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ORIGINAL CONTRIBUTION

Risk factors of autistic symptoms in children with ADHD

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Abstract Autistic symptoms are frequently observed in children with attention-deficit/hyperactivity disorder (ADHD), but their etiology remains unclear. The main aim of this study was to describe risk factors for increased autistic symptoms in children with ADHD without an autism or autism-spectrum diagnosis. Comorbid psychiatric disorders, developmental delay, current medication, prenatal biological and postnatal psychosocial risk factors as well as parental autistic traits were assessed in 205 children with ADHD. Linear regression models identified maternal autistic traits, current familial risk factors and hyperactive symptoms as predictors of autistic symptoms in children with ADHD. Findings are indicative of possible genetic as well as environmental risk factors mediating autistic symptoms in children with ADHD. An additional validity analysis by ROC, area under the curve (AUC), suggested a cut-off of 11 to differentiate between ADHD and high-functioning ASD by the Social Communication Questionnaire (SCQ).

Keywords Autism · ADHD · Parental traits · Risk factors · Comorbidity

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Introduction

Recently, there has been a growing interest in symptom overlap of attention-deficit/hyperactivity disorder (ADHD) and autism-spectrum disorders (ASD) (e.g. [1–3]). Both disorders are relatively common in child and adolescent psychiatry with ADHD showing a prevalence of 5% [4] and ASD showing a prevalence of 0.5–1% [5, 6] in the general population. Comorbidity of ADHD in ASD patients has been estimated to be around 30% by a recent epidemiologically based study [7]. No comparable study on the prevalence of ASD in children with ADHD does exist, but several studies have described disturbed social functioning in children with ADHD (for a review see [8]), which is a core diagnostic criterion for ASD but not for ADHD [9, 10].

Teacher and parents reported social impairments [11, 12] and emotion-processing difficulties [13] in ADHD children. Subclinical ASD symptoms in ADHD patients have been described by several clinical studies (e.g. [14, 15]). Population-based twin studies have observed elevated rates of ASD symptoms in children and adolescents with ADHD and found a shared heritability of approximately 50% of ADHD and ASD symptoms [16–18]. In contrast, another study in sibling pairs reported less strong familiarity of ADHD and ASD symptoms in boys and girls affected with ADHD despite increased rates of ASD symptoms in this clinical population [19].

In a clinical sample of children and adolescents with ADHD, ASD-like social impairments were associated with speech and language difficulties, repetitive behavior, developmental difficulties, affective and conduct problems, and several psychosocial environmental risk factors [20]. In an epidemiologically based twin study, an overlap of ASD symptoms with motor problems in children with the ADHD combined subtype was observed [21]. Comparable

results were observed in a more recent study on clinically ascertained children and adolescents aged 5–17 years with the ADHD combined subtype and their siblings [2]. ASD symptoms were assessed by the parent rated Social Communication Questionnaire (SCQ) [22, 23]. SCQ scores were increased compared to healthy control children, but below average scores of high-functioning ASD children. The subgroup of children with ADHD and ASD symptoms in the three ASD core domains (7% of the sample) showed increased rates of comorbid oppositional defiant disorder (ODD), conduct disorder (CD), and language delay. In addition, pregnancy and perinatal difficulties as well as motor problems were increased in children characterized by different pattern and severity of ASD symptoms. Psychosocial risk factors were not assessed in this study, and no quantitative analysis on the correlation of specific risk factors with ASD symptom severity in the ADHD children was performed.

It can be concluded that ASD symptoms are elevated especially in children with ADHD combined type as measured by different parent rating scales or telephone interviews with parents. Associated risk factors have not been assessed in all studies. In some studies, predominantly a genetically based overlap between increased ADHD and ASD symptoms was described, which was not observed in others. In addition, comorbid disorders, especially ODD and CD in ADHD seem to be related to parent rated autistic symptoms. The role of comorbid anxiety disorders was only controlled for in one study [19]. Biological environmental risk factors were only assessed in one study, and psychosocial environmental risk factors have hardly been studied. However, it might be possible that the nature of social interaction problems in ADHD is more due to environmental risk factors and different from the mainly genetically mediated social interaction problems in children with ASD.

Therefore, the aim of this study was to describe risk factors of increased ASD symptoms in a clinical sample of ADHD patients without ASD, including the different ADHD subtypes (the combined, the inattentive and the hyperactive–impulsive subtype). Previously described risk factors, especially child-specific characteristics as IQ, gender, developmental milestones, comorbid psychiatric disorders and severity of ADHD symptoms were assessed as predictors to replicate previous findings. In addition, biological and psychosocial environmental risk factors were also explored for association with increased ASD symptoms in the children with ADHD. Further, information on parental ADHD and a self-report measure of ASD symptoms were obtained from both parents. In accordance with results from previous studies, we expected that severity of ADHD symptoms, presence of ODD, CD, and history of motor and speech delay would be related to increased ASD symptoms in children with ADHD, pointing towards a possible subtype of ADHD with overlapping risk factors for ASD.

The second aim of this study was to test the utility of the SCQ, a frequently used screening tool for ASD, to differentiate between children with ADHD without ASD and IQ, gender and age-matched high-functioning ASD patients. Originally cut-offs of 15 in the English version [23] and 17 in the German version [24] were suggested in samples with predominantly low-functioning ASD. We expected a lower cut-off to differentiate ADHD from high-functioning ASD children with a high sensitivity, as the latter show less ASD symptoms compared to low-functioning ASD children. We added this analysis in this study, as it is of strong relevance for clinicians using the SCQ as a screening tool in children with ADHD and symptoms of ASD.

Methods

Participants: ADHD sample

Two hundred and five clinically referred unrelated German children with ADHD (16.1% female) aged 6–13 years ($M = 9.71$, $SD = 1.81$) with IQ ≥ 70 ($M = 101.12$, $SD = 10.88$) were included in this study. Twenty children were diagnosed with the hyperactive/impulsive subtype (9.8%) and 48 with the inattentive subtype (23.4%). The majority of the children showed the combined ADHD subtype ($N = 137$; 66.8%; see Table 1). The study was approved by the ethical committee of the medical association, Saarland, Germany. Informed consent was obtained by the parents. Children with ADHD clinically suspicious of ASD because of lack of eye contact, communication and social interaction problems as reported by parents or observed in direct clinical observation were assessed by the Autism Diagnostic Observation Schedule (ADOS), Module 3 [25] and were excluded from the study if they met autism or autism-spectrum criteria in the social interaction and communication domain of the ADOS.

General exclusion was as follows: non-German speaking parents, any medical/neurological condition possibly underlying the child's ADHD symptoms. Children with a birth weight below 2,000 g, born preterm before pregnancy week 32, with any severe peri- or postnatal biological or medical risk factor, psychotic symptoms, bipolar disorder, obsessive–compulsive disorder, history of epilepsy, mental retardation (IQ <70), a known genetic syndrome or any other severe medical condition (neurological or metabolic disorder) were excluded from the study.

Clinical assessment of the ADHD group

ADHD was diagnosed according to DSM-IV TR [9] criteria by a standardized, structured child psychiatric interview

Table 1 Comparison of SCQ scores, age, gender and IQ in the total ADHD and the ASD samples

	Number (%[a])	SCQ mean (SD)	Gender *N* (%[b])		Age mean (SD)	IQ mean (SD)
			Male	Female		
ADHD	205 (100)	8.6 (3.8)	172 (83.9)	33 (16.1)	9.7 (1.8)	101.1 (10.9)*
Inattentive	48 (23.4)	7.9 (3.9)	42 (87.5)	6 (12.5)	10.2 (1.7)	99.9 (11.1)
Hyperactive/impulsive	20 (9.8)	8.2 (3.8)	18 (90.0)	2 (10.0)	9.8 (1.1)	103 (9.2)
Combined	137 (66.8)	8.9 (3.7)	112 (81.8)	25 (18.2)	9.5 (1.2)	101.4 (11.0)
ASD	53 (100)	16.6 (5.8)	48 (90.6)	5 (9.4)	9.9 (3.0)	93.0 (13.6)*
High-functioning autism	8 (15.1)	20 (4.5)	8 (100)	–	9.3 (3.9)	90.9 (11.7)
Asperger syndrome	31 (58.5)	16.7 (4.8)	29 (93.5)	2 (6.5)	10 (2.9)	96.2 (14.1)
PDD-NOS	14 (26.4)	14.4 (7.6)	11 (78.6)	3 (21.4)	9.2 (2.8)	87.3 (11.9)

ADHD attention-deficit/hyperactivity disorder, *ASD* autism-spectrum disorder, *SCQ* Social Communication Questionnaire, *PDD-NOS* pervasive developmental disorder-not otherwise specified

* Significant IQ difference between the ASD and all ADHD patients ($t = 4.06$; $df = 70.21$; $p < 0.001$)

[a] Percentage in relation to respective sample size (ADHD: $N = 205$, ASD: $N = 53$)

[b] Percentage in relation to respective full sample size (ADHD, ASD) or clinical subtypes

(Kinder-DIPS) [26] and a German Hyperkinetic Syndrome diagnosis checklist (DCL-HKS), rating each DSM-IV TR-derived symptom on a scale between 0 and 3, a score of 3 indicating most severe problems [27]. Data on the DCL-HKS were obtained for lifetime most severe symptoms (e.g. prior to medication). Inattentive and hyperactive–impulsive symptoms were rated by this scale. In addition, parents and teachers filled in a questionnaire on DSM-IV TR-derived ADHD symptoms to ensure pervasiveness of ADHD symptoms across different settings. Comorbid conduct, oppositional defiant and anxiety disorder were also assessed according to DSM-IV by the standardized structured interview Kinder-DIPS and were coded as either absent or present. When CD was diagnosed, no additional diagnosis of ODD was given. In addition, history of enuresis or encopresis, motor or speech delay, current stimulant medication of the child, and prenatal risk factors (smoking and alcohol consumption during pregnancy, maternal prenatal infectious disease, thyroid medication during pregnancy) were assessed in a retrospective semi-structured interview and were also coded as either absent or present. The Kinder-DIPS showed satisfying very good inter-rater reliabilities, satisfying retest-reliabilities and a good validity [26, 28].

Intelligence testing was performed by a standardized intelligence test with current German norms (Kaufman-assessment battery for children [29], the Wechsler scales for children [30], the Culture Fair Intelligence Test, version 20R [31] or the Colored Progressive Matrices [32]).

Assessment of ASD traits and ADHD in parents of children with ADHD

ASD traits in parents of the ADHD children were assessed with the German version of the autism-spectrum quotient (AQ)-short version [33]. The AQ was developed to assess self-reported ASD traits in normal intelligent adults. The AQ-short version consists of 33 items answered on a 4-point Likert scale (from "definitely agree" to "definitely disagree") and shows good psychometric properties. The ASD traits are summed up to a total score and three different subscores can also be calculated. In a German sample, a cut-off of >17 showed a sensitivity of 89% and specificity of 92%. AQs with >10% missing items were excluded from the analysis.

Current parental ADHD was assessed by two self-report questionnaires on current (ADHS-SB) and childhood ADHD symptoms (Wurs-K) [34] as well as a clinical psychiatric history interview with one or both parents. Parental ADHD was categorized into present in at least one parent (either Wurs-K >30, and/or meeting criteria in the ADHS-SB, and/or meeting criteria in the clinical interview) and absent. If information of one parent was missing, he or she was classified as not having ADHD.

Assessment of psychosocial risk factors in children with ADHD

Psychosocial risk factors were assessed by a semi-structured, detailed interview with parents or mother on Axis V of the WHO multiaxial classification system [35] showing good reliability [36]. In the lifetime version, parents are questioned about psychosocial risk factors present in the first year of life of their child, during ages 1–3, 4–6, 7–9, 10–12 years and during the last 6 months. Psychosocial risk factors are assessed with regard to nine domains: (1) abnormal intra-familiar relationship patterns, (2) psychiatric disorder or disability in parent or sibling, (3) distorted communication within the family, (4) abnormal parenting,

(5) parental separation/divorce or institutional education outside the family, (6) acute life events independent of the child, (7) movement, migration, discrimination, (8) adverse school circumstances, and (9) acute life events due to child psychopathology. Items were coded as "not present" (0), "applies, questionable severity" (1), and "definitely applies" (2). In this study, summary scores of domains 1, 3, and 5 during the first 3 years of life (20 items) and during the last 6 months (10 items) were calculated as measures of early and current familial risk factors. In addition, current abnormal parenting conditions (domain 4 during the last 6 months; 7 items) as well as acute life events (domain 6 during the last 6 months; 6 items) were assessed as psychosocial risk factors.

Socio-economic status (SES) of the family was allocated by occupational status of both parents. According to this information, families were classified as lower class, lower middle class, higher middle class or upper class.

Assessment of ASD symptoms

ASD symptoms were assessed in the ADHD and the ASD sample by the German version of the Social Communication Questionnaire (SCQ) [24]. This questionnaire was developed as a companion tool to the ADI-R [37] and shows good psychometric properties. The SCQ consists of 40 yes/no questions answered by the main caregivers (together or separate) of the patients. A cut-off of 17 showed good sensitivity (92%) and specificity (99%) in the German sample. When SCQ information was available from both parents, the higher score was chosen for further analysis. Individuals with >10% missing items were excluded from the analysis ($N = 18/223$; 8.1% children with ADHD originally assessed).

Autism sample

This sample included 53 individuals diagnosed according to DSM-IV TR [9] [8 with autism, 31 with Asperger Syndrome and 14 with pervasive developmental disorder-not otherwise specified (PDD-NOS)] aged 4–16 years ($M = 9.88$; SD = 3.02), showing IQ $\geq$ 70 ($M = 93.02$; SD = 13.58). Children were diagnosed by a broad clinical assessment as previously described [38] including the German version of the ADOS [25] and the Autism Diagnostic Interview-revised [39], IQ-testing, a thorough medical history, a medical and cytogenetic examination and exclusion of fragile X syndrome. Intelligence testing was performed by a standardized intelligence test with current German norms (Snijders–Oomen non-verbal intelligence test (21/2 to 7) [40], the Kaufman-assessment battery for children [29] or the Wechsler scales for children [30]). Exclusion criteria for the ASD and ADHD group were identical (see above). The ASD sample was only included in the receiver operating characteristic (ROC) analysis.

Statistical analysis

Descriptive measures were compared by χ^2-test, Fisher's exact test or t tests as appropriate.

Risk factors of ASD symptoms in ADHD patients: To determine risk factors for increased ASD symptoms in children with ADHD, first, univariate linear regression analyses/ANOVA with the SCQ score as dependent variable were conducted to explore the univariate association with the following independent variables:

(1) Child factors: age, IQ, gender, inattentive and hyperactive–impulsive symptoms, comorbid CD/ODD, comorbid anxiety disorder, history of enuresis, encopresis, motor or speech delay, stimulant medication; (2) parental factors: parental ADHD, maternal and paternal ASD symptoms, (3) pregnancy risk factors, (4) familial risk factors, respectively.

Independent variables showing a p value of <0.05 in univariate analyses were included as predictors in the following multiple linear regression analysis. If any risk factors did not show an association in the multiple regression analysis (p value > 0.05), it was excluded by backward selection from the model. The final model was used to test the stated hypotheses. Cross-validation for stepwise statistical regression is highly recommended to avoid over fitting of the model and to ensure generalizability of the results [41]. Thus, the ADHD patients were split into two random subsamples, one with 80% and a smaller one with 20% of the full ADHD sample. The main analyses were run with the larger 80% sample (exploratory univariate and main analyses). Predicted scores were then created for the smaller sample using the regression coefficients produced by the main analysis. Finally, predicted scores and actual scores were correlated to describe R^2 for the smaller 20% sample. A large discrepancy between R^2 for the smaller and larger sample indicates a lack of generalizability, whereas comparable R^2 values support the validity of the model obtained in the first 80% subsample [41].

The two random subsamples of the ADHD patients did not differ in age ($t = 0.93$, $df = 203$, $p = 0.35$), IQ ($t = -0.71$, $df = 203$, $p = 0.47$), attention problems ($t = -0.10$, $df = 203$, $p = 0.92$), hyperactivity/impulsivity ($t = -0.02$, $df = 203$, $p = 0.98$) or gender ($\chi^2 < 0.01$, $df = 1$, $p = 0.96$).

In addition, co-linearity was tested with the Variance Inflation Factor (VIF). The VIF shows how much the standard error of a predictor is raised through co-linearity. VIFs >10 are indicating co-linearity [42]. No co-linearity of predictors was observed in this analysis. Residuals of the final model were normally distributed.

AQ scores of the fathers were only in available in 156 cases. Thus, paternal ASD symptoms were not considered in the multiple linear models, but analyzed separately.

Validity analysis of the SCQ to differentiate ADHD and ASD patients: To compare SCQ scores between ADHD and ASD patients and control for effects of intelligence, age or gender, a matched subgroup of ADHD children was constructed with Match It [43, 44]. Fifty-three ADHD patients were matched with the nearest-neighbor method regarding IQ, age and gender to the 53 ASD children. A receiver operating characteristic (ROC) curve was conducted to elicit if it was possible to distinguish ADHD and ASD (independent of age, IQ and gender) with an optimum sensitivity and specificity in this sample.

Statistics were calculated by SPSS version 17.0.

Results

Descriptive data on both samples are shown in Table 1. The ADHD and ASD sample differed in the mean intelligence score ($t = 4.1$; $df = 70.2$; $p < 0.001$); therefore, matching was done for the ROC analysis. No difference regarding gender ($\chi^2 = 1.5$, $df = 1$, $p = 0.220$) or age ($t = -0.4$; $df = 61.9$; $p = 0.690$) were found.

ADHD sample: frequency of the assessed risk factors and comorbid disorders

Frequencies of child factors (current stimulant medication, comorbid disorders), parental risk factors, pregnancy risk factors as well as family risk factors are summarized in Table 2 for the complete ADHD sample. Eighty-one (39.5%) ADHD patients were treated with stimulants, 36 were diagnosed with comorbid CD (17.6%), 84 with comorbid ODD (41%), and 59 patients were diagnosed with a comorbid anxiety disorder (28.8%). Maternal ASD symptoms (AQ scores) ranged between 0 and 25 ($M = 9.4$, SD = 4.7), and 7.3% of the mothers showed an AQ score higher than the cut-off of 17 [33]. The AQ scores of the fathers ranged between 1 and 26 ($M = 9.6$, SD = 5.4) with 11.5% of the fathers showing AQ scores above the cut-off.

Risk factors of increased SCQ scores in children with ADHD

Maternal AQ score [$F(1, 154) = 9.5$, $p = 0.002$], hyperactive/impulsive symptoms [$F(1, 154) = 12$, $p = 0.001$], current familial risk factors [$F(1, 154) = 7.2$, $p = 0.008$], parental ADHD [$F(1,154) = 4.6$, $p = 0.034$] and current stimulant medication [$F(1, 154) = 4.6$, $p = 0.034$] were related to the child SCQ score in univariate analyses in the 80% detection subsample (see Table 3 for all univariate analyses). In addition, there was a trend for an association with attention problems [$F(1, 154) = 3.0$, $p = 0.083$], early familial risk factors [$F(1, 203) = 3.2$, $p = 0.075$] and gender [$F(1, 154) = 3.3$, $p = 0.072$]. None of the other factors were associated with SCQ values, especially paternal ASD symptoms were not related to increased SCQ score in the child [$F(1, 154) = 0.3$, $p = 0.615$].

The associated factors ($p < 0.05$) parental ADHD, hyperactive/impulsive symptoms, current familial risk factors, current stimulant medication and maternal ASD symptoms were included in a multiple linear regression model with the total SCQ score as dependent variable. By backward selection parental ADHD and stimulant medication (in this order) were excluded from the model. The final model included maternal ASD symptoms [$F(1, 152) = 6.6$, $p = 0.011$], current familial risk factors [$F(1, 152) = 4.4$, $p = 0.037$], and hyperactive/impulsive

Table 2 Frequency of current stimulant medication, comorbid disorders, parental ADHD, pregnancy risk factors and familial risk factors in children with ADHD

	Present *N* (%)	Not present *N* (%)
Child factors		
Stimulant medication	81 (39.5%)	124 (60.5%)
Comorbid ODD[a]	84 (41%)	121 (59%)
Comorbid CD	36 (17.6%)	169 (82.4%)
Comorbid AD	59 (28.8%)	146 (71.2%)
History of motor delay	7 (3.4%)	198 (96.6%)
History of speech delay	24 (11.7%)	181 (88.3%)
History of enuresis	12 (5.9%)	193 (94.1%)
History of encopresis	14 (6.8%)	191 (93.2%)
Parental risk factors		
Parental ADHD	76 (37.1%)	129 (62.9%)
AQ score mother	$M = 9.4$ (SD = 4.7)	
AQ score father	$M = 9.6$ (SD = 5.4)	
Pregnancy risk factors		
Smoking	66 (32.2%)	139 (67.8%)
Alcohol consumption	32 (15.6%)	173 (84.4%)
Maternal infectious disease	28 (13.7%)	177 (86.3%)
Maternal thyroid medication	22 (10.7%)	183 (89.3%)
Familial risk factors		
Early familial risk factors	$M = 2.8$ (SD = 4.3)	
Current familial risk factors	$M = 2.1$ (SD = 2.3)	
Current abnormal parenting conditions	$M = 0.9$ (SD = 1.3)	
Acute life events	$M = 0.7$ (SD = 1.1)	
Socio-economic status	$M = 2.7$ (SD = 0.6)	

AD anxiety disorder, *ADHD* attention-deficit/hyperactivity disorder, *AQ* autism quotient, *ASD* autism-spectrum disorder, *CD* conduct disorder, *M* mean, *ODD* oppositional defiant disorder, *SD* standard deviation

[a] Only children with ODD without CD are shown

Table 3 Univariate correlation of risk factors with SCQ scores in children with ADHD (80% sample)

	SCQ-value (mean/SD, respectively, r_p)		F value (df)	p value
Metric child factors				
Age	$r_p = 0.08$		0.3 (1, 154)	0.593
IQ	$r_p = 0.03$		1.1 (1, 154)	0.298
SES	$r_p = -0.21$		0.2 (1, 154)	0.654
Binary child factors				
Gender	Male	Female	3.3 (1, 154)	**0.072**
	8.9 (3.7)	7.4 (3.3)		
Comorbid ODD/CD			1.6 (2, 154)	0.213
ADHD-only	8.3 (3.8)			
ADHD + ODD	8.5 (3.6)			
ADHD + CD	9.7 (3.7)			
	Yes	No		
Anxiety disorder	9.1 (3.5)	8.4 (3.8)	1.3 (1, 154)	0.264
History of motor delay	7.8 (4.6)	8.7 (3.7)	0.3 (1, 154)	0.596
History of speech delay	8.9 (3.9)	8.6 (3.7)	0.1 (1, 154)	0.729
History of enuresis	8.9 (4.4)	8.6 (3.7)	<0.1 (1, 154)	0.824
History of encopresis	7.9 (3.1)	8.7 (3.7)	0.5 (1, 154)	0.494
Current stimulant medication	9.4 (3.8)	8.1 (3.5)	4.6 (1, 154)	**0.034**
ADHD symptoms				
Inattention	$r_p = 0.11$		3.0 (1, 154)	**0.083**
Hyperactive/impulsive	$r_p = 0.17$		12 (1, 154)	**0.001**
Parental factors				
Parental ADHD	9.4 (3.8)	8.1 (3.6)	4.6 (1, 154)	**0.034**
Maternal AQ score	$r_p = 0.18$		9.5 (1, 154)	**0.002**
Paternal AQ score ($N = 156$)	$r_p = 0.04$		0.3 (1,154)	0.615
Pregnancy risk factors				
Smoking	9.2 (3.6)	8.4 (3.6)	1.7 (1, 154)	0.193
Alcohol consumption	9.3 (3.5)	8.5 (3.7)	1 (1, 154)	0.330
Infections	8.5 (4.1)	8.6 (3.6)	<0.1 (1, 154)	0.868
Maternal thyroid medication	9.3 (3.7)	8.5 (3.7)	1.5 (1, 154)	0.230
Maternal infectious disease (antibiotic medication)	4.5 (3.5)	8.7 (3.7)	2.5 (1, 154)	0.113
Familial risk factors				
Current familial risk factors	$r_p = 0.32$		7.2 (1, 154)	**0.008**
Early familial risk factors	$r_p = 0.12$		3.2 (1, 154)	**0.075**
Current abnormal parenting conditions	$r_p = 0.25$		1.3 (1, 154)	0.258
Acute life events	$r_p = 0.36$		2 (1, 154)	0.160

ADHD attention-deficit/hyperactivity disorder, *AQ* autism-spectrum quotient, *CD* conduct disorder, r_p Pearson-correlation, *ODD* oppositional defiant disorder; *SES* socio-economic status, *SCQ* Social Communication Questionnaire

symptoms [$F(1, 152) = 8.3$, $p = 0.005$]. Higher maternal ASD symptoms [$\beta = 0.15$, 95%-confidence-interval ($CI_{95\%}$) 0.04–0.26], current familial risk factors [$\beta = 0.24$, $CI_{95\%}$ 0.01–0.47] and hyperactive–impulsive symptoms ($\beta = 0.14$, $CI_{95\%}$ 0.04–0.23) predicted elevated SCQ scores of the patients (Table 4).

Cross-validation for the regression model did not indicate over fitting. Compared to the larger sample, correlation of the predicted SCQ scores and actual scores in the smaller sample was equally high with $R^2 = 0.10$ compared to the main analysis ($R^2 = 0.14$; corrected $R^2 = 0.12$). A list of observed current familial risk factors is presented in detail in Table 5.

Validity of the SCQ to differentiate ADHD and ASD: ROC analysis

After matching, the subgroup of 53 matched ADHD children did not differ from ASD with regard to IQ ($t = 0.7$, $df = 104$, $p = 0.485$), age ($t = -0.9$, $df = 104$,

Table 4 Risk factors predicting increased SCQ scores in children with ADHD: results of the multiple linear regression model in the random 80% subsample

	F value (*df*)	β	$CI_{95\%}$ for β	*p* value	Effect size η^2
Intercept	19.4 (1, 152)			0.000	0.11
Hyperactive/impulsive symptoms	8.3 (1, 152)	0.14	0.04–0.23	0.005	0.05
Current familial risk factors	4.4 (1, 152)	0.24	0.01–0.47	0.037	0.03
Maternal AQ score	6.6 (1, 152)	0.15	0.04–0.26	0.011	0.04

First model with the predictors current stimulant medication, parental ADHD, maternal AQ score, hyperactive/impulsive symptoms, and current familial risk factors: $R^2 = 0.15$ (corrected $R^2 = 0.13$)

Reduced model with three predictors: $R^2 = 0.14$ (corrected $R^2 = 0.12$)

AQ autism-spectrum quotient, *SCQ* Social Communication Questionnaire

Table 5 Incidence of current familial risk factors in the ADHD patients

	Coded with "0" number	Coded with "1" number	Coded with "2" number
1. Abnormal intra-familial relationships			
1.0 Lack of warmth in parent–child relationship	184	19	2
1.1 Intra-familial discord among adults or children	169	25	11
1.2 Hostility towards or scapegoating of the child	155	45	5
1.3 Physical child abuse	176	23	6
1.4 Sexual abuse	202	2	1
3. Inadequate or distorted intra-familial communication	158	38	9
5. Abnormal immediate environment			
5.0 Institutional upbringing	195	9	1
5.1 Anomalous parenting situation			
5.1a Abnormal parenting situation	155	11	39
5.1b Abnormal family situation	197	5	3
5.2 Isolated family	156	38	11
5.3 Living conditions that create a potentially hazardous psychosocial situation	178	22	5

0, not present; 1, applies, questionable severity; 2, definitely applies

$p = 0.353$) and gender (Fisher-exact: $p = 0.437$). The ASD patients (SCQ $M = 16.6$, SD = 5.8) approximately twice as high SCQ scores than the matched ADHD children ($M = 8.5$, SD = 3.5; $t = -8.7$; $df = 104$; $p < 0.001$). A cut-off of >11 showed highest sensitivity = 0.87 and specificity = 0.83, thus at this cut-off 87% of the ASD patients are correctly classified as ASD cases and 83% of the ADHD sample are correctly classified as no ASD cases. The area under the curve (AUC) was 89% (Fig. 1).

Discussion

In the present study, we observed increased ASD symptoms in this clinical sample of children with ADHD without ASD. Mean SCQ scores in this study were similar to the mean SCQ scores of 8.5 (SD = 6.2) obtained in a clinical sample of children with ADHD combined subtype without ASD in another study, and were considerably higher than in healthy control children who showed a mean SCQ score of 3.9 (SD = 2.8) [2]. Hyperactive–impulsive behavior problems, maternal ASD traits and current familial psychosocial risk factors were positively associated with increased ASD symptoms in children with ADHD.

Hyperactive–impulsive symptoms showed the most significant association with the SCQ score. Therefore, there might be a genetic association between hyperactive–impulsive symptoms and ASD symptoms in children with ADHD. Furthermore, hyperactive behavior is a predictor of poor self control and inappropriate behavior, which can lead to peer rejection. Thus, those children often have less positive reciprocal relationships and therefore are less able to develop social skills (for a review see [8]). Elevated ASD symptoms in early adolescence might result from this adverse development process. While we only found an association with hyperactive–impulsive symptoms, a previous study reported an association of inattentive problems

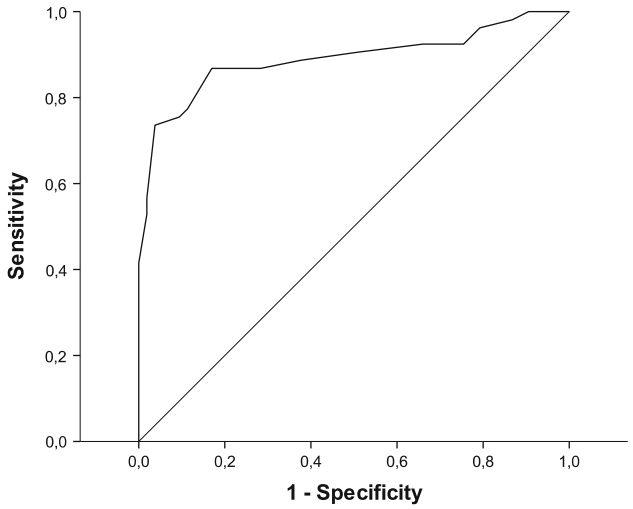

Fig. 1 ROC analysis for total SCQ score in ASD and matched ADHD children

and ASD-like social dysfunction problems [19]. This inhomogeneity might partly be due to the use of different ASD behavior questionnaires. We recommend future studies to assess different domains of both ADHD and ASD symptoms in large samples to describe specific association patterns in more detail, e.g. by latent class analysis.

A positive relationship between elevated ASD symptoms in children and their mothers was also found. As we did not employ a genetically informative design, we cannot, however, draw any firm conclusions about a genetic cause of this correlation. Still, recent twin studies support the theory of at least partly genetic cause of ASD symptoms in ADHD which seems to overlap with the genetic risk for ASD, in general (for recent review see [45]). In our data, paternal ASD symptoms were not associated with SCQ scores. This might either point towards a more specific role of maternally derived genetic risk factors on ASD traits in their offspring, as has been shown, e.g. for fragile X syndrome or chromosome 15q11-13 duplications [46]. On the other hand, as most SCQs were filled in by mothers or both parents together, correlation of maternal and offspring scores might reflect a reporting bias instead of a genetically mediated association.

Interestingly, current familial risk factors were associated with ASD symptoms pointing towards the relevance of psychosocial risk factors in addition to possible genetic risk factors for increased ASD symptoms in children with ADHD. This association was shown for the first time. In univariate analyses, early familial risk factors were also correlated by trend with increased SCQ symptoms. Early and current familial risk factors were correlated ($r = 0.69$, $p < 0.001$) and thus indicate chronic risk factors for the respective child. However, as the study was a cross-sectional study, it cannot be excluded that higher current familial risk factors were due to the increased ASD symptoms of the child and that this situation might have influenced the retrospective rating. Longitudinal studies need to replicate the association and elicit causality. If familial risk factors will be proved to play a causative role for ASD symptoms in children with ADHD, this would argue against a predominantly genetic cause of ASD symptoms in this population.

In contrast to previous studies no association between ASD symptoms and CD, ODD, speech- and motor delay or pre- and perinatal risk factors, respectively, were found [2, 20]. This discrepancy may result from the inclusion and exclusion criteria in the present study. We not only included ADHD combined type, which is known to show higher prevalences of comorbid aggressive disorders [47], but we also included the ADHD inattentive and hyperactive/impulsive subtype. In addition, in contrast to previous studies, we excluded patients with a birth weight below 2,000 g, born preterm before pregnancy week 32, with any severe peri- or postnatal biological or medical risk factor or any metabolic disorder. Therefore, our sample showed lower rates of comorbid psychiatric disorders and developmental delays than the ADHD children in previous studies, which might cause a too small power to detect effects. In addition, our exclusion criteria could also be risk factors of elevated ASD symptoms and should therefore be included in further studies. On the other hand, we found similar elevated SCQ scores as the study by Mulligan et al., what speaks against a high impact of those factors on ASD symptoms in the examined population.

Comparison of SCQ scores between groups and ROC analysis shows that mean SCQ scores do clearly differ between ADHD and ASD, but are still increased in children with ADHD without ASD compared to healthy control children. Interestingly, the cut-off of 11 to differentiate between ADHD and ASD obtained by ROC analyses is supported by findings of another study assessing the SCQ in preschool-aged children at risk of developmental problems [48]. The sensitivity of 87% and specificity of 83% obtained with a cut-off of 11 support the SCQ as a clinically useful screening tool for high-functioning children suspicious of ASD compared to children with ADHD or other clinical groups.

As a limitation it has to be mentioned first that we did not control for multiple testing in the stepwise multiple regression analysis. We overcame this limitation by cross-validation which showed stable results in the smaller subsample. Secondly, our final model only explained 12% ($R^2 = 0.12$) of the variance of the SCQ, which is a small effect ($f^2 = 0.01$) [49]. But it has to be considered that our model included only three predictors. There certainly are more factors which influence ASD symptoms in ADHD, e.g. genetic variations, which we have not assessed in our study. Furthermore, parental, familial and child-specific

risk factors were mainly assessed by parent-ratings. For future studies, we recommend to use additional ratings (e.g. by therapist or teacher) to exclude parental rater biases. Finally, as our study was cross-sectional, conclusions regarding causality should be drawn caution.

Summing up, we replicated increased SCQ scores in children with ADHD without ASD, scoring between healthy control children and children with ASD. We found a positive association of maternal and offspring ASD symptoms, and of hyperactive–impulsive symptoms and ASD symptoms in children with ADHD. Current familial risk factors were first described to be associated with increased ASD symptoms in an ADHD population which points toward a partly different etiology of ASD symptoms in children with ADHD than in children with ASD. This finding has to be replicated and assessed for causality in longitudinal studies.

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Conflict of interest None.

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