaměřen na rozvoj multidisciplinární péče pro děti s perinatální zátěží. Konkrétně se jednalo o obory: pneumologie, rehabilitace, psychologie a psychiatrie, pediatrie – antropometrie. Hlavním řešitelem projektu byla MUDr. Daniela Marková.

Dílčím cílem bylo zmapování psychického vývoje dětí v předškolním a mladším školním věku s VNPH a ENPH. Výzkumný soubor tvořilo celkem 120 dětí (74 předškolního a 46 mladšího školního věku). Socioemoční a kognitivní vývoj byl zmapován vybranými subtesty z IDS (Intelligence and Development Scales), NEPSY II (Developmental Neuropsychological Assessment – II), dále bylo využito CPT (Conners Continuous Performance), TKF (Rey-Osterriethova komplexní figura) a škála pro hodnocení exekutivních funkcí u dětí – BRIEF (Behavior Rating Inventory of Executive Function). Všechny děti byly sledovány a terapeuticky vedeny v Centru komplexní péče pro děti s perinatální zátěží na KDDL VFN a 1. LF UK v Praze. Nejvýraznější oslabení byla pozorována ve vývoji zrakového vnímání, selektivní pozornosti, plánování a organizace, pracovní paměti a kontrole chování, stále však v pásmu širší normy a bez statisticky významného rozdílu mezi dětmi s VNPH a ENPH.[36] Z výsledků výzkumu se můžeme domnívat, že péče rodičů a odborníků může napomoci zdárnému vývoji dítěte, neboť všechny děti, které byly v rámci výzkumu testovány, byly sledovány v Centru komplexní péče pro děti s perinatální zátěží na KDDL VFN a 1. LF UK v Praze, a byla jim tak poskytována výborná péče, které se bohužel všem dětem s NPH vždy nedostane.

Ačkoliv nebyly shledány statisticky významné rozdíly mezi dětmi s ENPH a VNPH ani výrazná oslabení v kognitivním či socioemoční vývoji, zůstává nízká porodní hmotnost stále rizikovým faktorem pro budoucí vývoj dětí a je nezbytné se nadále tomuto tématu věnovat. Aktuálně probíhá analýza dat kontrolního vzorku, kdy bylo vyšetřeno 50 předškolních a 50 mladších školních dětí s porodní hmotností ≥ 2500 g, doposud bez psychologické a psychiatrické péče.

ZÁVĚR

Děti s VNPH a ENPH mají větší vulnerabilitu k vývojovým odchylkám v kognitivní, behaviorální, motorické i socioemoční oblasti. I když dle dosavadních studií převažují spíše mírnější odchylky nad vážnými poruchami, je zřejmé, že některá oslabení mohou přetrvávat do období adolescence či dospělosti a při nedostatečně včasné intervenci mohou změnit nejen svou intenzitu, ale i podobu. Dlouhodobé sledování může napomoci k minimalizaci rizik a zajištění optimálního vývoje dítěte s perinatální zátěží. Bohužel v současné době je následná systematická psychologická péče spíše výjimkou.

Vývoj dětí s perinatální zátěží je ovlivněn vysokým počtem různých faktorů, které se prolínají napříč nejrůznějšími obory. Je proto nezbytné, pro dosažení co nejvyšší kvality života dětí s nízkou porodní hmotností, poskytnout těmto dětem a jejich rodinám komplexní a především dlouhodobou péči.

Spolu se zvyšujícím se počtem přežívajících dětí se stále nižší porodní hmotností stoupá také potřeba dalšího zmapování duševního vývoje těchto dětí. Pro lepší pochopení celé problematiky je žádoucí podporovat další výzkumy v této oblasti nejen u dětí v raném věku, ale také u adolescentů a dospělých, kteří se narodili s nízkou porodní hmotností. Vliv a důsledky nízké porodní hmotnosti nejsou pro tato období stále dostatečně popsána.

LITERATURA

1. ÚZIS ČR. Narození a zemřelí do 1 roku 2018. Praha: ÚZIS ČR 2019: 76.
2. ÚZIS ČR. Zdravotnická ročenka České republiky 2016. Praha: ÚZIS ČR 2017: 211.
3. Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics 2009; 124 (2): 717–728.
4. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002; 288 (6): 728–737.
5. Mathewson KJ, Chow CH, Dobson KG et al. Mental health of extremely low birth weight survivors: A systematic review and meta-analysis. Psychol Bull 2017; 143 (4): 347–383.
6. Marková D, Weberová-Chvílová M, Raušová P et al. Péče o předčasně narozené dítě: Kdy začíná a kdy končí? Čes-slov Pediatr 2014; 69 (1): 53–62.
7. Zoban P. Pozdní morbidita dětí s velmi nízkou porodní váhou porozených v letech 1997–2004 v ČR. Neonatologické listy 2007; 13 (2): 11–14.
8. Michálková Grézlová T, Marková D, Ptáček R, Goetz M. Psychiatrická problematika u předčasně narozených dětí. Pediatr Praxi 2016; 17 (6): 348–352.
9. Indredavik MS, Vik T, Evensen, KAI, Skranes J et al. Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age. J Dev Behav Pediatr 2010; 31 (4): 286–294.
10. Stålnacke SR, Tessma M, Böhm B, Herlenius E. Cognitive development trajectories in preterm children with very low birth weight longitudinally followed until 11 years of age. Front Physiol 2019; 10: 307.
11. Pascal A, Govaert P, Oostra A, Naulaers G, Ortibus E, Van den Broeck C. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. Developmental Medicine & Child Neurology 2018; 60 (4): 342–355.
12. České zdravotnické fórum. Multioborová analýza současného stavu péče o předčasně narozené děti v ČR. Praha: ČZF 2014: 50.
13. Upadhyay RP, Naik G, Choudhary TS et al. Cognitive and motor outcomes in children born low birth weight: a systematic review and meta-analysis of studies from South Asia. BMC Pediatr 2019; 19 (1): 1–15.
14. Orchinik LJ, Taylor HG, Espy KA et al. Cognitive outcomes for extremely preterm/extremely low birth weight children in kindergarten. J Int Neuropsychol Soc 2011; 17 (6): 1067–1079.
15. Leijon I, Ingemansson F, Nelson N, Wadsby M, Samuelsson S. Reading deficits in very low birthweight children are associated with vocabulary and attention issues at the age of seven. Acta Paediatr 2016; 105 (1): 60–68.
16. Feder KP, Majnemer A, Bourbonnais D et al. Handwriting performance in preterm children compared with term peers at age 6 to 7 years. Dev Med Child Neurol 2005; 47 (3): 163–170.
17. Barre N, Morgan A, Doyle LW, Anderson PJ. Language abilities in children who were very preterm and/or very low birth weight: a meta-analysis. J Pediatr 2011; 158 (5): 766–774.
18. Stolt S, Matomäki J, Lind A et al. The prevalence and predictive value of weak language skills in children with very low birth weight – a longitudinal study. Acta Paediatrica 2014; 103 (6): 651–658.
19. van Houdt CA, Oosterlaan J, van Wassenaer-Leemhuis AG, van Kaam AH, Aarnoudse-Moens CS. Executive function deficits in children born preterm or at low birthweight: a meta-analysis. Dev Med Child Neurol 2019; 61 (9): 1015–1024.
20. Luu TM, Ment L, Allan W, Schneider K, Vohr BR. Executive and memory function in adolescents born very preterm. Pediatrics 2011; 127 (3): e639–e646.
21. Vicari S, Caravale B, Carlesimo GA, Casadei AM, Allemand F. Spatial working memory deficits in children at ages 3-4 who were low birth weight, preterm infants. Neuropsychology 2004; 18 (4): 673–678.
22. Scott MN, Taylor HG, Fristad MA et al. Behavior disorders in extremely preterm/extremely low birth weight children in kindergarten. J Dev Behav Pediatr 2012; 33 (3): 202–213.
23. Spittle AJ, Treyvaud K, Doyle LW et al. Early emergence of behavior and social-emotional problems in very preterm infants. J Am Acad Child Adolesc Psychiatry 2009; 48 (9): 909–918.
24. Anderson PJ, De Luca CR, Hutchinson E et al. Attention problems in a representative sample of extremely preterm/extremely low birth weight children. Dev Neuropsychol 2011; 36 (1): 57–73.
25. Franz AP, Bolat GU, Bolat H et al. Attention-Deficit/Hyperactivity Disorder and Very Preterm/Very Low Birth Weight: A Meta-analysis. Pediatrics 2017; e20171645.
26. Hrdlička M, Čihař M, Beranová Š, Dudová I. Výskyt autismu u dětí s extrémně nízkou a velmi nízkou porodní hmotností. Čes a slov Psychiat 2012; 108 (5): 245–249.
27. Dudová I, Kašparová M, Marková D et al. Screening for autism in preterm children with extremely low and very low birth weight. Neuropsychiatr Dis Treat 2014; 10: 277–282.
28. Treyvaud K, Ure A, Doyle LW et al. Psychiatric outcomes at age seven for very preterm children: rates and predictors. J Child Psychol Psychiatry 2013; 54 (7): 772–779.
29. Nomura Y, Wickramaratne PJ, Pilowsky DJ et al. Low birth weight and risk of affective disorders and selected medical illness in offspring at high and low risk for depression. Compr Psychiatry 2007; 48 (5): 470–478.
30. Pal A, Manna S, Dhara PC. Comparison between the motor function of school-aged children with normal birth weight and children with low birth weight: a cross-sectional study. Turk J Pediatr 2019; 61 (3): 374–385.
31. Pietz J, Peter J, Graf R et al. Physical growth and neurodevelopmental outcome of nonhandicapped low-risk children born preterm. Early Hum Dev 2004; 79 (2): 131–143.
32. Davis NM, Ford GW, Anderson PJ, Doyle LW. Developmental coordination disorder at 8 years of age in a regional cohort of extremely-low-birthweight or very preterm infants. Dev Med Child Neurol 2007; 49 (5): 325–330.
33. de Kieviet JF, Piek JP, Aarnoudse-Moens CS, Oosterlaan J. Motor development in very preterm and very low-birth-weight children from birth to adolescence: a meta-analysis. JAMA 2009; 302 (20): 2235–2242.
34. Saigal S, Hoult LA, Streiner DL, Stoskopf BL, Rosenbaum PL. School difficulties at adolescence in a regional cohort of children who were extremely low birth weight. Pediatrics 2000; 105 (2): 325–331.
35. Sobotková D, Dittrichová J. Vztah mezi perinatální morbiditou a dalším neuropsychickým vývojem dítěte. In: Štembera Z, Dittrichová J, Sobotková D (eds). Perinatální neuropsychická morbidita dítěte. Praha: Karolinum 2014: 461–480.
36. Švandová L. Psychický vývoj dětí s nízkou porodní hmotností. Diplomová práce. Praha, Katedra psychologie FF UK 2017.

Příloha 3

Švandová, L, Ptáček, R., Marková, D., & Vňuková, M. (2021). Hodnocení socioemočního a kognitivního vývoje u skupiny velmi (VLBW) a extrémně nezralých dětí (ELBW). In D. Marková & M. Chvílová Weberová (Eds.), *Předčasně narozené dítě: Následná péče. Kdy začíná a kdy končí?* (pp. 103-105). Praha: Grada.

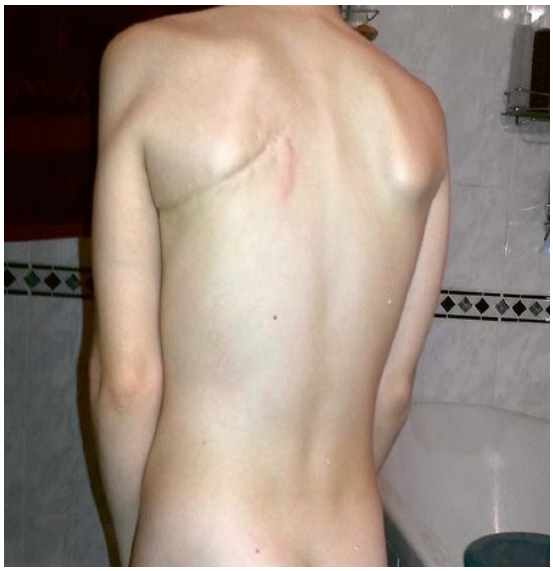
funkce. Výsledky DDST se v této komponentě shodovaly s výsledky komponenty pro hodnocení dynamické a statické rovnováhy z testu MABC-2.

Společně s pohybovou složkou MABC-2 byly v rámci komplexního posouzení motorických schopností dětí **posuzovány i psychické faktory**. Cílem bylo zjistit, které vlastnosti v chování dítěte mohly ovlivnit jeho výkon při testování.

Častým projevem byla **rozptýlenost, impulzivita a přílišná aktivita**. Řada dětí **přeceňovala své schopnosti**, nebo naopak **neměla potřebnou vytrvalost a soustředění** k tomu, aby testy správně provedla.

Častá porucha rovnováhy byla způsobena mnoha faktory. **Rovnováha** patří mezi **koordinační schopnosti** a k jejímu provedení je třeba vyvážené **svalové aktivity agonistů a antagonistů**. Nezbytná je též **pozornost a koncentrace**, tedy vlastnosti, které tyto děti často postrádají, což se při provádění testů významně projevovalo.

Nesoustředění a vadné držení těla lze označit za hlavní důvody nedostatečného splnění úloh rovnováhy. Nejčastějšími **kineziologickými projevy vadného držení** těla již v předškolním věku bývají ochablé a vyklenuté bříško, kulatá záda a vystouplé lopatky. Tento nález vede k poruchám polohocitu a pohybocitu, k narušení pohybových koordinačních schopností dětí, což se následně projevilo v nejnižším hodnocení statických a dynamických úkolů.



Obr. 10.6 Vadné držení těla u školního dítěte, jizva je po ligaci PDA

Nečekanou komplikací testování byla časová náročnost. Provedení testů za běžných asi 20–40 minut zvládl z dětí jen málokdo**.** Vyšetřování se často přerušovalo pro jejich úzkostnost, nezbytné povzbuzování rodiči, únavnost, nesoustředěnost, ale i nejistotu při samostatné práci na základě jejich celkové nevyzrálosti.

Při ovlivnění pohybových nedostatků u dětí je **role rodičů** zásadní a nezastupitelná. Po ukončení nezbytné fyzioterapie však děti velmi často nemají dostatek pohybové aktivity a pohybově strádají. Jejich vývojové poruchy motoriky tak mohou přetrvávat dále, nejčastěji ve **formě dyspraxie** (DCD, developmental coordination disorder – developmental dyspraxia).
Dyspraxií trpí podle různých zdrojů 6–10 % lidí. Nejzávažnější byla u naší testované skupiny dětí **výkonná (exekutivní) porucha**, charakterizovaná:

- poruchami selektivní hybnosti, poruchou posturální adaptace,
- poruchami rovnováhy, silového přizpůsobení, porušenou relaxací,
- poruchami plynulosti, rychlosti a rytmu pohybu,
- poruchami pohybového odhadu.

Výsledky testů v obou věkových skupinách bohužel jednoznačně **ukázaly dlouhodobou absenci pohybových aktivit** ve volnočasové době. Proto byla ergoterapeutem a fyzioterapeuty vypracována **individuální doporučení pro rodiče** všech dětí obou věkových kategorií. Speciální doporučení pro **zlepšení rovnovážných funkcí** byla předána rodičům.

V pohybovém vzdělávání je třeba pokračovat, často celý život, protože nezralost a její dyspraktické **důsledky si děti mohou nést celoživotně**.

10.3.3 Psychologie

Hodnocení socioemočního a kognitivního vývoje u skupiny velmi (VLBW) a extrémně nezralých dětí (ELBW)

Lucie Švandová, Radek Ptáček, Daniela Marková, Martina Vňuková

Výsledky aktuálních výzkumů prokázaly negativní **dopad nezralosti i nízké porodní hmotnosti na neurokognitivní a psychosociální zrání**. Závažnost postižení psychického vývoje se však podle jednotlivých studií liší. Některé studie dokládají u dětí s velmi

nízkou (VNPH, < 1500 g) a extrémně nízkou porodní hmotností (ENPH, < 1000 g) středně závažné až závažné problémy v kognitivním, motorickém i socioemočním vývoji, kdy intenzita oslabení často koreluje s mírou nezralosti/porodní hmotností. Podle dalších studií se jedná spíše o lehké odchylky ve vývoji. Nejčastěji jsou zmiňována oslabení ve vývoji řeči, poruchy pozornosti a paměti, oslabení exekutivních funkcí a snížený intelekt. V oblasti socioemočního vývoje bývají patrné snížené socioemoční kompetence, potíže s regulací a ovládáním emocí a chování. Daná oslabení mohou přetrvávat i do adolescence či dospělosti. V rámci výše uvedeného projektu jsme zkoumali psychický vývoj dětí v předškolním a mladším školním věku s velmi nízkou (VNPH, < 1500 g) a extrémně nízkou porodní hmotností (ENPH, < 1000 g). Výzkumný soubor tvořilo celkem 150 dětí, z nichž u 120 dětí (80 %) se podařilo vyšetření dokončit (74 předškolního a 46 mladšího školního věku) (tab. 10.4). Vyloučeny byly děti s těžkými smyslovými vadami, děti s mutismem či s těžkým stupněm poruchy autistického spektra (PAS).

Tab. 10.4 Výzkumný soubor

Porodní hmotnost	Předškolní věk		Mladší školní věk		Celkem	
	N	%	N	%	N	%
ENPH	45	60,81	33	71,74	78	65
VNPH	29	39,19	13	28,26	42	35
Celkem	74	100,00	46	100,00	120	100

Socioemoční a kognitivní vývoj byl zmapován vybranými **subtesty z IDS (Intelligence and Development Scales)**, **NEPSY II (Developmental Neuropsychological Assessment** – II), dále bylo využito **CPT (Conners Continuous Performance), TKF (Rey-Osterriethova komplexní figura)** a škála pro hodnocení exekutivních funkcí u dětí **BRIEF (Behavior Rating Inventory of Executive Function)**. Všechny děti byly dlouhodobě sledovány a terapeuticky vedeny v CKP.

Kvantitativní analýza neprokázala statisticky významný rozdíl mezi předškolními dětmi s VNPH a ENPH v kognitivním vývoji (p = 0,711) ani v oblasti exekutivních funkcí (p = 0,510). Stejně tak nebyl nalezen statisticky významný rozdíl mezi mlad- šími školními dětmi s VNPH a ENPH v kognitivním vývoji (p = 0,345) ani v oblasti exekutivních funkcí (p = 0,175). Nejvýraznější **oslabení** byla v obou skupinách pozorována ve **vývoji zrakového vnímání, selektivní pozornosti, plánování a organizace, pracovní paměti a kontrole chování,** bez statisticky významného rozdílu mezi dětmi s VNPH a ENPH. Nebyly nalezeny statisticky významné rozdíly ani v socioemočním vývoji u předškolních dětí s ENPH a VNPH (p = 0,284). Podobně u dětí v mladším školním věku (p = 0,135), výsledky jsou podrobněji uvedeny v tabulce 10.5.

Kognitivní i socioemoční vývoj dětí v našem souboru celkově **odpovídal pásmu širší normy.** K přesnějšímu porovnání výsledků našeho souboru s běžnou populací aktuálně probíhá analýza dat kontrolního vzorku, kdy bylo vyšetřeno 50 předškolních a 50 mladších školních dětí s porodní hmotností ≥ 2500 g, doposud bez potřeby psychologické či psychiatrické péče.

Jedním z důvodů, proč naše studie neukázala závažnější oslabení v kognitivním ani socioemočním vývoji u dětí s VNPH ani ENPH, bylo pravděpodobně **vyřazení nejrizikovějších dětí se sníženou schopností spolupráce během vyšetření** (těžké smyslové poruchy, PAS, mutismus apod.).

Tab. 10.5 Výsledky vybraných subtestů

	Předškolní věk				Mladší školní věk			
	Průměrný vážený skór		t	p	Průměrný vážený skór		t	p
	ENPH	VNPH			ENPH	VNPH		
IDS – IQ	98,38	97,00	t (72) = 0,372	0,711	95,12	99,92	t (44) = -0,956	0,345
IDS selektivní pozornost	9,16	8,31	t (72) = 1,213	0,229	7,52	8,38	t (44) = -0,982	0,331
IDS receptivní řeč	9,20	9,48	t (72) = -0,447	0,656	10,18	10,92	t (44) = -0,670	0,506
IDS expresivní řeč	9,27	8,97	t (72) = 0,446	0,656	9,70	8,54	t (44) = 1,068	0,291
NEPSY II rozpoznávání emocí	8,64	9,45	t (72) = -1,078	0,284	9,58	8,31	t (44) = 1,522	0,135
	Průměrný T-skór		t	p	Průměrný T-skór		t	p
BRIEF inhibice	49,22	47,69	t (72) = 0,685	0,495	52,38	49,33	t (42) = 0,769	0,446
BRIEF přesun pozornosti	50,87	50,03	t (72) = 0,315	0,754	53,28	49,83	t (42) = 0,810	0,422
BRIEF emoční kontrola	52,78	49,59	t (72) = 1,313	0,191	55,25	54,67	t (42) = 0,166	0,868
BRIEF – globální exekutivní kompozit	51,71	49,90	t (72) = 0,662	0,510	55,38	49,83	t (42) = 1,378	0,175

Výsledky podporují nutnost **zaměřit se na další výzkumy** v dané oblasti, a to nejen v dětském věku, ale i u adolescentů a dospělých, neboť podle mnohých studií mohou oslabení přetrvávat. V současně době probíhá testování kontrolní skupiny 100 stejně starých dětí, které byly narozeny v termínu, bez perinatální zátěže.

10.3.3 Hodnocení výsledku vyšetření dvouletých dětí s porodní hmotností pod 1500 g

Daniela Marková, Pavla Raušová, Evženie Knězů, Blanka Zlatohlávková, Jan Smíšek

V korigovaných dvou letech bylo vyšetřeno 75 % dětí s porodní hmotností méně než 1500 g, propuštěných z neonatologického oddělení VFN a přijatých do sledování CKP v letech 2012–2016 (92,5 % pod 750 g, 85 % 750–999 g a 65 % 1000–1499 g). Nízký podíl dětí ztracených ze sledování ve skupině novorozenců extrémně nízké porodní hmotnosti (jen 11 % dětí s porodní hmotností pod 1000 g) nás opravňuje považovat výsledky za validní – riziko závažného postižení klesá se zvyšující se hmotností a také nepřímo dokládá potřebu specializované péče. Více než třetina nevyšetřených dětí velmi nízké porodní hmotnosti (35 % s porodní hmotností 1000–1499 g) pravděpodobně svědčí o tom, že tyto děti během prvních dvou let specializovanou péči nepotřebovaly.

10.3.4 Vyšetření plicních funkcí u nespolupracujících dětí

Jana Tuková, Petr Koťátko, Daniela Marková, Jan Šulc

Strukturální a funkční abnormity plicního parenchymu a dýchacích cest u předčasně narozených dětí vedou k **rozvoji dlouhodobé ventilační poruchy** a mohou významně zhoršit mechaniku dýchání. Metody vyšetření plicních funkcí u nespolupracujících dětí (tj. u dětí v kojeneckém a batolecím věku) umožňují časné zhodnocení typu a závažnosti ventilační poruchy.

V Centru komplexní péče VFN v Praze bylo provedeno funkční plicní vyšetření u **74 předčasně**

Příloha 4

Ptacek, R., Stefano, G. B., Weissenberger, S., Akotia, D., Raboch, J., Papezova, H., **Domkarova, L.,** ... & Goetz, M. (2016). Attention deficit hyperactivity disorder and disordered eating behaviors: links, risks, and challenges faced. *Neuropsychiatric Disease and Treatment, 12*, 571-579. **IF: 2,198.**

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REVIEW

Attention deficit hyperactivity disorder and disordered eating behaviors: links, risks, and challenges faced

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Abstract: Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that often persists in adulthood. It is defined by inattention and/or hyperactivity–impulsivity. ADHD is associated with many comorbidities, including eating disorders (EDs). In the last decade, studies have reported that ADHD is linked with binge EDs, bulimia nervosa, and anorexia nervosa. Many postulates have been proposed to explain the association: 1) impulsive behavior in ADHD patients leads to disordered eating behavior; 2) other psychologic comorbidities present in ADHD patients account for eating behavior; 3) poor eating habits and resulting nutritional deficiencies contribute to ADHD symptoms; and 4) other risk factors common to both ADHD and EDs contribute to the coincidence of both diseases. Additionally, sex differences become a significant issue in the discussion of EDs and ADHD because of the higher incidence of bulimia nervosa and anorexia nervosa in females and the ability of females to mask the symptoms of ADHD. Interestingly, both EDs and ADHD rely on a common neural substrate, namely, dopaminergic signaling. Dopaminergic signaling is critical for motor activity and emotion, the latter enabling the former into a combined motivated movement like eating. This linkage aids in explaining the many comorbidities associated with ADHD. The interconnection of ADHD and EDs is discussed from both a historical perspective and the one based on the revealing nature of its comorbidities.

Keywords: ADHD, eating disorders, obesity, disordered eating, dopamine, motivation

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by an age inappropriate level of attention, impulsivity, and hyperactivity.[1] The prevalence of ADHD is ~5.3% in the pediatric population and 3.4% in the adult population.[2,3] Treatment for ADHD includes cognitive behavioral therapy and pharmacologic treatment. The drug of choice is methylphenidate, a psychostimulant. Other drugs include amphetamine and nonpsychostimulant drugs, such as atomoxetine and guanfacine.[4]

Interestingly, ADHD is rarely present as an isolated disorder. Previous studies have reported that ~70% of ADHD patients display at least one other comorbid disorder or specific neurological problems.[5–7] In the last decade, researchers report a significant coincidence of ADHD and eating disorders (EDs).[5,8,9] The EDs mostly associated with ADHD are binge eating disorder (BED) and bulimia nervosa (BN). BED is characterized by recurrent binge eating episodes and associated feelings of guilt and lack of control. BN is characterized by recurrent binge eating episodes followed by self-induced vomiting or other compensatory behavior. Anorexia nervosa (AN) is characterized by

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distorted body image and excessive dieting.[1] Although the link between AN and ADHD is more controversial, some studies suggest an association between the two.[10]

Other psychiatric comorbidities of ADHD include conduct disorders, oppositional defiant disorders (ODDs), mood disorders, anxiety disorders, learning disabilities, mental retardation, Tourette's syndrome, borderline personality disorders, etc.[11] In this extensive literature review, Biederman et al proposed that ADHD patients with different comorbidities represent unique subgroups with different clinical courses and require different treatment strategies. Since 1991, many researchers have echoed this belief.[11]

In addition to psychiatric comorbidities, ADHD is associated with devastating health outcomes: substance abuse, suicide, physical injuries, risky sexual behavior, obesity, diabetes type 2, hypertension, higher health care visits, and early mortality.[12,13] Although the reason behind these associations is not clear, impairment of executive function in patients with ADHD is hypothesized to be the most simple explanation.[14] Thus, they are unable to plan and execute healthy behaviors, including caring for their own hygiene and health. The adverse health outcome mostly related to disordered eating is obesity. Besides this, it is unclear whether ADHD may be connected with specific changes in somatic growth.[15–17]

The topic of sex differences in ADHD also becomes significant. In pediatric populations, ADHD is estimated to be three times more common in boys than in girls. In adults, the incidence of ADHD is similar in both sexes.[18] Males with ADHD are more likely to externalize their symptoms, and females are more likely to internalize their symptoms.[19,20] Compounding these observations some believe that, in reality, the prevalence of ADHD in girls is higher than reported, because of their ability to better "mask" their symptoms during childhood.[21] BN and AN are disorders that mainly affect females. The phenomena that ADHD is underdiagnosed in girls and EDs are more prevalent have clinical implications.

Eating patterns and nutrition for subjects with ADHD

Recent studies have found a significant link between the ADHD and an abnormal dietary pattern, ie, the consumption of "junk food" and nonadherence to a "traditional" three-meal daily diet. The first of such studies was the Raine study, which analyzed the eating patterns of 1,799 adolescents.[22] Of the participants, 115 adolescents were found to have ADHD. Subjects were classified as "western" or "traditional" at the 14-year follow-up after birth. The western diet pattern was linked with higher intake of fat, sugar, and sodium and lower intake of omega-3 fatty acids, fiber, and folate. The study found that the subjects with ADHD symptoms were more likely to have a western style diet than a traditional healthy diet (odds ratio [OR] =2.21), potentially suggesting dietary problems, which may be associated with processed foods.

Similar to the Raine study, a Korean group studied the dietary patterns of children with ADHD.[23] The four dietary patterns discovered were "seaweed-egg", "traditional-healthy", "traditional", and "snack". The seaweed-egg pattern was characterized with high intakes of fats and sweets. The study found a significant association between the ADHD and the seaweed-egg dietary pattern. Another Korean study of 12,350 participants reports a significant association between ADHD and unhealthy foods, such as soft drinks, westernized fast food, and instant noodles.[24] Our group studied the eating behaviors of premedicated newly diagnosed ADHD boys using structured interviews of parents. We found that patients with ADHD are more likely to skip breakfast and dinner and have more than five meals throughout the day. We also found that these disruptive dietary patterns were accompanied by diminished consumption of fruits and vegetables and increased consumption of sweetened beverages.[25] Even prior to the Raine trial, many nutritional deficiencies had been associated with ADHD.[26] Iron deficiency and low serum ferritin levels have been linked to ADHD and impaired cognitive behavioral development.[27–29] Zinc deficiency, especially in the Middle East, has also been associated with ADHD. Zinc is an important cofactor implicated in the metabolism of dopamine, a neurotransmitter involved in ADHD pathophysiology. Arnold et al reported that zinc supplementation decreased the optimal dose of amphetamine treatment.[30,31] Consumption of food additives and artificial sweeteners has been reported to contribute to abnormal levels of hyperactivity in developing children.[32] Considerable research has been devoted to the omega-3 and -6 polyunsaturated fatty acid (PUFA) supplementation. Similar to zinc, polyunsaturated fatty acids are also involved in neuronal development and have protective effects against ADHD symptoms.[33–35] As a result of the previous findings, there has been an interest for dietary interventions with hopes of improvement in symptoms or prevention of ADHD in children.[36]

Coupling of obesity and ADHD

The link between ADHD and disordered eating behavior is evident by the observation that obesity is more prevalent in individuals with ADHD compared to the general population. Altfas was the first to describe the comorbidity of the two

disorders.[37] Altfas found an unusual prevalence of ADHD (27.4%) among obese adults. After treatment of symptoms, weight loss was greater in the treated ADHD obese adults compared to non-ADHD obese adults.[37] Shortly after, two other groups reported similar finding in hospitalized obese children and obese women. Further studies reported that obese patients with ADHD had predominantly inattentive symptoms.[38,39]

The comorbidity was later supported by massive community surveys, smaller clinical cross-sectional studies, and some longitudinal studies. A large cross-sectional study of 43,297 US adolescents revealed a statistically significant adjusted OR of 1.5.[13] Similar results were found in adolescent population of 9,619 adolescents aged.[40] A study with 1,633 adult German participants found that the prevalence of ADHD was 9.3% in individuals who are obese. This abnormally high prevalence was not observed in overweight (3.8%) and normal weight individuals (4.3%). Conversely, the study reported that participants with ADHD were twice as likely to be obese than the general population (22.1% vs 10.2%).[41] Furthermore, Cortese et al found that obese adults were more likely to have had a diagnosis of childhood ADHD in the past. Notably, their study consisted of 34,653 face-to-face interviews of young adults and also found that impulsive and inattentive symptoms, but not hyperactive symptoms, mediated the association.[42] Also notable was a 33-year longitudinal study of 207 participants, by the same author, which found that men who had childhood ADHD had higher BMI and obesity rates.[43]

Other smaller cross-sectional studies of children and adolescents seeking treatment for ADHD suggest a comorbidity between higher BMI and ADHD. A cross-sectional study by a group in Poland examined boys aged 6–18 years who were diagnosed with ADHD and demonstrated that overweight status but not obesity was statistically significant in the ADHD group.[44] Another study of 158 children with ADHD aged 6–16 years found that patients with ADHD had a higher prevalence of obesity. The study also found that the patients with combined subtype of ADHD were significantly more likely to be obese and overweight compared to those with only inattentive or only hyperactive symptoms.[45]

A possible explanation for the comorbidity between the two disorders is a common genetic and neurobiological pathway. Obesity genes in the pathways of dopaminergic circuitry, such as FTO (fat mass–and obesity-associated variant) and melanocortin 4 receptor, have been associated with ADHD.[46–48] A case study reported that a 13-year-old obese boy with ADHD (BMI =47.2) and a melanocortin 4 receptor mutation showed a dramatic decrease in BMI after atomoxetine treatment.[49] Co-occurrence of ADHD and obesity has also been attributed to common immune and inflammatory processes, common fetal programming mechanisms, and common perinatal risk factors.[12,50]

Coupling of BEDs and ADHD

Various investigators propose that the link between obesity and ADHD lies in the common symptom of impulsivity. Here, it is surmised that ADHD predisposes an individual to BED, again due to common impulsivity symptoms. Impulsivity is defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions.[51] Inhibition, working memory, planning, and sustained attention are necessary for executive function or the ability to perform a sequence of goal-oriented tasks.[52,53] Cortese et al argue that the impulsivity of ADHD patients causes executive dysfunction, which prevents the patient from executing the goal of controlling eating behavior or losing weight.[14]

Clinically, impulsivity in ADHD patients can be found with the Barratt Impulsiveness Scale (BIS). It is a 30-item self-reporting questionnaire.[54] Impulsiveness can also be demonstrated using the go–no-go paradigm. ADHD patients with predominantly impulsive symptoms have more commitment errors in the go–no-go task. For example, when receiving a cue for a string of consecutive "go" responses, the subject is more likely to commit to go even after presented with a cue for "no-go". Commitment errors represent a lack of response inhibition, an essential ingredient of executive functioning.[55] Because of impulsiveness, patients with ADHD and BED are not able to "inhibit" their impulse to eat food, even when faced the task of dieting and losing weight.[56] This hypothesis is corroborated by many cross-sectional studies of BED patients in weight loss or prebariatric surgery clinics. It is found that symptoms of impulsiveness and inattention correlate with severity of BED symptoms.[57,58] For example, Docet et al found that obese patients with ADHD were more likely to have binge eating episodes, to eat snacks between meals, to eat large amounts of food, and to eat in secret.[59] In another study, methylphenidate treatment in obese individuals with ADHD resulted in significant weight loss in obese patients with ADHD.[60]

The link between impulsivity and BED was also demonstrated using a combination of magnetoencephalography, the go–no-go task, and the BIS.[61,62] The study used food stimuli or toys as the go–no-go cues and a population of subjects with and without BED. It was found that, in BED, impulsiveness according to BIS scores correlated with decreased

food-specific response inhibition in the prefrontal control network during the go–no-go task.[63] This is consistent with other studies on response inhibition to food cues in BED using functional magnetic resonance imaging.[64,65]

Often young children may not have BED at the time of diagnosis of ADHD; however, some have a similar condition called "loss of control eating" (LOC).[66] It is defined by subjective feelings of binge eating or subjective loss of control while consuming a normal or small amount of food. Thus, a subject who may not have an official diagnosis of BED may still be considered to have LOC. Reinblatt et al reported that LOC was much higher in children with ADHD (adjusted OR =12.68).[67] LOC eating in childhood may be a predictor of disordered eating behavior in adolescence.[68] Although promising and educational, it is still not known whether a combination of LOC and ADHD in childhood longitudinally translate into objective BED. Food addiction, or eating behavior that involves overconsumption of specific foods that are highly palatable in an addiction-like manner, has also been associated with inattentive impulsive symptoms. It is thought that ADHD consists of dopamine and norepinephrine circuits in the brain, which are involved in reward processing. This accounts for the high prevalence of substance abuse disorders in ADHD subjects. Thus, food addiction, like substance abuse, is also comorbid with ADHD.[69,70]

Although executive dysfunction has been shown to play a role in BED, it does not encompass the entire picture. Steadman and Knouse found that although impulsivity in ADHD correlates with BED symptoms, impulsivity alone does not mediate the association.[71] Other comorbidities in ADHD patients are thought to contribute to binge eating behavior. Affective diseases, mainly depression, have been associated with higher incidence of BED. Many studies found that the presence of depressive symptoms in obese adults with ADHD correlated with severity of BED symptoms.[72–75] The other comorbidity that may mediate the association between BED and ADHD is ODD. Pauli-Pott et al reported that ODD symptoms, not ADHD symptoms alone, were associated with disordered eating behaviors.[76,77] This suggests that patients with ADHD and another psychiatric comorbidity are necessary for the development of BED. Expectedly, in the same study, participants with symptoms of anxiety and depression showed emotional and binge eating.

ADHD symptomatology in women with BN

BN, as noted for the other disorders, is associated with eating and has also been linked to ADHD. In the case of BN, sex differences become significant and apparent from the literature. The prevalence of ADHD is three times higher in boys than girls.[42] This may be due to the phenomena that girls are more likely to internalize and "mask" their symptoms, while boys externalize them. There is also a higher level of clinical suspicion of the disorder in boys, which may contribute to underdiagnosis in girls.[18,21] On the other hand, BN is nearly 12 times more common in girls than boys.[78]

Owing to underdiagnosis of ADHD in girls, by the time a female realizes she has a psychiatric disorder, she may already be in late adolescence or adulthood. This phenomenon is evident in a series of case studies, which were the first presentations of the association between BN and ADHD. These studies paint a common picture of a young adult female who had a seemingly normal childhood. Her attention was sufficient to perform her school duties and manage her family and social life during childhood and early adolescence.[79] When faced with greater challenges, such as attending university, managing her time, having a relationship, and making her own life decisions, her deficits in executive functions became apparent. Symptoms of depression and/or anxiety were present, and bulimic symptoms of binging and purging were out of control. Pharmacologic therapy for ADHD symptoms in this patient improved her executive functions and, interestingly, decreased her purging behaviors.[79–84] A number of studies support the initial findings of the previously mentioned case studies. In a study of 20 women with BN and 20 age-matched controls, symptoms of impulsivity measured with the BIS were significantly higher in the BN group.[85] In a larger study of 89 women with ED, Yates et al found that inattentive symptoms of ADHD were common among women with BN. Furthermore, Yates et al also confirmed that inattentive symptoms correlated with bulimic behavior and depressive symptoms.[86] A number of other studies reported similar findings.[87,88] In addition to depression, the presence of anxiety and disruptive disorders was reported. Impulsivity alone does not account for the link between ADHD and BN. Other comorbidities, such as depression, anxiety, and disruptive behavior, were also found to mediate the association between BN and ADHD.[11] Girls with ADHD and depressive symptoms were found to be at the highest risk of BN.[11] Notably, among studies of BN, there are two longitudinal studies by Mikami et al in a 5-year prospective longitudinal study of ADHD girls aged 6–12 years.[89] Mikami et al found that baseline impulsivity symptoms predicted adolescent pathology. Interestingly, the group found that baseline peer rejection and parent–child relationship predicted eating pathology. Punitive parenting

in childhood also predicted pathological eating behaviors.[89] In an 8-year follow-up, the Eating Disorder Inventory-II was used to collect data about body image dissatisfaction and personality characteristics associated with EDs. It was found that boys and girls with ADHD were at risk with symptoms of BN in mid-adolescence. The association was stronger in girls than in boys.[90] Similar studies have the same results.[84,85] In summary, girls with ADHD and symptoms of depressive, anxiety, and disruptive disorders are at risk of developing BN. In adolescents with BN, there is a high prevalence of suicide attempts, alcohol consumption, and illegal drug use.[91]

Evidences from modern neurobiology methods corroborate the abovementioned findings. For example, the Catechol-O-methyltransferase gene, involved in the dopaminergic pathways of ADHD, was also implicated in BN.[92] From a neuroimaging perspective, ADHD and BN share many neural pathways. Abnormalities in these pathways in the frontostriatal circuit may account for the coincidences in these two disorders.[93] Much is not known about the effect of puberty on ADHD and BN. It is thought that sex differences may be accounted for by different hormones in boys and girls during puberty.[94–96] Biederman et al found that girls with ADHD tend to have an earlier onset of menarche; however, the reason behind this finding is currently not understood.[95] The link between AN and ADHD is not clear despite the hypothesis of a common neural substrate.[97–100] The number of studies is small, and the studies that do exist have a small number of subjects.[10,101,102] Thirty-two female patients diagnosed with ED had no correlation between severity of ADHD and severity of ED symptoms; however, there was an association between impulsivity and avoidance of fattening food.[101] A larger study of 191 patients reports that girls with AN had a higher correlation with ADHD symptomatology than girls with BN.[10] The symptoms with the highest correlation included novelty seeking, impaired self-directedness, and impaired cooperativeness. Similarly, Wentz et al found that in a small study of individuals with EDs, there was a high prevalence of ADHD.[102]

Hazards and challenges

The literature suggests that it may be beneficial to interview and counsel patients and parents regarding eating behaviors. We surmise, from the data analysis, that special attention should be given to females since they are more likely to internalize their symptoms and display depressive behaviors, thus masking symptoms of ADHD. This may account for the observation that the ratio of ADHD children who seek treatment is ~3:1 (girls to boys).[2] This was especially evident in the series of case studies on BN. These case studies paint the picture of a young adult female who was able to mask her ADHD symptoms throughout childhood. During adulthood, when faced with tasks that required higher executive function (for example, time management in university), the symptoms of ADHD caused havoc in her life. This is compounded by the problem that it is a challenge to diagnose ADHD early, regardless of the population. The solution for this problem may be in educating the general population, which will allow people to seek early advice if symptoms of ADHD are present. However, this may lead to an overdiagnosis of ADHD but is better than underdiagnosing this debilitating condition. Moreover, the solution for early detection is in the hands of neonatologists or pediatricians. In this regard, many risks factors for ADHD are perinatal, for example, prematurity.[103] Furthermore, research should be focused on identifying babies who are more likely to have ADHD.

In addition to early diagnosis, it is also important to monitor affective symptoms of ADHD. Most of the literature on BN and AN suggest that depression may mediate bulimic and anorexic symptoms. Monitoring depressive symptoms in addition to eating behaviors in girls, especially, appears to be critical. In addition to depressive symptoms, these patients have a distorted body image.[89,90] Importantly, regarding dietary contributing factors, care must be taken when counseling girls about diet.[8] Impulsive behavior is related to avoidance of food in anorexic girls.[101] Anorexic and bulimic girls are already obsessed and guilty due to their eating behaviors. Counseling eating behavior should be done in a positive manner, which rehabilitates self-confidence, not in a manner that makes the girls feel even more "guilty".

A challenge in the study of EDs and ADHD is the cyclical nature of the symptoms of both diseases. Investigators have found that predominant symptoms of ADHD may change, persist, or remit throughout the lifetime.[104,105] The general trend is that inattentive symptoms are more persisting.[103] Patients with EDs have been found to cycle through symptoms of BN, AN, and EDs not otherwise specified.[106,107] No study to our knowledge has longitudinally examined the complex interaction that may arise due to cyclical shifting between different subtypes of EDs and ADHD. One can only imagine that it is very complex, and more research and understanding about the relationship between the two is needed.

Conclusion

ADHD and eating behavior are strongly tied together and correlated throughout age groups.[5,8,9] Furthermore, unhealthy eating habits as well as food-associated additives, in general,

are directly correlated with ADHD and healthier diets have been associated with improved symptomatology.[22] ADHD is also correlated with pathological eating behaviors that are characterized as mental illnesses, such as, BN, AN as well as abnormal BMI ranges known as obesity.[1,13,18] It is important to note that catecholamines, eg, dopamine, are heavily involved in both motor regulation and emotions, working together to provide the motivation for motor activity, using few chemical messengers in both invertebrates and vertebrates, especially humans.[108] Thus, it is not a surprise that ADHD comorbidities involve EDs, which may result from altered cognitive and emotional neural substrates.[5,11] Furthermore, it is not a surprise that ADHD comorbidities involve EDs, which may result from altered cognitive and emotional neural substrates given their dependencies.[109] This is also somewhat evident from the COMT data, which involve ADHD behavioral states and EDs.[110,111] Taken together, although ADHD is complex and multifaceted as are EDs, it appears that they may represent a logical comorbidity. Hence, early diagnostic indicators for ADHD may be at hand in the form of novel discoveries in gene expression patterns.

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References

1. American Association of Pediatrics. *Diagnostic and Statistic Manual of Mental Disorders*. 5th ed. Washington DC: American Psychiatric Publishing; 2013.
2. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry*. 2007;164(6):942–948.
3. Fayyad J, De Graaf R, Kessler R. Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *Br J Psychiatry*. 2007;190:402–409.
4. Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894–921.
5. Nazar BP, Pinna CM, Coutinho G, et al. Review of literature of attention-deficit/hyperactivity disorder with comorbid eating disorders. *Rev Bras Psiquiatr*. 2008;30(4):384–389.
6. Goetz M, Schwabova J, Hlavka Z, et al. Cerebellar symptoms are associated with omission errors and variability of response time in children with ADHD. *J Atten Disord*. 2014.
7. Nováková M, Paclt I, Ptáček R, Kuželová H, Hájek I, Sumová A. Salivary melatonin rhythm as a marker of the circadian system in healthy children and those with attention-deficit/hyperactivity disorder. *Chronobiol Int*. 2011;28(7):630–637.
8. Quinn PO. Attention-deficit/hyperactivity disorder and its comorbidities in women and girls: an evolving picture. *Curr Psychiatry Rep*. 2008;10(5):419–423.
9. Cortese S, Angriman M, Maffeis C, et al. Attention-deficit/hyperactivity disorder (ADHD) and obesity: a systematic review of the literature. *Crit Rev Food Sci Nutr*. 2008;48(6):524–537.
10. Fernández-Aranda F, Agüera Z, Castro R, et al. ADHD symptomatology in eating disorders: a secondary psychopathological measure of severity? *BMC Psychiatry*. 2013;13(1):166–173.
11. Biederman J, Newcorn J, Sprich S. Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety, and other disorders. *Am J Psychiatry*. 1991;148(5):564–577.
12. Nigg JT. Attention-deficit/hyperactivity disorder and adverse health outcomes. *Clin Psychol Rev*. 2013;33(2):215–228.
13. Halfon N, Larson K, Slusser W. Associations between obesity and comorbid mental health, developmental, and physical health conditions in a nationally representative sample of US children aged 10 to 17. *Acad Pediatr*. 2013;13(1):6–13.
14. Cortese S, Comencini E, Vincenzi B, Speranza M, Angriman M. Attention-deficit/hyperactivity disorder and impairment in executive functions: a barrier to weight loss in individuals with obesity? *BMC Psychiatry*. 2013;13:286–292.
15. Ptacek R, Kuzelova H, Stefano G, Raboch J, Kream R, Goetz M. ADHD and growth: questions still unanswered. *Neuro Endocrinol Lett*. 2014;35(1):1–6.
16. Ptacek R, Kuzelova H, Paclt I, Zukov I, Fischer S. ADHD and growth: anthropometric changes in medicated and non-medicated ADHD boys. *Med Sci Monit*. 2009;15(12):CR595–CR599.
17. Ptacek R, Kuzelova H, Paclt I, Zukov I, Fischer S. Anthropometric changes in non-medicated ADHD boys. *Neuro Endocrinol Lett*. 2009;30(3):377–381.
18. Quinn PO, Madhoo M. A review of attention-deficit/hyperactivity disorder in women and girls: uncovering this hidden diagnosis. *Prim Care Companion CNS Disord*. 2014;16(3):CC.13r01596.
19. Gershon J. A meta-analytic review of gender differences in ADHD. *J Atten Disord*. 2002;5:143–154.
20. Biederman J, Faraone SV, Spencer T, Wilens T, Mick E, Lapey KA. Gender differences in a sample of adults with attention deficit hyperactivity disorder. *Psychiatry Res*. 1994;53(1):13–29.
21. Quinn P, Wigal S. Perceptions of girls and ADHD: results from a national survey. *MedGenMed*. 2004;6(2):2.
22. Howard AL, Robinson M, Smith GJ, Ambrosini GL, Piek JP, Oddy WH. ADHD is associated with a "western" dietary pattern in adolescents. *J Atten Disord*. 2011;15(5):403–411.
23. Woo HD, Kim DW, Hong YS, et al. Dietary patterns in children with attention deficit/hyperactivity disorder (ADHD). *Nutrients*. 2014;6(4):1539–1553.
24. Kim EJ, Kwon HJ, Ha M, et al. Relationship among attention-deficit hyperactivity disorder, dietary behaviours and obesity. *Child Care Health Dev*. 2014;40(5):698–705.
25. Ptacek R, Kuzelova H, Stefano GB, et al. Disruptive patterns of eating behaviors and associated lifestyles in males with ADHD. *Med Sci Monit*. 2014;20:608–613.
26. Konikowska K, Regulska-Ilow B, Rozanska D. The influence of components of diet on the symptoms of ADHD in children. *Rocz Panstw Zakl Hig*. 2012;63(2):127–134.
27. Halterman JS, Kaczorowski JM, Aligne CA, Auinger P, Szilagyi PG. Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States. *Pediatrics*. 2001;107(6):1381–1386.
28. Konofal E, Lecendreux M, Arnulf I, Mouren MC. Iron deficiency in children with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med*. 2004;158(12):1113–1115.
29. Millichap JG, Yee MM, Davidson SI. Serum ferritin in children with attention-deficit hyperactivity disorder. *Pediatr Neurol*. 2006;34(3):200–203.
30. Arnold LE, Disilvestro RA, Bozzolo D, et al. Zinc for attention-deficit/hyperactivity disorder: placebo-controlled double-blind pilot trial alone and combined with amphetamine. *J Child Adolesc Psychopharmacol*. 2011;21(1):1–19.

31. Toren P, Eldar S, Sela BA, et al. Zinc deficiency in attention-deficit hyperactivity disorder. *Biol Psychiatry*. 1996;40(12):1308–1310.
32. Bateman B, Warner JO, Hutchinson E, et al. The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. *Arch Dis Child*. 2004;89(6):506–511.
33. Mitchell EA, Aman MG, Turbott SH, Manku M. Clinical characteristics and serum essential fatty acid levels in hyperactive children. *Clin Pediatr*. 1987;26(8):406–411.
34. Colter AL, Cutler C, Meckling KA. Fatty acid status and behavioural symptoms of attention deficit hyperactivity disorder in adolescents: a case-control study. *Nutr J*. 2008;7:8–19.
35. Richardson AJ, Montgomery P. The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics*. 2005; 115(5):1360–1366.
36. Millichap JG, Yee MM. The diet factor in attention-deficit/hyperactivity disorder. *Pediatrics*. 2012;129(2):330–337.
37. Altfas JR. Prevalence of attention deficit/hyperactivity disorder among adults in obesity treatment. *BMC Psychiatry*. 2002;2:9–17.
38. Agranat-Meged AN, Deitcher C, Goldzweig G, Leibenson L, Stein M, Galili-Weisstub E. Childhood obesity and attention deficit/hyperactivity disorder: a newly described comorbidity in obese hospitalized children. *Int J Eat Disord*. 2005;37(4):357–359.
39. Fleming JP, Levy LD, Levitan RD. Symptoms of attention deficit hyperactivity disorder in severely obese women. *Eat Weight Disord*. 2005;10(1):e10–e13.
40. Phillips KL, Schieve LA, Visser S, et al. Prevalence and impact of unhealthy weight in a national sample of US adolescents with autism and other learning and behavioral disabilities. *Matern Child Health J*. 2014;18(8):1964–1975.
41. de Zwaan M, Gruss B, Müller A, et al. Association between obesity and adult attention-deficit/hyperactivity disorder in a German community-based sample. *Obes Facts*. 2011;4(3):204–211.
42. Cortese S, Faraone SV, Bernardi S, Wang S, Blanco C. Adult attention-deficit hyperactivity disorder and obesity: epidemiological study. *Br J Psychiatry*. 2013;203(1):24–34.
43. Cortese S, Ramos Olazagasti MA, Klein RG, Castellanos FX, Proal E, Mannuzza S. Obesity in men with childhood ADHD: a 33-year controlled, prospective, follow-up study. *Pediatrics*. 2013;131(6): e1731–e1738.
44. Hanć T, Słopień A, Wolańczyk T, et al. ADHD and overweight in boys: cross-sectional study with birth weight as a controlled factor. *Eur Child Adolesc Psychiatry*. 2015;24(1):41–53.
45. Yang R, Mao S, Zhang S, Li R, Zhao Z. Prevalence of obesity and overweight among Chinese children with attention deficit hyperactivity disorder: a survey in Zhejiang Province, China. *BMC Psychiatry*. 2013; 13(1):133–140.
46. Albayrak Ö, Pütter C, Volckmar AL, et al; Psychiatric GWAS Consortium: ADHD Subgroup. Common obesity risk alleles in childhood attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet*. 2013;162b(4):295–305.
47. Choudhry Z, Sengupta SM, Grizenko N, et al. Association between obesity-related gene FTO and ADHD. *Obesity (Silver Spring)*. 2013; 21(12):E738–E744.
48. Agranat-Meged A, Ghanadri Y, Eisenberg I, Ben Neriah Z, Kieselstein-Gross E, Mitrani-Rosenbaum S. Attention deficit hyperactivity disorder in obese melanocortin-4-receptor (MC4R) deficient subjects: a newly described expression of MC4R deficiency. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147b(8):1547–1553.
49. Pott W, Albayrak O, Hinney A, Hebebrand J, Pauli-Pott U. Successful treatment with atomoxetine of an adolescent boy with attention deficit/hyperactivity disorder, extreme obesity, and reduced melanocortin 4 receptor function. *Obes Facts*. 2013;6(1):109–115.
50. Verlaet AA, Noriega DB, Hermans N, Savelkoul HF. Nutrition, immunological mechanisms and dietary immunomodulation in ADHD. *Eur Child Adolesc Psychiatry*. 2014;23(7):519–529.
51. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. *Am J Psychiatry*. 2001;158(11):1783–1793.
52. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull*. 1997; 121(1):65–94.
53. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol Psychiatry*. 2005;57(11):1336–1346.
54. Barratt ES. Factor analysis of some psychometric measures of impulsiveness and anxiety. *Psychol Rep*. 1965;16(2):547–554.
55. Trommer BL, Hoeppner JA, Lorber R, Armstrong KJ. The go-no-go paradigm in attention deficit disorder. *Ann Neurol*. 1988;24(5):610–614.
56. Schag K, Schonleber J, Teufel M, Zipfel S, Giel KE. Food-related impulsivity in obesity and binge eating disorder – a systematic review. *Obes Rev*. 2013;14(6):477–495.
57. Gruss B, Mueller A, Horbach T, Martin A, de Zwaan M. Attention-deficit/hyperactivity disorder in a prebariatric surgery sample. *Eur Eat Disord Rev*. 2012;20(1):e103–e107.
58. Reinblatt SP, Leoutsakos JM, Mahone EM, Forrester S, Wilcox HC, Riddle MA. Association between binge eating and attention-deficit/hyperactivity disorder in two pediatric community mental health clinics. *Int J Eat Disord*. 2014;48(5):505–511.
59. Docet MF, Larranaga A, Perez Mendez LF, Garcia-Mayor RV. Attention deficit hyperactivity disorder increases the risk of having abnormal eating behaviours in obese adults. *Eat Weight Disord*. 2012; 17(2):e132–e136.
60. Levy LD, Fleming JP, Klar D. Treatment of refractory obesity in severely obese adults following management of newly diagnosed attention deficit hyperactivity disorder. *Int J Obes*. 2009;33(3):326–334.
61. Wilson TW, Franzen JD, Heinrichs-Graham E, White ML, Knott NL, Wetzel MW. Broadband neurophysiological abnormalities in the medial prefrontal region of the default-mode network in adults with ADHD. *Hum Brain Mapp*. 2013;34(3):566–574.
62. Hege MA, Stingl KT, Kullmann S, et al. Attentional impulsivity in binge eating disorder modulates response inhibition performance and frontal brain networks. *Int J Obes*. 2015;39(2):353–360.
63. Hege MA, Preissl H, Stingl KT. Magnetoencephalographic signatures of right prefrontal cortex involvement in response inhibition. *Hum Brain Mapp*. 2014;35(10):5236–5248.
64. Balodis IM, Grilo CM, Kober H, et al. A pilot study linking reduced fronto-striatal recruitment during reward processing to persistent binge-ing following treatment for binge-eating disorder. *Int J Eat Disord*. 2014; 47(4):376–384.
65. Lock J, Garrett A, Beenhakker J, Reiss AL. Aberrant brain activation during a response inhibition task in adolescent eating disorder subtypes. *Am J Psychiatry*. 2011;168(1):55–64.
66. Blomquist KK, Roberto CA, Barnes RD, White MA, Masheb RM, Grilo CM. Development and validation of the eating loss of control scale. *Psychol Assess*. 2014;26(1):77–89.
67. Reinblatt SP, Mahone EM, Tanofsky-Kraff M, et al. Pediatric loss of control eating syndrome: association with attention-deficit/hyperactivity disorder and impulsivity. *Int J Eat Disord*. 2015;48(6):580–588.
68. Tanofsky-Kraff M, Yanovski SZ, Schvey NA, Olsen CH, Gustafson J, Yanovski JA. A prospective study of loss of control eating for body weight gain in children at high risk for adult obesity. *Int J Eat Disord*. 2009;42(1):26–30.
69. Gearhardt AN, Yokum S, Orr PT, Stice E, Corbin WR, Brownell KD. Neural correlates of food addiction. *Arch Gen Psychiatry*. 2011;68(8):808–816.
70. Meule A, Hermann T, Kubler A. Food addiction in overweight and obese adolescents seeking weight-loss treatment. *Eur Eat Disord Rev*. 2015;23(3):193–198.
71. Steadman KM, Knouse LE. Is the relationship between ADHD symptoms and binge eating mediated by impulsivity? *J Atten Disord*. 2014.
72. Muller A, Claes L, Wilderjans TF, de Zwaan M. Temperament subtypes in treatment seeking obese individuals: a latent profile analysis. *Eur Eat Disord Rev*. 2014;22(4):260–266.

73. Nazar BP, Suwwan R, de Sousa Pinna CM, et al. Influence of attention-deficit/hyperactivity disorder on binge eating behaviors and psychiatric comorbidity profile of obese women. *Compr Psychiatry*. 2014; 55(3):572–578.
74. Alfonsson S, Parling T, Ghaderi A. Self-reported symptoms of adult attention deficit hyperactivity disorder among obese patients seeking bariatric surgery and its relation to alcohol consumption, disordered eating and gender. *Clin Obes*. 2013;3(5):124–131.
75. Khalife N, Kantomaa M, Glover V, et al. Childhood attention-deficit/hyperactivity disorder symptoms are risk factors for obesity and physical inactivity in adolescence. *J Am Acad Child Adolesc Psychiatry*. 2014; 53(4):425–436.
76. Pauli-Pott U, Becker K, Albayrak O, Hebebrand J, Pott W. Links between psychopathological symptoms and disordered eating behaviors in overweight/obese youths. *Int J Eat Disord*. 2013;46(2):156–163.
77. Pauli-Pott U, Neidhard J, Heinzel-Gutenbrunner M, Becker K. On the link between attention deficit/hyperactivity disorder and obesity: do comorbid oppositional defiant and conduct disorder matter? *Eur Child Adolesc Psychiatry*. 2014;23(7):531–537.
78. Surman CB, Randall ET, Biederman J. Association between attention-deficit/hyperactivity disorder and bulimia nervosa: analysis of 4 case-control studies. *J Clin Psychiatry*. 2006;67(3):351–354.
79. Dukarm CP. Bulimia nervosa and attention deficit hyperactivity disorder: a possible role for stimulant medication. *J Womens Health (Larchmt)*. 2005;14(4):345–350.
80. Schweickert LA, Strober M, Moskowitz A. Efficacy of methylphenidate in bulimia nervosa comorbid with attention-deficit hyperactivity disorder: a case report. *Int J Eat Disord*. 1997;21(3):299–301.
81. Sokol MS, Gray NS, Goldstein A, Kaye WH. Methylphenidate treatment for bulimia nervosa associated with a cluster B personality disorder. *Int J Eat Disord*. 1999;25(2):233–237.
82. Guerdjikova AI, McElroy SL. Adjunctive methylphenidate in the treatment of Bulimia nervosa co-occurring with bipolar disorder and substance dependence. *Innov Clin Neurosci*. 2013;10(2):30–33.
83. Keshen A, Ivanova I. Reduction of bulimia nervosa symptoms after psychostimulant initiation in patients with comorbid ADHD: five case reports. *Eat Disord*. 2013;21(4):360–369.
84. Loannidis K, Serfontein J, Muller U. Bulimia nervosa patient diagnosed with previously unsuspected ADHD in adulthood: clinical case report, literature review, and diagnostic challenges. *Int J Eat Disord*. 2014; 47(4):431–436.
85. Wolfe BE, Jimerson DC, Levine JM. Impulsivity ratings in bulimia nervosa: relationship to binge eating behaviors. *Int J Eat Disord*. 1994; 15(3):289–292.
86. Yates WR, Lund BC, Johnson C, Mitchell J, McKee P. Attention-deficit hyperactivity symptoms and disorder in eating disorder inpatients. *Int J Eat Disord*. 2009;42(4):375–378.
87. Seitz J, Kahraman-Lanzerath B, Legenbauer T, et al. The role of impulsivity, inattention and comorbid ADHD in patients with bulimia nervosa. *PLoS One*. 2013;8(5):e63891.
88. Nazar BP, Pinna CM, Suwwan R, et al. ADHD rate in obese women with binge eating and bulimic behaviors from a weight-loss clinic. *J Atten Disord*. 2012.
89. Mikami AY, Hinshaw SP, Patterson KA, Lee JC. Eating pathology among adolescent girls with attention-deficit/hyperactivity disorder. *J Abnorm Psychol*. 2008;117(1):225–235.
90. Mikami AY, Hinshaw SP, Arnold LE, et al. Bulimia nervosa symptoms in the multimodal treatment study of children with ADHD. *Int J Eat Disord*. 2010;43(3):248–259.
91. Fischer S, le Grange D. Comorbidity and high-risk behaviors in treatment-seeking adolescents with bulimia nervosa. *Int J Eat Disord*. 2007;40(8):751–753.
92. Yilmaz Z, Kaplan AS, Zai CC, Levitan RD, Kennedy JL. COMT Val158Met variant and functional haplotypes associated with childhood ADHD history in women with bulimia nervosa. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(4):948–952.
93. Broft A, Shingleton R, Kaufman J, et al. Striatal dopamine in bulimia nervosa: a pet imaging study. *Int J Eat Disord*. 2012;45(5): 648–656.
94. Ostojic D, Miller CJ. Association between pubertal onset and symptoms of ADHD in female university students. *J Atten Disord*. 2014.
95. Biederman J, Ball SW, Monuteaux MC, Surman CB, Johnson JL, Zeitlin S. Are girls with ADHD at risk for eating disorders? Results from a controlled, five-year prospective study. *J Dev Behav Pediatr*. 2007; 28(4):302–307.
96. Katayama K, Yamashita Y, Yatsuga S, Koga Y, Matsuishi T. ADHD-like behavior in a patient with hypothalamic hamartoma. *Brain Dev*. 2016;38(1):145–148.
97. Stefano GB, Ptáček R, Kuželová H, et al. Convergent dysregulation of frontal cortical cognitive and reward systems in eating disorders. *Med Sci Monit*. 2013;19:353–358.
98. Stefano G, Ptacek R, Kuzelova H. Endogenousmorphine – up-to-date review 2011. *Folia Biol*. 2012;58(2):49–56.
99. Ptacek R, Kuzelova H, Stefano G. Genetics in psychiatry up-to-date review 2011. *Neuro Endocrinol Lett*. 2011;32(4):389–399.
100. Kream R, Stefano G, Ptacek R. Psychiatric implications of endogenous morphine: up-to-date review. *Folia Biol*. 2010;56(6):231–241.
101. Stulz N, Hepp U, Gachter C, Martin-Soelch C, Spindler A, Milos G. The severity of ADHD and eating disorder symptoms: a correlational study. *BMC Psychiatry*. 2013;13(1):44–50.
102. Wentz E, Lacey JH, Waller G, Rastam M, Turk J, Gillberg C. Childhood onset neuropsychiatric disorders in adult eating disorder patients. A pilot study. *Eur Child Adolesc Psychiatry*. 2005;14(8):431–437.
103. Mick E, Biederman J, Prince J, Fischer MJ, Faraone SV. Impact of low birth weight on attention-deficit hyperactivity disorder. *J Dev Behav Pediatr*. 2002;23(1):16–22.
104. Hart EL, Lahey BB, Loeber R, Applegate B, Frick PJ. Developmental change in attention-deficit hyperactivity disorder in boys: a four-year longitudinal study. *J Abnorm Child Psychol*. 1995;23(6):729–749.
105. Biederman J, Mick E, Faraone SV. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *Am J Psychiatry*. 2000;157(5):816–818.
106. Anderluh M, Tchanturia K, Rabe-Hesketh S, Collier D, Treasure J. Lifetime course of eating disorders: design and validity testing of a new strategy to define the eating disorders phenotype. *Psychol Med*. 2009;39(1):105–114.
107. Castellini G, Lo Sauro C, Mannucci E, et al. Diagnostic crossover and outcome predictors in eating disorders according to DSM-IV and DSM-V proposed criteria: a 6-year follow-up study. *Psychosom Med*. 2011;73(3):270–279.
108. Stefano GB, Kream RM. Endogenous morphine synthetic pathway preceded and gave rise to catecholamine synthesis in evolution (review). *Int J Mol Med*. 2007;20(6):837–841.
109. Esch T, Kim JW, Stefano GB. Neurobiological implications of eating healthy. *Neuro Endocrinol Lett*. 2006;27(1–2):21–33.
110. Mantione KJ, Kream RM, Stefano GB. Catechol-O-methyltransferase: potential relationship to idiopathic hypertension. *Arch Med Sci*. 2010; 6(3):291–295.
111. Mantione K, Kream RM, Stefano GB. Variations in critical morphine biosynthesis genes and their potential to influence human health. *Neuro Endocrinol Lett*. 2010;31(1):11–18.