Low hair cortisol concentration predicts the development of attention deficit hyperactivity disorder

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A B S T R A C T

Objective: Low activity of the hypothalamic-pituitary-adrenal axis (HPAA) resulting from genetic and early environmental factors has been thought to indicate risk for the development of attention deficit hyperactivity disorder (ADHD) and externalizing disorders. However, longitudinal research on this issue is scarce. We analyzed whether hair cortisol concentration (HCC), i.e. accumulated long-term HPAA activity, predicts the development of ADHD between preschool and school age.
Methods: A community-based sample of 126 children was assessed at the ages of 4, 5 and 8 years. ADHD and symptoms of oppositional defiant and conduct disorder (ODD/CD), callous unemotional (CU) traits, and internalizing symptoms were measured by clinical parent interviews and parent and teacher questionnaires. HCC was analyzed in the most proximal 3-cm scalp hair segment using luminescence immunoassay.
Results: Low HCC at preschool age predicted an increase in ADHD symptoms between preschool and school age while adjusting for gender of child, maternal education level, and internalizing symptoms ($F_{(1,119)} = 6.5$; $p = .012$). The prediction held after additionally adjusting for ODD/CD symptoms and CU traits ($F_{(1,116)} = 4.1$; $p = .045$). The same was true for the prediction of the ADHD diagnosis at the age of 8 years ($Chi^2_{(1)} = 7.3$; $p = .007$). The prediction of ADHD was mainly based on the presentation of inattention symptoms ($F_{(1,119)} = 7.4$, $p = .008$).
Conclusion: Low HCC in preschool children indicates an increased risk of developing ADHD at school age. In future research, it would be of theoretical and clinical importance to further circumscribe this HCC-related developmental pathway and track its further course of development.

1. Introduction

Dysregulation of the hypothalamic-pituitary-adrenal axis (HPAA) has been found in several psychiatric disorders (e.g. Lupien et al., 2009). Potentially underlying mechanisms comprise influences of glucocorticoids on the transcription of genes involved in the disorders (Koss and Gunnar, 2018), lasting "programming effects" on the HPAA through early-life stress exposure (Koss and Gunnar, 2018; Lupien et al., 2009), adverse experiences in later life, influences of genetic predispositions, and interaction processes between these factors (Ouellet-Morin et al., 2011; Struber et al., 2014). The early developing HPAA characteristics might have the potential to indicate specific pathogenic mechanisms and to predict the development of psychiatric disorders. Nevertheless, it is also possible that the cortisol markers reflect (past) influences of psychopathological symptoms on adjustment processes

involving the HPAA. Longitudinal research is needed to analyze whether the HPAA characteristics actually precede and predict the development of a psychiatric disease.

In attention-deficit hyperactivity disorder (ADHD) and the broader domain of externalizing disorders (ED) comprising oppositional defiant disorder (ODD), conduct disorder (CD) and ADHD (Achenbach et al., 1991), many studies have been conducted on HPAA functions. Meta-analyses of this research revealed a lower basal cortisol secretion in ADHD (Scassellati et al., 2012) and in ED (Alink et al., 2008), while cortisol reactivity measures were not consistently associated with ADHD or ED (Scassellati et al., 2012; Alink et al., 2008). Two more recent large cross-sectional studies on psychopathological symptoms in childhood underscore the notion that hypocortisolism in particular is associated with externalizing symptoms (White et al., 2017) and psychopathological symptoms under adverse environmental conditions

(Fuchs et al., 2018). The low activity of the HPAA in ED has been explained by theories of low arousal and low anxiety. Low arousal has been thought to reflect an aversive physiological state which the individual attempts to normalize (increase) by seeking sensation through impulsive, risky and rule-breaking behaviors. Low anxiety has been suggested to lead to inadequate social learning because children do not fear the negative consequences of their behaviors (Raine, 2002). It has been proposed that the conditions result from early-life adversities (White et al., 2017; Fuchs et al., 2018) and/or from genetic predispositions that also affect HPAA development (Fairchild et al., 2018; Platje et al., 2013). As crucial normative adjustment processes of the HPAA occur in infancy and toddlerhood (Lupien et al., 2009), low HPAA activity might represent an early-emerging biomarker of risk (Davis et al., 2015) for the development of ED (indicating the environmentally and/or genetically induced HPAA deviation). As mentioned, however, longitudinal research is necessary to analyze this notion.

While numerous cross-sectional studies have been conducted on the association between cortisol parameters and ED, there are only a small number of longitudinal studies examining the predictive associations between cortisol markers and ED symptom development. Two large-scale longitudinal studies found no associations between preceding salivary cortisol markers of HPAA activity in early childhood and parent-rated ED symptoms at the age of 3 years (Hill-Soderlund et al., 2015; Saridjan et al., 2014). Salis et al. (2016) studied children at the ages of 6 and 9 years, and found that an attenuated diurnal salivary cortisol profile at age 6 predicted an increase in parent-rated ED symptoms between 6 and 9 years. Two further studies analyzed developing ODD/CD symptoms in late childhood and mid-adolescence: Platje et al. (2013) found that the cortisol awakening response at age 15 predicted an increase in self-reported ODD/CD symptoms between 15 and 17 years. Sondeijker et al. (2008), however, did not find any predictive or concurrent associations between the morning cortisol level (three saliva samples) and the development of ODD/CD symptoms over two years in a sample of 10-12-year-olds.

All of these studies considered developmental periods characterized by major changes in ED symptoms. First symptoms of ADHD and ODD typically emerge in the preschool and early school years, while CD symptoms increase between late childhood and mid-adolescence (Fairchild et al., 2013). Nevertheless, the results of these longitudinal studies are mixed. Several issues might be responsible for the discrepant findings. The preschool studies analyzed ED symptoms, i.e. used composite scores on symptoms of ADHD and ODD/CD. The late childhood/mid-adolescence studies addressed ODD/CD symptoms and did not control for comorbid ADHD symptoms. No study considered so-called callous-unemotional (CU) traits (i.e. limited prosocial emotions, e.g. lack of remorse, guilt or empathy, shallow or deficient emotional expression, characterizing a minority of youth with CD (DSM-5; APA, 2013)). In recent years, the CU traits of children with ODD/CD have been found to explain the association between ODD/CD and cortisol reactivity to emotionally challenging events (Fairchild, et al., 2018; Stadler et al., 2011). No longitudinal study has analyzed ADHD symptoms. Attention problems, however, were found to be associated with hypocortisolism in the context of early childhood adversity (Koss et al., 2016). Moreover, ED symptoms have almost exclusively been assessed by caregiver or self-report questionnaires, while clinical interviews or a more complete multi-informant approach have not been employed.

A further reason for the inconsistent results might lie in the methods used to assess HPAA activity. All of the reported studies used salivary cortisol measures, which reflect the cortisol concentration only at a single time point (Russell et al., 2012). The collection of multiple saliva samples across consecutive days, however, often does not extend the time period (and reliability of measurement) to a satisfactory degree, and has the disadvantage of causing considerable stress (and a consequent increase in cortisol) due to the sampling procedure (Russell et al., 2012). The hair cortisol concentration (HCC), by contrast,

appears to be free of these disadvantages and has proven to reliably and validly capture the accumulated, integrated long-term activity of the HPAA (Kirschbaum et al., 1990; Short et al., 2016; Stalder et al., 2017). For these reasons, we used HCC in the present study. To our knowledge, this is the first study to use HCC in the context of ADHD and the first longitudinal study on HCC and ADHD or externalizing symptom development.

In recent research, gender has been assumed to represent a significant moderator variable of the link between HPAA activity and ED (Fairchild et al., 2018). The longitudinal studies reported above, however, found no differences between boys and girls in the prediction of ED symptoms by HPAA activity (Hill-Soderlund et al., 2015; Saridjan et al., 2014; Platje et al., 2013; Sondeijker et al., 2008). At the first assessment wave of the current longitudinal study, we found a significant interaction effect between child's gender and HCC on ADHD symptoms: Low HCC was associated with high ADHD symptoms exclusively in boys (Pauli-Pott et al., 2017). The use of HCC as marker of HPAA activity might have facilitated the identification of the moderator effect.

Against this background, the present longitudinal study aims to analyze the predictive associations between HCC and ADHD development while considering ODD/CD symptoms and CU traits. As first symptoms of ADHD typically manifest in the preschool years and then successively stabilize until school age, we investigate the period between preschool and school age. We hypothesize that low HCC at preschool age predicts an increase in ADHD symptoms between preschool and school age as well as a diagnosis of ADHD at school age. Moreover, we explore differences between boys and girls in the prediction by HCC and examine the roles of the comorbid symptoms of ODD/CD, CU traits, and internalizing symptoms in this prediction.

2. Methods

2.1. Participants

A community-based sample of 198 children (115 boys, 58%) was recruited from childcare facilities located in the district of Marburg, Middle-West Germany. Parents and their 4-5-year-old children were invited to take part in a longitudinal study on child development from preschool to school age. Exclusion criteria were: IQ < 80, motor disabilities, sensory handicaps, chronic physical and mental diseases involving brain functions, indication of a trauma (serious physical maltreatment, life-threatening injury) experienced by the child, any continuous pharmacological treatment, and insufficient German language skills of parents or child. To sufficiently represent emerging ADHD symptoms, the sample was enriched with children scoring in the upper range of an ADHD screening questionnaire (FBB-ADHS-V, (Döpfner et al., 2008; description see below) completed by parents at recruitment. The final sample comprised 113 preschoolers who scored at or above the 70th percentile of the German norms of the screening questionnaire, and 85 children who scored below this point (see Pauli-Pott et al., 2017 for further details).

The 4-year-olds (n = 125) were seen for a second time 12 months later at the age of 5 years (n = 120, the dropout rate between 4 and 5 years was n = 5, i.e. 4%). Therefore, 193 children and their families were seen at the age of 5 years (M = 66.2, SD = 3.5 months). Of these children, 179 participated in the assessment at 8 years (M = 101.4, SD = 3.65 months). The dropout rate between the 5- and the 8-years assessment was 7.2% (n = 14 cases). No differences emerged between those children who participated in the 8-years assessment and those who dropped out with respect to gender and age of the child (Chi^2 = 0.22; t = -.00), preschool HCC, ADHD symptoms, or symptoms of anxiety/depression and oppositional symptoms of the child (t-scores between -1.78 and 0.96).

HCC was analyzed in 137 children at the age of 4 or 5 years. The remaining children had to be excluded (n = 48 because parents refused

Table 1
Description of the sample.

n = 126 children	
Gender	n (%)
male	59 (46.8)
female	67 (53.2)
Education level of mother	n (%)
no compl./ basic education	8 (6.3)
work qualification	45 (35.7)
high school	23 (18.3)
college	50 (39.7)
Education level of father	n (%)
basic education	21 (16.7)
work qualification	25 (19.8)
high school	32 (25.4)
college	46 (36.5)
(no reply)	2 (1.6)
5-years assessment	m (s, range)
ADHD score (PrePACS interview)	4.5 (3.9, 0-18)
ADHD score (FBB-ADHS-V parent)	0.86 (0.5, 0-2.4)
ADHD score (FBB-ADHS-V teacher)	0.63 (0.6, 0-2.0)
ODD/CD score (FBB-SSV parent)	0.45 (0.4, 0-1.9)
Hair cortisol concentration[*] (HCC) pg/mg	6.85 (5.94, 0.53-36.98)
8-years assessment	
ADHD diagnosis	n (%)
yes	16 (12.7)
no	110 (87.3)
	m (s, range)
ADHD score (CAPA interview)	4.9 (3.6, 0-16)
ADHD score (FBB-ADHS parent)	0.74 (0.5, 0-2.6)
ADHD score (FBB-ADHS teacher)	0.56 (0.6, 0-2.6)
ODD/CD symptoms (clinical parent interview)	2.21 (1.8, 0-8)
ODD/CD score (SDQ behavior problems parent)	1.77 (1.89, 0-10)
ODD/CD score (SDQ behavior problems teacher)	2.96 (1.86, 0-8)
CU score (SDQ/ASPD parent)	3.7 (2.6, 0-11)
CU score (SDQ/ASPD teacher)	4.4 (3.3, 0-14)

* HCC before log-transformation; ADHD: attention deficit hyperactivity disorder; ODD/CD: oppositional defiant disorder/ conduct disorder; CU: callous-unemotional traits; m mean, s standard deviation.

to take part in the hair collection part of the study or the child did not fulfill the criterion of minimum hair length of 3 cm, n = 11 because insufficient hair was collected, n = 2 were outliers of the HCC distributions, see below). Children with available HCC data (n = 137) were compared with children with missing data (n = 61). While no significant differences emerged in maternal and paternal education level (Chi^2 (3) scores were 6.9 and 5.4), significantly more boys than girls were excluded from the analysis due to the shorter haircuts of the boys (Chi^2 (1) = 23.6, p < .001). After controlling for this gender difference, there were no differences between children with and without HCC data in the psychopathological symptom scores (on ADHD, ODD/CD, anxiety/depression symptoms, CU traits) at 4/5 and 8 years and ADHD diagnoses at 8 years (F$_{(1,195)}$ scores between 1.56 and 0.08). In all further analyses, gender of child was taken into account.

Of these 137 children, 126 participated in the 8-years assessment. At 8 years, two children, who had been diagnosed with ADHD in the interim, were medicated with methylphenidate. We did not exclude these children because the 8-years ADHD diagnosis is considered as a criterion variable and it is impossible for the preschool HCC measure to be affected by the later pharmacological treatment. Table 1 contains descriptive data of the sample of 126 children with complete data. Parents gave their written informed consent to participate in the study, and received an expense allowance of 50 Euros at the preschool assessment and 70 Euros at the school-age assessment. The study was approved by the Ethics Committee of the Medical Faculty, University of Marburg.

2.2. Procedure

At each assessment wave, data were collected within the scope of two meetings. At 4, 5, and 8 years, a home visit was conducted. At 4

and 5 years, the home visit was followed by a "playroom" session at the childcare facilities (data from which will be published elsewhere) and a telephone interview with the mothers. At 8 years, the playroom session was conducted at our lab. At each wave, the two meetings were conducted within a maximum of six weeks. During the home visits, interviews with the mother were conducted, the child underwent an intelligence test, and the hair samples were collected. The playroom sessions comprised neuropsychological tests of the child and structured clinical interviews with the mothers. Parents and teachers completed questionnaires on ADHD symptoms as well as symptoms of ODD/CD, anxiety/depression and CU traits.

2.3. Variables

2.3.1. Hair cortisol concentration (HCC)

At the 4- and 5-years assessments, hair samples of the children were collected. Several thin hair strands were cut as close to the scalp as possible from the posterior vertex region of the head. The first proximal scalp-near 3-cm segment was used for the determination of HCC. This 3-cm segment is thought to reflect the cumulative cortisol secretion of the past 3 months (Wennig, 2000) and therefore corresponds to the assessment of the child's ADHD symptoms in the past 3 months in the clinical parent interview. Hair-washing and cortisol extraction procedures were based on a laboratory protocol first described by Stalder et al. (2012), with minor modifications. In brief, hair samples were washed twice for 3 min using 3 mL isopropanol. For cortisol extraction, 10.0 ± 0.5 mg whole, finely cut hair samples were incubated in 1.8 mL methanol for 18 h at room temperature. After incubation, 1.6 mL of the extract was evaporated at 50 °C under a constant stream of nitrogen until the samples were completely dried. Finally, 150 μl HPLC gradient grade water (Fisher Scientific) was added and vials were vortexed for 20 s. For cortisol determination (single samples were run for analysis), 50 μL was applied for analysis using a commercially available cortisol luminescence immunoassay (LIA; IBL, Hamburg, Germany). Due to the longitudinal nature of data collection, samples were assayed in two batches. The intra-assay and inter-assay coefficient of variance (CV) of the first batch of the assay were 4.6% and 7.3%, respectively. The intra-assay and inter-assay coefficient of variation (CV) of the second batch of the assay were 2.8 and 5.5%, respectively.

The HCC showed a skewed distribution at both assessments. The distributions were therefore normalized by exclusion of outliers exceeding the mean + 3 SD (one case at each assessment) and subsequent log-transformation. The stability of HCC between the assessments at 4 and 5 years (12-month interval) was r = .54 (n = 62). Potential influences of several confounders on the HCC scores were checked. We found no significant association of HCC at the first and second assessment with the concurrent body mass index of the child (Spearman's Rho = -.03 and -.13), the number of cigarettes smoked by the mother (Spearman's Rho = -.14 and -.18), hair color and curling, hair-washing frequency, or use of hair products (gel, spray) (t-scores 1.83 to 1.02). To increase the number of cases for the present analyses, we used the z-transformed 4- or 5-years score if only one score was available and averaged the 4- and 5-years scores in cases with both scores.

2.3.2. ADHD symptoms and diagnosis

At each assessment wave, ADHD symptoms of the child were assessed using a structured clinical parent interview and by parent and teacher questionnaires. At the ages of 4 and 5 years, the Parental Account of Childhood Symptoms (PACS) interview (Taylor et al., 1986) in the modified preschool version (PrePACS) (Daley, 2010) was conducted with the mother. In this interview, parents are asked to assess the intensity and frequency of the circumscribed symptoms (Taylor et al., 1986) in the last 3 months (Bufferd et al., 2012). The ADHD scale of the interview shows good test-retest reliability (.78, 15-week interval) and discriminates significantly between children with ADHD and healthy controls (Sonuga-Barke, 2003). Parents and preschool

teachers completed the preschool version of the ADHD rating scale (FBB-ADHS-V) of the "Diagnostik-System für Psychische Störungen" [Diagnostic System for Psychiatric Disorders] (DISYPS-II) by Döpfner et al. (2008). This questionnaire captures ADHD symptoms according to the ICD-10. The parent and teacher version show high internal consistency (Cronbach's alpha: .94 and .93) and good validity (differentiation between children with and without an ADHD diagnosis) (Breuer and Dopfner, 2008). With regard to HCC, we created a preschool (4/5 years) composite score by averaging the 4 and 5 years scores after z-transformation.

At the age of 8 years, the ADHD diagnostic module of the Child and Adolescent Psychiatric Interview (CAPA) by Angold et al. (1995) in the German DSM-5 Version (translated by Dr. Yvonne Otto, Child and Adolescent Psychiatric Clinic, University of Leipzig) was conducted with the mother. The CAPA is a well-validated, widely established clinical interview, which allows clinical diagnoses to be made according to the DSM-5 and also enables the creation of dimensional symptom scores. The CAPA has proven to be particularly useful for scoring psychopathology in terms of quantitative traits (Angold et al., 2012). Moreover, it has shown good correspondence with other established clinical interviews and questionnaires and discriminates well between clinical and non-clinical cases (Angold et al., 2012). Parents and school teachers completed the FBB-ADHS of the DISYPS-III. The questionnaires capture ADHD symptoms according to ICD-10 and DSM-5, and show good psychometric properties, as reported above.

At the 4/5- and 8-years assessments, the three ADHD scores (see Table 1 for the distributions) showed substantial inter-correlations (r's between .34; p < .001 and .66; p < .001 at 4/5 years; between .62; p < .001 and .82; p < .001 at 8 years; see Table 2 for the internal consistency of the composite scores). At 8 years, moreover, an ADHD research diagnosis (see Table 1) was made based on the CAPA. In the following, we use the 4/5 and 8 years composite scores as well as the ADHD diagnosis at 8 years.

2.4. Control variables

For control purposes, i.e. to analyze whether the prediction by HCC is specific for ADHD symptoms or relies on the comorbid symptoms, the following variables were measured.

2.4.1. Symptoms of ODD/CD and CU traits

At 4 and 5 years, mothers completed the German FBB-SSV questionnaire of the DISYPS-II by Döpfner et al. (2008), which measures ODD/CD symptoms of the child. The scale shows high internal consistency (Cronbach's alpha = .91) and validly discriminates between children with ODD/CD and controls (Gortz-Dorten et al., 2014). The 4 and 5 years scores were averaged after z-transformation.

At 8 years, ODD/CD diagnostic modules of the CAPA interview were conducted with the mother. Mothers and teachers completed the "behavior problems" scale of the Strengths and Difficulties Questionnaire (SDQ) by Goodman (1999), German Version by Woerner et al. (2002). The scale has shown an internal consistency of .60 (Cronbach's alpha) and factorial validity (Woerner et al., 2002). Correlations among these three ODD/CD measures ranged between r = .35 (p < .001) and r = .48 (p < .001). We built a composite score by summing up the three z-transformed scores. CU traits were assessed at 8 years using the "prosocial behavior" scale of the SDQ and the "callous-unemotional" scale of the Antisocial Process Screening Device (APSD; by Frick and Hare (2001)), completed by mothers and teachers. The items of the two scales have been proven to validly capture CU traits in 4-9-year-old children (Dadds et al., 2005). The CU scale of the APSD correlated significantly with ODD/CD symptoms and ADHD symptoms in 4-12-year-old children (Dadds, et al., 2005; Koglin and Petermann, 2012; Pasalich et al., 2011). In our study, the parent and teacher CU scores correlated significantly (r = .35, p < .001). We built a composite score by summing up the z-transformed scores.

2.4.2. Symptoms of anxiety and depression

At 4 and 5 years, the anxiety/depression symptoms scale of the Child Behavior Checklist (CBCL4-18) by Achenbach et al. (1991) in the German version by Döpfner et al. (1994) was employed. The scale shows significant associations with anxiety and emotional disorders, indicating good validity (Döpfner et al., 1994). As with the other variables, we created a composite score of the 4- and 5-years assessments. At the 8-years assessment, the screening interview of the DISYPS-III by Döpfner and Görtz-Dorten (2017) was conducted with the mother. Items referring to anxiety and depressive disorders were summed up.

2.5. Statistical analysis

To facilitate the interpretation of the multivariate results and for the purpose of transparency, in a preliminary analysis, the uncorrected correlations between HCC and symptoms of ADHD, ODD/CD, and CU traits were calculated for all children as well as separately for girls and boys. These correlations and their significance levels have to be understood as descriptive statistics. To test the first hypothesis, i.e. whether HCC predicts an increase in ADHD symptoms between 4/5 and 8 years, hierarchical multiple regression analyses were conducted (Aiken and West, 1991; Cohen et al., 2003), with ADHD symptoms at 8 years as the criterion variable. In consecutive steps, control variables were introduced into the regression equation. To model "change in ADHD symptoms between 4/5 and 8 years", the preschool ADHD score was introduced into the regression analysis first, followed by the other control variables (i.e. gender of child, maternal education level if significantly associated with the 8-years ADHD score, and anxiety/depression symptoms). The HCC score was added in the final step. The change statistics of the regression analysis for HCC reflect the predictive effect of HCC over and above the previously introduced control variables, i.e. the prediction of change in ADHD symptoms between 4/5 and 8 years by the preschool HCC score while controlling for gender, maternal education level and anxiety/depression symptoms. In the case of a significant prediction by HCC, we analyzed (in a further regression model) whether the prediction by HCC held after controlling for ODD/CD and CU traits.

To analyze whether the prediction by HCC was stronger in boys than in girls, we tested the interaction effect between gender of child and HCC on ADHD symptoms at 8 years (Aiken and West, 1991) while controlling for the ADHD symptoms at 4/5 years and the other control variables. Finally, we analyzed whether the obtained associations might be affected by the recruitment of a sample of children with increased ADHD symptoms. For this purpose, we compared the variance explained by HCC in the ADHD score at 8 years in the complete regression model (with all control variables) in children scoring above and below the 70th percentile on the ADHD screening questionnaire.

To analyze whether the HCC predicted the ADHD diagnosis, we conducted a logistic regression analysis with stepwise introduction of the control variables. In the logistic regression models, we also adjusted for the ADHD score at 4/5 years in order to analyze whether HCC adds predictive information over and above the concurrent preschool ADHD symptoms.

The interaction effect between gender of child and HCC was tested by introducing the interaction term (product of HCC and gender) into the regression equation in a final step (Aiken and West, 1991). To further explore possible gender differences, we also repeated the regression analysis in boys and girls separately. However, because of the limited sample size of these sub-groups, we do not consider the "comorbid" psychopathological symptoms of the child in these analyses.

Hypotheses were tested with an alpha error of 5% (level of significance of 0.05).

Table 2

Internal consistency statistics of the composite scores and correlations among study variables in all children (n = 126) and in boys (n = 59) and girls (n = 67) separately.

	mean[1] r	Cronbach's[2] α	1	2	3	4	5	6	7	8	9	10	11
1 HCC 4/5y	.79	–	–	–.06	–.14	–.08	–.20*	–.13 (-.09; -.15)	–.13	–.07	.02	.03	–.19*
2 ADHD score 4/5y	.43	.82	–.33* .11	–	.50***	.31***	.42***	.63** (.62***; .51***)	.27**	.25**	.21*	–.33***	–.11
3 ODD/CD score 4/5y	.75	–[4]	–.15 -.19	.49*** .50***	–	.50***	.33***	.36** (.41***; .24**)	.35***	.40***	.13	–.11	–.14
4 anx./dep. score 4/5y	.51	–[4]	–.22 .03	.40** .25*	.58*** .46***	–	.16	.17 (.16; .15)	.15	.14	.52***	–.15	.05
5 ADHD diagnosis 8y	–	–	–.39* -.09	.42** .41***	.07 .61***	.15 .18	–	.65** (.61***; .55***)	.34***	.24*	.23*	–.20*	–.14
6 ADHD score 8y (6a: hyp/ imp; 6b: inattent)	.72 (.68; .66)	.89 (.86; .86)	–.31* (-.22; -.34**) -.09 (-.07; -.09)	.65*** (.59***; .59***) .61** (.66***; .41***)	.24 (.28*; .14) .46*** (.52***; .28*)	.24 (.20; 22) .16 (.15; 13)	.65*** (.58***; .60***) .62** (.64***; .45***)	–	.49** (.48***; .40***)	.41** (.39***; .35***)	.33*** (.24**; .35***)	–.22* (-.18*; -.22*)	–.28** (-.25***; -.25**)
7 ODD/CD score 8y	.39	.66	–.14 -.23	.21 .31*	.25 .47***	.19 .15	.24 .47***	.47*** .44***	–	.60***	.47***	–.03	–.22*
8 CU score 8y	.35	–[5]	.06 -.06	.16 .32*	.31* .49***	.21 .13	.10 .39***	.38* .31*	.64*** .45***	–	.29***	–.06	–.32***
9 anx./dep. score 8y	.39	.72	–.14 .23	.32* .08	.14 .13	.49*** .59***	.28* .16	.41*** .24*	.59*** .30*	.46*** .01	–	–.08	.02
10 maternal education	–	–	.10 -.04	–.39* -.30*	–.03 -.19	–.11 -.18	–.16 -.28*	–.30* -.21	–.05 -.03	–.02 -.16	–.19 .06	–	–
11 gender of child	–	–	–	–	–	–	–	–	–	–	–	–	–

Above the diagonal: correlations in all children; below the diagonal: correlations in boys (first line of cell) and girls (second line of cell). Correlation coefficients and p-values have to be regarded as descriptive statistics. [1]Mean correlation of the single scores (4 and 5 years clinical parent interview, 8 years clinical parent interview, parent and teacher questionnaire, respectively) of the composite score; [2]. Internal consistency of the composite score; [3]. HCC at 4 and 5 years, Cronbach's α not acceptable for two scores; [4]. 4 and 5 years parent and teacher questionnaire, Cronbach's α not acceptable for two scores; [5]. 8 years parent and teacher questionnaire, Cronbach's α not acceptable for two scores.

ADHD: attention deficit hyperactivity disorder; ODD/CD: oppositional defiant disorder/ conduct disorder; CU: callous-unemotional traits; anx./dep.: anxiety/depression symptoms; HCC: hair cortisol concentration; 4/5 y: composite score 4 and 5 years; 8y: composite score 8 years.

*p < .05, ** p < .01, *** p < .001.

3. Results

3.1. Preliminary analyses

Table 2 shows the inter-correlations of the study variables in all children and in girls and boys, separately. The cross-sectional association between HCC and ADHD symptoms in the preschool years was significant and of medium magnitude in the boys: The lower the HCC, the higher the ADHD symptoms. Moreover, the HCC at 4/5 years was significantly associated with the ADHD diagnosis at 8 years: Children with ADHD at age 8 showed lower HCC in the preschool years than children without an ADHD diagnosis. In the subgroup of the boys, this latter association was of medium magnitude and highly significant, as was the association between the HCC and the 8-years ADHD symptom score. In girls, both associations were of small magnitude and did not reach statistical significance. No significant cross-sectional or longitudinal associations of the HCC with 4/5- and 8-years ODD/CD and anxiety/depression symptoms emerged, and there were no associations with the child's CU traits at the age of 8 years.

3.2. Prediction of ADHD development by preschool HCC

Gender of child and maternal education level were significantly associated with the ADHD score at 8 years (Table 2). We therefore controlled for these variables. Table 3 shows the results of the hierarchical multiple linear regression analyses on the hypothesized prediction of change in ADHD symptoms between 4/5 and 8 years. In the first model, we adjusted for 4/5-years ADHD symptoms (to model change in ADHD symptoms) and for anxiety/depression symptoms, besides gender of child and maternal education, by introducing these variables into the regression equation in the first and second step. HCC

was introduced into the regression in a third step. The respective change statistics indicate a significant prediction of change in ADHD symptoms between 4/5 and 8 years by the 4/5-years HCC score. The ß-coefficient of the HCC variable indicates that low HCC predicts an increase in ADHD symptoms. This association is illustrated in Fig. 1. In a second model, moreover, we controlled for the ODD/CD symptoms and CU scores (Table 3, model A2). The prediction remained statistically significant. The 4/5-years HCC score predicted an increase in ADHD symptoms over and above gender of child, maternal education level and the other psychopathological symptoms of the child.

To assess the role of the recruitment procedure, we repeated the regression analyses (model A2) within the groups of children scoring above and below the 70th percentile of the preschool ADHD screening questionnaire. The percentage of explained variance by HCC in the ADHD score was of comparable magnitude (low preschool ADHD symptoms: 1.6%, high preschool ADHD symptoms: 1.4%).

To analyze the hypothesized prediction of the ADHD diagnosis, hierarchical multiple logistic regression analyses were conducted (Table 4). In the first model (A1), we adjusted for ADHD symptoms at 4/5 years (to control for the concurrent HCC-ADHD association) as well as for gender of child, maternal education level, and anxiety/depression symptoms. The 4/5-years HCC score significantly predicted the 8-years ADHD diagnosis over and above the previously introduced variables. This association is illustrated in Fig. 2. The prediction by 4/5-years HCC remained statistically significant after additionally controlling for ODD/CD and CU scores (Table 4, model A2). Children who showed low HCC in preschool years were more likely to have received an ADHD diagnosis at 8 years.

Table 3
Prediction of change in ADHD symptoms between 5 and 8 years.

Multiple hierarchical linear regression analyses						
Criterion: 8-years ADHD symptom score						
Model A1: Adjustment for gender of child, maternal education level, anxiety/depression symptoms scores						
Step	Variable(s) added	R	R^2_{change}	$F_{change\ (df)}$	p_{change}	Model (A1: step 1-3 variables), ß-coefficients
1	ADHD symptom score 4/5y	.63	.40	82.2 (1;124)	< .001	.57***
2	gender of child	.71	.10	6.3 (4;120)	< .001	−.25***
	maternal education level					−.05
	anx./dep. score 4/5y					−.17*
	anx./dep. score 8y					.30***
3	HCC 4/5y	**.73**	**.03**	**6.5 (1;119)**	**.012**	−.16*
4	HCC 4/5y X gender of child	.73	.00	0.1 (1;118)	.80	–
Model A2: Additional adjustment for ODD/CD, CU scores						Model (A2: step 1-4 variables), ß-coefficients
1	ADHD symptom score 4/5y	.63	.40	82.2 (1;124)	< .001	.52***
2	gender of child	.71	.10	6.3 (4;120)	< .001	−.18*
	maternal education level					−.05
	anx./dep. score 4/5y					−.12
	anx./dep. score 8y					−.17*
3	ODD/CD score 4/5y	.74	.05	4.2 (3;117)	.008	−.01
	ODD/CD score 8y					.18*
	CU score 8y					.09
4	HCC 4/5y	**.75**	**.02**	**4.1 (1; 116)**	**.045**	−.13*
5	HCC 4/5 y X gender of child	.75	.00	0.1 (1;115)	.80	–

ADHD: attention deficit hyperactivity disorder; ODD/CD: oppositional defiant disorder/conduct disorder; anx./dep.: anxiety/depression symptoms; HCC: hair cortisol concentration.
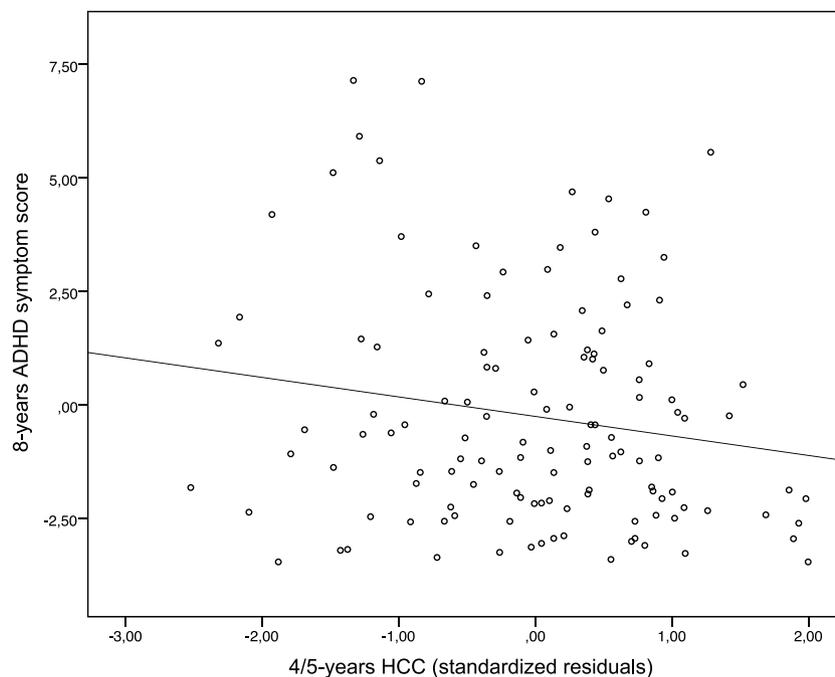
Fig. 1. Prediction of 8-years ADHD symptoms by 4/5-years HCC adusted for 4/5-years ADHD, maternal education, gender of child, anxiety/depression symptoms (4/5 and 8 years).

Note. Regression line corresponds to ß = -.16, R^2 = .03 (model A1, Table 3).

3.3. Exploration of gender differences in the prediction of ADHD

We explored potential moderator effects by gender of child. For this purpose, the interaction effect between gender and HCC was introduced into the regression equations in a final step (Tables 3 and 4). In no cases did the interaction effect reach statistical significance. The prediction of change in ADHD symptoms by HCC thus did not significantly differ between boys and girls. We conducted the regression analysis on the prediction of ADHD symptoms and diagnosis by HCC in boys and girls separately. Due to the limited sample sizes, we did not control for maternal education level or comorbid psychopathological symptoms in these analyses. We found no significant prediction of ADHD symptoms in boys (n = 59, F_{change} = 1.04, ß-coefficient = -.11) or girls (n = 67, F_{change} = 3.27, ß-coefficient = -.17). In boys, the prediction of the 8-years ADHD diagnosis over and above the 4/5-years ADHD score by HCC was statistically significant (n = 59, including n = 12 boys with an ADHD diagnosis; Chi^2_{change} (1) = 4.44, p = .035, unstandardized B-coefficient = -.69). In the girls, the prediction was not significant (n = 67 including n = 7 girls with an ADHD diagnosis; Chi^2_{change} (1) = 1.70, unstandardized B-coefficient = -.47). Low HCC at 4/5 years thus predicts an ADHD diagnosis at 8 years primarily in boys.

3.4. Exploration of differences in the prediction of ADHD symptom presentation

The presentation of ADHD symptoms, i.e. whether inattention symptoms or hyperactivity/impulsivity symptoms predominate, changes over the course of development (Willcutt et al., 2012). We therefore explored whether the HCC predicts both presentations to a comparable extent. HCC significantly predicted an increase in inattention symptoms between 4/5 and 8 years while controlling for gender of child, maternal education level and anxiety/depression symptoms (F_{change} = 7.4, p = .008, R^2_{change} = 0.04) and also while additionally controlling for ODD/CD symptoms and CU traits (F_{change} = 6.5, p = .012, R^2_{change} = 0.03). HCC did not predict an increase in hyperactivity/impulsivity symptoms (F_{change} = 2.2 and 0.6).

4. Discussion

The present longitudinal study analyzed the prediction of ADHD development between preschool and school age by HCC (capturing the accumulated long-term activity of the HPAA). Consistent with expectations, low HCC developmentally preceded an increase in ADHD symptoms between preschool and school age and an ADHD diagnosis at school age. Therefore, low HCC can be regarded as a peripheral biomarker of risk for ADHD development.

Low HCC in preschool age was associated with concurrent and 8-years ADHD symptoms in boys. In all children, HCC correlated with the 8-years ADHD diagnosis: i.e. children with and without school-age ADHD differed significantly in the preschool HCC. This association, however, was somewhat more pronounced in boys than in girls. The corresponding cross-sectional and longitudinal associations between HCC and ODD/CD symptoms, CU traits and internalizing symptoms were weak. Low HCC predicted the developmental course of ADHD while controlling for these "comorbid" psychopathological symptoms. Thus, it can be concluded that low HCC is particularly involved in the development of ADHD.

This finding is in line with the results of a recent review by Fairchild et al. (2018), who summarized that a link between low cortisol reactivity to emotionally challenging events (i.e. HPAA reactivity) and ODD/CD has consistently been found, while results on HPAA activity in ODD/CD are mixed and inconclusive. It might be that low basal HPAA activity is characteristic for ADHD. Although Scassellati et al. (2012) did not control for comorbid ODD/CD in their meta-analysis, they found a significant (albeit small) association of ADHD with basal cortisol levels and no association with cortisol reactivity measures. Moreover, we found that the significant prediction by low HCC was mainly based on the inattention symptoms. Hyperactivity/impulsivity symptoms, which have been assumed to overlap with ODD/CD (Beauchaine and McNulty, 2013), were not significantly predicted by HCC.

In terms of cognitive deficits and deviations in brain circuitry, ADHD is a heterogeneous disorder. Some children with ADHD show an under-activation of the alerting network comprising frontoparietal and thalamic brain circuitry (Faraone et al., 2015). Low cortical arousal and

Table 4
Prediction of 8-years ADHD diagnosis.

Multiple hierarchical logistic regression analyses				
Criterion: 8-years ADHD diagnosis				
Model A1: Adjustment for gender of child, maternal education level, anxiety/ depression symptoms scores				
Step	Variable(s) added	Chi^2_{change} (df)	p_{change}	OR (CI$_{95}$) Model A1
1	ADHD symptom score 4/5y	19.1 (1)	< .001	1.6 (1.2;2.2)
2	gender of child	5.1 (4)	.271	2.2 (0.6;7.4)
	maternal education level			0.8 (0.5;1.4)
	anx./dep. score 4/ 5y			0.7 (3.2;1.6)
	anx./dep. score 8y			2.0 (1.0-4.4)
3	HCC 4/5y	7.0 (1)	.008	0.5 (0.3;0.9)
4	HCC 4/5y X gender of child	0.4 (1)	.523	–
Model A2: Additional adjustment for ODD/CD, CU scores				Model A2
1	ADHD symptom score 4/5y	19.4 (1)	< .001	1.4 (1.0;2.0)
2	gender of child	4.9 (4)	.296	1.7 (0.4;6.5)
	maternal education level			0.8 (0.4;1.3)
	anx./dep. score 4/ 5y			0.5 (0.2;1.5)
	anx./dep. score 8y			1.8 (0.7;4.9)
3	ODD/CD score 4/5y	5.7 (3)	.125	1.7 (0.7;4.6)
	ODD/CD score 8y			1.7 (0.6;4.9)
	CU score 8y			1.0 (0.4;2.5)
4	HCC 4/5y	4.2 (1)	.040	0.6 (0.3;1.0)
5	HCC 4/5y X gender of child	1.1 (1)	.313	–

ADHD: attention deficit hyperactivity disorder; ODD/CD: oppositional defiant disorder/conduct disorder; anx./dep.: anxiety/depression symptoms; HCC: hair cortisol concentration.

attention deficits such as a low capacity to sustain attention are associated with this deviation. It is possible that low HPAA activity (which has been found to be associated with deviation in the frontal brain (Lupien et al., 2009)) is an early-developing indicator of impairment/ hypoactivity of this basal attention system. The full-blown phenotypic inattention symptoms of ADHD may manifest later, e.g. become obvious when attention capacity is demanded in the school context. Therefore, it is conceivable that low HCC indicates risk for ADHD early in development, over and above the concurrent ADHD symptoms, which are less stable than the ADHD symptoms of later childhood and less clearly distinguishable from other psychopathological problems or from normative development (Harvey et al., 2015; Sonuga-Barke et al., 2005). As mentioned in the introduction, these deviations in HPAA activity and/or the frontal brain can in principle result from genetic and environmental factors (such as early chronic adversity and deprivation) and gene-environment interaction effects (see e.g. Koss and Gunnar, 2018; McLaughlin et al., 2014). In future longitudinal research, it would be worthwhile to assess early chronic stress and to analyze the mediation and moderator processes between these conditions, low HCC, and psychopathology.

Although we found significant, medium-sized associations between low HCC and concurrent and subsequent ADHD in boys and no such associations in girls, the prediction of change in ADHD symptoms did not significantly differ between boys and girls. The finding is in line

with other longitudinal research. Salis et al. (2016); Hill-Soderlund et al. (2015) and Platje et al. (2013) did not find gender differences in the prediction of ED symptoms by salivary cortisol measures. One reason might lie in an insufficient statistical power of our study to detect a gender-risk interaction effect (see e.g. Zahn-Waxler et al., 2008). Further exploration, however, revealed that the prediction of the 8-years ADHD diagnosis was stronger in boys than in girls. It might be speculated that the result corresponds to findings from pre-clinical models indicating larger effects of chronic stress on the frontal brain circuitry and attention deficits in male than in female rats (Bangasser and Valentino, 2014; Bangasser et al., 2019).

The present study is the first to examine the link between HCC and ADHD. Further strengths of the study include the longitudinal design, a relatively large community-based sample of children showing a broad range of ADHD symptoms, a multi-informant approach to ADHD assessment, and the consideration of ODD/CD symptoms, CU traits and internalizing symptoms. Moreover, as we recruited preschoolers with increased ADHD symptoms, there was a high rate (12.7%) of school-age ADHD research diagnoses, allowing for a more reliable description of ADHD development. However, this procedure necessitated comparisons of the HCC effects in different regions of the preschool ADHD distribution (ADHD symptoms are clearly continuously distributed in the population; i.e. ADHD is not a natural category; (Coghill and Sonuga-Barke, 2012; Thapar et al., 2006)). The magnitude of variance explained in the 8-years ADHD score was similar within the lower, upper, and whole range of the preschool ADHD score (i.e. 1.6%, 1.4%, and 1.6%), indicating no influence of the considered range of ADHD symptoms distribution and therefore the generalizability of the results. Nevertheless, the size of the predictive effect was small. To test the prediction by HCC, we used a conservative, restrictive approach. ADHD symptoms were aggregated across several measures and informants, leading to a reliable and stable composite score (between 4/5 and 8 years: r = .65). In the regression model, we adjusted for this stability and other psychopathological symptoms as well as for gender of child and the mother's education level in order to rule out these influences. The small effect was due to this procedure. The effect of the uncorrected association between preschool HCC and 8-years ADHD symptoms and diagnosis in the boys was medium-sized. As mentioned, ADHD is a heterogeneous disorder with different etiological pathways and subtypes, and it is probable that low HPAA activity is involved in just some of these pathways. Accordingly, the amount of explained variance in ADHD development cannot be expected to be large. In future research, it might be revealing to analyze in whom and under which conditions the "low HCC-related pathway" develops. A limitation of our study is that we did not prospectively capture early chronic adversity. We therefore have to leave open the question of whether or not early chronic stressors precede the development of low HCC and subsequent ADHD symptoms.

The present findings give rise to the conclusion that low HCC in preschool children indicates an increased risk of developing ADHD in school age, over and above the preschool ADHD and other psychopathological problems. It would be of theoretical and clinical importance to describe this pathway further in future research. Particularly interesting would be to add neuropsychological measures on attention and executive functions. Moreover, considering the potential (genetic and/or environmental) sources of low HCC in future studies would allow for mediation analyses which help to understand the origins of low HCC in developing ADHD.

From a clinical perspective, HCC might contribute to an early identification of risk for the development of attention problems in a circumscribed group of preschool children. Such knowledge might allow for the establishment of tailored, etiologically informed preventive measures.

a.
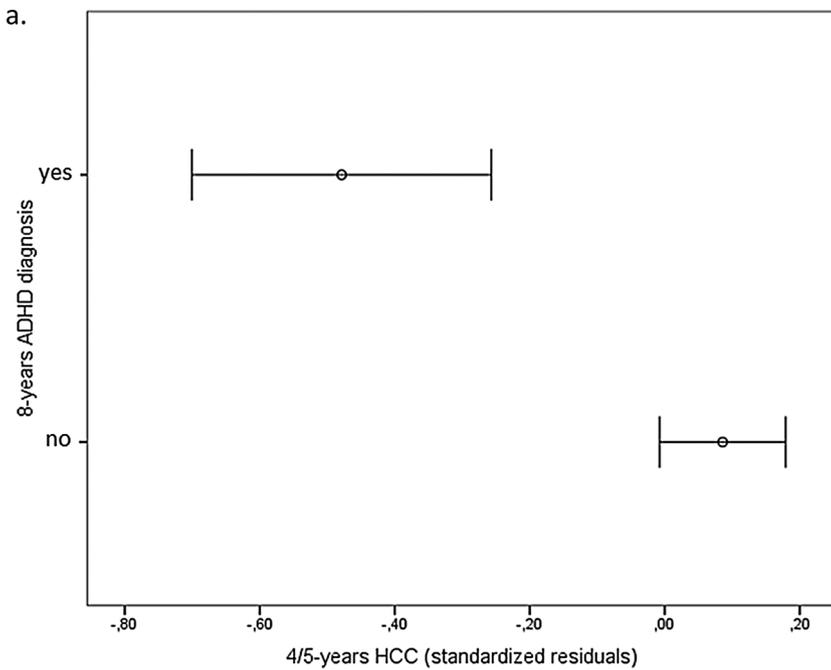
Fig. 2. a. Prediction of 8-years ADHD diagnosis by 4/5-years HCC adjusted for 4/5-years ADHD symptoms, maternal education, gender of child, anxiety/depression symptoms (4/5 and 8 years) in all children.
Note. For reasons of simplicity, means and standard errors of the means (m +/- 1 sem) in the adjusted HCC score are depicted. The mean difference corresponds to a t-score of 2.42.
b. Prediction of 8-years ADHD diagnosis by 4/5-years HCC adjusted for 4/5-years ADHD symptoms in boys and girls separately.
Note. For reasons of simplicity, means and standard errors of the means (m +/- 1 sem) in the adjusted HCC score are depicted. The mean difference in boys corresponds to t = 2.07, the mean difference in girls to t = 1.05.

b.
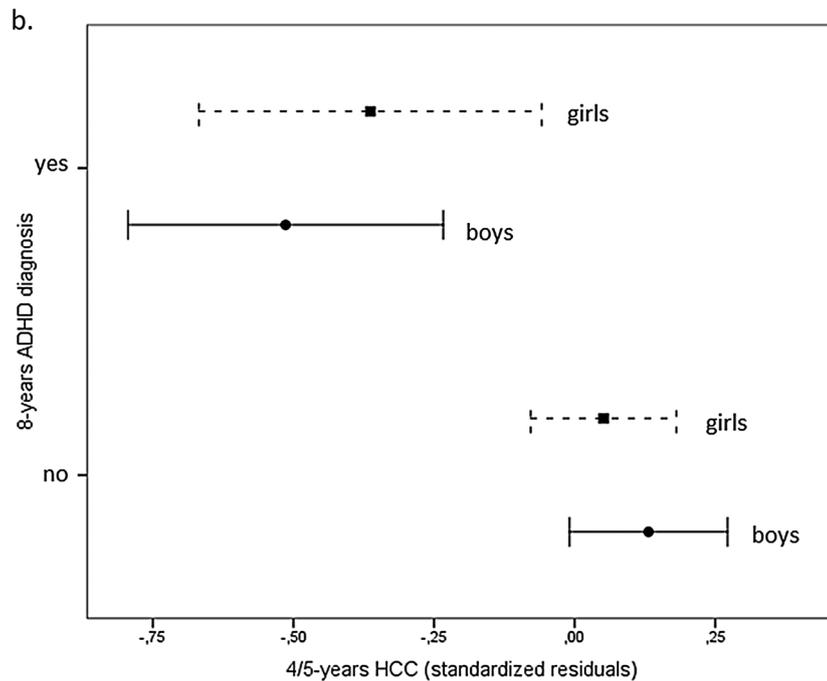
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Declaration of Competing Interest

None.

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