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ABSTRACT

Objectives The aim of this study was to assess comorbidity patterns and functional impairment in children with and without attention deficit hyperactivity disorder (ADHD).

Design Hospital-based retrospective cross-sectional study; data collection occurred between 2016 and 2019.

Settings and patients A total of 8256 children and adolescents, 6–17 years of age, with suspected ADHD agreed to participate in this hospital-based cross-sectional study over a 4-year period in China. Comorbidities and social functions were assessed according to the scales Vanderbilt ADHD Diagnostic Parent Rating Scale and Weiss Functional Impairment Rating Scale-Parent Form, which were completed by the parents of the study participants.

Results Of the 8256 children, 5640 were diagnosed with ADHD. Other 2616 children who did not meet the ADHD diagnostic criteria were classified as the N-ADHD group. The proportion of comorbidities (47.4%) and functional impairments (84.5%) in the ADHD group were higher than the N-ADHD group ($p \leq 0.001$). The functional impairment scores in all of the six domains, including family, academic, life skills, self-concept, social activities and risky activities, were significantly higher in the ADHD group than the N-ADHD group ($p \leq 0.001$). The functional impairment in ADHD group with comorbidities was more severe than those without comorbidities ($p \leq 0.001$). Comorbidities and core symptoms both can affect the functions of children with ADHD. Logistics regression analysis indicated that in all of the six functional domains, the effect of comorbidities on functional impairment exceeded the effects of ADHD core symptoms.

Conclusions Comorbidities had the greatest influence on different areas of adaptive functioning in children with ADHD. Clinical management of children suspected to have ADHD should address multiple comorbidities and functional impairments assessment, as well as core symptom analysis.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder. The first aim was to determine the differences in comorbidities

Strengths and limitations of this study

- The study was aimed to assess patterns of comorbidities and functional impairments in children with and without attention deficit hyperactivity disorder (ADHD).
- This was a hospital-based cross-sectional study with a large sample size.
- The study compared multiple comorbidities and functional impairments between two groups. All participants exhibited clinical symptoms, but only 5640 of 8256 met the diagnostic criteria for ADHD; others were classified as the N-ADHD group.
- Family and social environmental factors should be the focus of a corollary study.

and functional impairments between children with mental disorder in children and adolescents. Recent studies have shown that the worldwide prevalence in children and adolescents is 3.4%,¹ and the prevalence in China is 5.7%.² Therefore, prevention and treatment of ADHD have become urgent global public health goals.

The characteristic symptoms of ADHD are inattentiveness, hyperactivity and impulsiveness, which are more inappropriate than those in children of a comparable age. As a result, the disorder can be categorised as follows: ADHD, predominantly inattentive type (ADHD-I); ADHD, predominantly hyperactivity (ADHD-H); and ADHD, combined type (ADHD-C).³ Most children with ADHD have functional impairments in family, academic, social activities and self-concept. The more severe the symptoms of ADHD are, the greater the functional impairments. Furthermore, ADHD persists into adulthood in approximately 50% of patients,⁴ and

patients with ADHD are at higher risk for other mental disorders.⁵

Comorbidities are thought to be one of the most important aspects of ADHD. The overall prevalence of psychiatric disorders associated with ADHD ranges from 40% to 80%, depending on the composition of the sample.⁶ The most common comorbidities include oppositional defiant disorder (ODD), anxiety disorders,⁷ conduct disorder (CD), learning disorders and tic disorders (TDs).⁸ Among the comorbidities, ODD has the highest prevalence (32%–50%),^{9,10} while the prevalence of CD, anxiety disorder and depression have been reported to be 24%–30%, 25%–33% and 20%, respectively.^{10,11} The comorbidity rates vary because of confounding factors, such as age, ADHD symptom severity and medication use.⁷ Although ADHD comorbidities have been widely studied,^{10,12} some issues remain unsolved. In clinical practice, comorbidities may mask the core symptoms of ADHD; in contrast, ADHD may be masked by comorbidities, thus making the diagnostic process challenging. While most studies have only focused on the current prevalence of ADHD comorbidities, few studies have addressed the effects of comorbidities on social functions in children with ADHD.^{13,14} Most of the existing studies involving children with ADHD in China have been conducted on small-scale community samples. The core symptoms and comorbidities were relevant and also affected functional impairments. Given the limited research conducted on this topic and its importance for prevention and intervention strategies, this hospital-based cross-sectional study addressed the associations between comorbidities, core symptoms of ADHD and functional impairments in children with ADHD. The first aim was to determine the differences in comorbidities and functional impairments between children with and without ADHD. The second aim was to analyse the effects of comorbidities on the functional impairments in children with ADHD. The third aim was to analyse the effects of different subtypes of ADHD on the functional impairments in children with ADHD. Finally, we analysed the risk factors related to each functional impairment in children with ADHD based on logistic regression analysis.

METHODS

Survey design and data

A total of 10 698 children, 6–17 years of age, were enrolled in a hospital-based retrospective cross-sectional study in China between August 2016 and April 2019.

The study participants were evaluated for behavioural problems, such as inattentiveness and hyperactivity, for the first time in the Department of Child and Adolescent Healthcare, Children's Hospital of Soochow University, in Suzhou, China. Each participant was assessed IQ using the Weschler Intelligence Scale for Children. Patients were excluded if they met any of the following criteria: (1) organic lesions of the nervous system, intellectual disability (IQ <70 points), a psychotic disorder or an extensive developmental disorder; and (2) history of treatment with central nervous

system stimulants, including drugs for ADHD, or long-term pharmaceutical treatment for other chronic diseases.

Based on the exclusion criteria, 485 children and adolescents were excluded; 1957 declined to participate in the study or withdrew consent. Thus, the study cohort consisted of 8256 children and adolescents (77.2%). Written informed consent was obtained from the parents or guardians of the participants.

Patient and public involvement

Neither the patients nor the public were directly involved in the design, recruitment or assessment of this study.

Measures

The patients were diagnosed and classified by developmental paediatricians after obtaining a relevant history and clinical assessment using an ADHD rating scale with diagnostic criteria consistent with the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*.³ Those children and adolescents who met the diagnostic criteria were classified as the ADHD group; the children and adolescents who did not meet the diagnostic criteria were classified as the N-ADHD group. Among the 18 symptoms, patients were diagnosed with ADHD-I when at least six of the inattentive symptoms were met, ADHD-H when at least six of the hyperactivity symptoms were met and ADHD-C when the patients qualified as ADHD-I and ADHD-H. The Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)¹⁵ was filled out by parents under the guidance of specialists and was used for comorbidity screening. Twenty-nine comorbidity symptoms were screened, among which 8 items were used to assess ODD, 14 items were used to assess CD and 7 items were used to assess anxiety and depression disorder (Anx-Dep). Each item was rated as never (0), occasionally (1), often (2) or always (3). ODD was diagnosed when at least four items of the ODD symptoms scored 2 or 3, CD was diagnosed when at least three items of the CD symptoms scored 2 or 3 and Anx-Dep was diagnosed when at least three items of the Anx-Dep symptoms scored 2 or 3. Patients with at least one positive diagnosis (ODD, CD or Anx-Dep) were considered to have a comorbidity. Xiao *et al*¹⁶ examined a Chinese adaption of the VADPRS in a clinical sample of children with ADHD and verified that the specificity was 0.63 and the sensitivity was 0.83.

The Weiss Functional Impairment Rating Scale-Parent Form (WFIRS-P) was completed by the parents of the patients under the guidance of specialists and was used to assess the functional impairments of children with ADHD. The scale consists of six dimensions, including family, academic, life skills, self-concept, social activities and risky activities. Each dimension includes a number of items, and each item is rated from 0 to 3 (0=never, 1=sometimes, 2=often and 3=always or frequently). Functional impairment of each domain was present based on a score of 3 in any item, a score of 2 in both items or an average score >1.5. Higher scores indicate more severe functional impairment. All of the dimensions demonstrated good reliability, and the Cronbach's alpha coefficient was >0.7 for all domains.¹⁷

Statistical analyses

SPSS V.22 (IBM Corp, Armonk, New York, USA) was used for statistical analysis. Measurement data, such as age, IQ and VADPRS and WFIRS-P scores, are expressed as the mean (95% CI). Comparisons between two groups were made using t-tests. Comparisons between ADHD-I, ADHD -H and ADHD-C were made with the analysis of variance. Classification data, such as gender, proportion of comorbidities and proportion of functional impairments, are expressed as the percentage (95% CI), and χ^2 tests were used for comparisons between two groups. Binary logistic regression analysis was used to determine the associations between functional impairments and core ADHD symptoms, comorbidities, age, gender and IQ. The effects of independent variables on dependent variables are represented by ORs. Statistical significance was set at a $p < 0.05$.

RESULTS

Baseline comparisons between the ADHD and N-ADHD groups

According to the ADHD clinical diagnostic criteria in *DSM-5*, 5640 children were diagnosed with ADHD. The remaining 2616 children were included in the N-ADHD group. There were 4717 males (83.6%) in the ADHD group, which was a significantly higher percentage than the N-ADHD group

($p < 0.05$). Although the average age did not differ significantly between the two groups, the average IQ was lower in the ADHD group than the N-ADHD group ($p \leq 0.001$) (table 1).

Comparisons of comorbidities and functional impairments between the ADHD and N-ADHD groups

Comorbidities (including ODD, CD and Anx-Dep) were identified in 2675 children (47.4%) in the ADHD group, which was a significantly higher percentage than the N-ADHD group ($p \leq 0.001$). The proportion with ODD (42.6%), CD (6.3%) and Anx-Dep (12.4%) in the ADHD group were higher than the N-ADHD group ($p \leq 0.001$). Additionally, the proportion with one comorbidity (35.3%), two comorbidities (10.4%) and three comorbidities (1.8%) in the ADHD group were higher than the N-ADHD group ($p \leq 0.001$).

The proportion of functional impairments in the ADHD group was higher than the N-ADHD group ($p \leq 0.001$). Similarly, the functional impairment scores in all domains were significantly higher in the ADHD group than the N-ADHD group ($p \leq 0.001$; table 1).

Effects of comorbidities on functional impairment in children and adolescents with ADHD

Functional impairment in children and adolescents with comorbidities was more severe than those without

Table 1 Comparisons of comorbidities and functional impairments between the ADHD and N-ADHD groups

Characteristic	ADHD (n=5640)	N-ADHD (n=2616)	t/ χ^2	P value
Gender				
Male	83.6 (82.7 to 84.6)	81.3 (79.7 to 82.8)	6.61	0.011
Female	16.4 (15.5 to 17.4)	18.7 (17.2 to 20.1)		
Age	8.27 (8.22 to 8.30)	8.23 (8.16 to 8.30)	0.84	0.403
IQ	113.85 (113.40 to 114.30)	115.61 (114.96 to 116.27)	-4.37	0.000
Proportion with total comorbidities	47.4 (46.1 to 48.7)	24.1 (22.6 to 25.9)	400.30	0.000
Proportion with ODD comorbidity	42.6 (41.3 to 43.9)	21.5 (19.9 to 23.1)	344.619	0.000
Proportion with CD comorbidity	6.3 (5.7 to 7.0)	1.3 (0.8 to 1.7)	101.999	0.000
proportion with Anx-Dep comorbidity	12.4 (11.6 to 13.3)	5.2 (4.3 to 6.0)	103.745	0.000
Proportion with one comorbidity	35.3 (34.0 to 36.5)	20.8 (19.2 to 22.3)	176.931	0.000
Proportion with two comorbidites	10.4 (9.6 to 11.2)	3.2 (2.6 to 3.9)	122.482	0.000
Proportion with three comorbidites	1.8 (1.4 to 2.1)	0.2 (0 to 0.4)	33.142	0.000
Proportion of functional impairments	84.5 (83.6 to 85.5)	66.9 (65.1 to 68.7)	333.90	0.000
WFIRS-P score				
Family	0.62 (0.61 to 0.63)	0.36 (0.35 to 0.38)	26.06	0.000
Academic	0.79 (0.78 to 0.80)	0.49 (0.48 to 0.50)	30.92	0.000
Life skills	0.93 (0.92 to 0.94)	0.68 (0.67 to 0.69)	28.55	0.000
Self-concept	0.77 (0.76 to 0.79)	0.52 (0.50 to 0.54)	17.62	0.000
Social activities	0.75 (0.74 to 0.77)	0.54 (0.52 to 0.55)	19.84	0.000
Risky activities	0.28 (0.28 to 0.29)	0.18 (0.17 to 0.18)	20.56	0.000

t-Tests were used to compare normally distributed data, and the Mann-Whitney U test was used to compare non-normally distributed data. Continuous variables were presented as mean (95% CI). Categorical variables were presented as percentages (95% CI). ADHD, attention deficit hyperactivity disorder; Anx-Dep, anxiety and depression disorder; CD, conduct disorder; ODD, oppositional defiant disorder; WFIRS-P, Weiss Functional Impairment Rating Scale-Parent Form.

Table 2 Comparison of WFIRS-P results in children from the ADHD group with or without comorbidities

WFIRS-P score	ADHD children with comorbidities (n=2675)	ADHD children without comorbidities (n=2965)	t	P value
Family	0.79 (0.77 to 0.81)	0.46 (0.45 to 0.47)	30.14	0.000
Academic	0.87 (0.85 to 0.89)	0.73 (0.71 to 0.74)	12.23	0.000
Life skills	1.03 (1.01 to 1.04)	0.84 (0.83 to 0.85)	18.55	0.000
Self-concept	0.96 (0.93 to 0.98)	0.61 (0.59 to 0.63)	21.27	0.000
Social activities	0.90 (0.88 to 0.92)	0.62 (0.61 to 0.64)	22.30	0.000
Risky activities	0.34 (0.33 to 0.35)	0.23 (0.22 to 0.23)	19.25	0.000

Continuous variables were presented as mean (95% CI).

ADHD, attention deficit hyperactivity disorder; WFIRS-P, Weiss Functional Impairment Rating Scale-Parent Form.

comorbidities; the differences were statistically significant (table 2). Designating the impairment scores of each functional domain for children and adolescents with ADHD as dependent variables and the number of comorbidities as an independent variable, univariate linear regression analysis showed that as the number of comorbidities increased, so did the degree of functional impairment for each dimension in children with ADHD (table 3).

Comparison of functional impairments in children and adolescents with different subtypes of ADHD

The degree of functional impairment was dependent on the subtype of ADHD. Specifically, the degree of functional impairment was higher in the ADHD-C group than in either of the other two groups. The most apparent impairment among the six WFIRS-P functional domains in all three types of ADHD (I, H and C) was life skills (table 4).

Logistic regression analysis of risk factors related to functional impairment in children and adolescents with ADHD

The functional impairments included six domains, as follows: family; academic; life skills; self-concept; social activities; and risky activities. Designating the existence of impairment (evaluated based on a score of 3 in any item, a score of 2 in both items or an average score >1.5) in each functional domain as the dependent variable, and the inattentiveness, hyperactivity, ODD, CD and Anx-Dep

scores¹²; the number of comorbid disorders, and the ADHD subtype (ADHD-I: 1, ADHD-H: 2 and ADHD-C: 3) as independent variables, and after correcting for confounding factors (age, gender and IQ), binary logistic regression analysis showed that the ODD, CD, Anx-Dep, inattentiveness and hyperactivity scores were associated with functional impairments in different domains. The severity of comorbidities had greater impact on all of the six functional domains compared with the severity of core symptoms. For the domains of family (OR=1.30), academic (OR=1.21) and risk activities (OR=1.36), CD symptom score had the most significant influence. However, life skills (OR=1.21) and self-concept (OR=1.78) were most significantly influenced by Anx-Dep symptom score, and social activities (OR=1.35) was most influenced by the number of comorbidities (table 5).

DISCUSSION

The first objective of this study was to determine the differences in comorbidities and adaptive functioning in different domains of daily life between children and adolescents with and without ADHD. We found that the overall rate of functional impairment in children and adolescents with ADHD was significantly higher than in children and adolescents with N-ADHD. Functional impairment scores for each of the six domains (family, academic, life skills, self-concept, social activities and risky activities) were significantly higher for children and adolescents with ADHD. These findings are consistent with previous studies showing that children and adolescents with ADHD had more problems across a wide range of academic, social and family function indicators.^{18 19} Although the core symptoms of inattentiveness and hyperactivity are partially alleviated during development, ADHD symptoms for 70%–85% of children persist into adolescence and can persist into adulthood for approximately 50% of children.⁴ When symptoms persist, people can easily develop antisocial personality disorder, CD, drug and/or alcohol abuse and/or juvenile delinquency.^{20 21} The high prevalence of functional impairment (84.5%) in children and adolescents with

Table 3 Univariate linear regression analysis: number of comorbidities on functional impairment

WFIRS-P score	B (95% CI)	SE	t	P value
Family	0.268 (0.254 to 0.282)	0.007	37.62	0.000
Academic	0.131 (0.116 to 0.146)	0.008	16.78	0.000
Life skills	0.145 (0.132 to 0.158)	0.007	21.55	0.000
Self-concept	0.291 (0.269 to 0.312)	0.011	26.69	0.000
Social activities	0.239 (0.223 to 0.255)	0.008	29.50	0.000
Risky activities	0.101 (0.093 to 0.109)	0.004	25.01	0.000

Continuous variables were presented as mean (95% CI).

WFIRS-P, Weiss Functional Impairment Rating Scale-Parent Form.

Table 4 Comparison of the WFIRS-P results in children with different subtypes of ADHD

WFIRS-P score	ADHD-I (n=2784)	ADHD-H (n=530)	ADHD-C (n=2326)	F	P value
Family	0.53 (0.51 to 0.55)	0.56 (0.53 to 0.60)	0.74 (0.72 to 0.76)*	149.76	0.000
Academic	0.73 (0.72 to 0.75)*	0.62 (0.59 to 0.65)*	0.90 (0.88 to 0.92)*	142.45	0.000
Life skills	0.87 (0.86 to 0.89)*	0.83 (0.80 to 0.85)*	1.02 (1.00 to 1.04)*	116.91	0.000
Self-concept	0.79 (0.76 to 0.81)	0.57 (0.52 to 0.62)*	0.80 (0.76 to 0.83)	30.29	0.000
Social activities	0.68 (0.66 to 0.70)	0.69 (0.66 to 0.73)	0.85 (0.83 to 0.87)*	89.01	0.000
Risky activities	0.24 (0.23 to 0.25)*	0.26 (0.24 to 0.28)*	0.34 (0.33 to 0.35)*	122.83	0.000

Continuous variables were presented as mean (95% CI).

*Statistical differences between this group and either of the other two groups.

ADHD, attention deficit hyperactivity disorder; ADHD-C, ADHD, combined type; ADHD-H, ADHD, predominantly hyperactive; ADHD-I, ADHD, predominantly inattentive type; WFIRS-P, Weiss Functional Impairment Rating Scale-Parent Form.

ADHD indicated that existing management strategies do not meet the needs.

The second objective of this study was to analyse the effects of comorbidities on functional impairment in children and adolescents ADHD. Most children with ADHD have at least one comorbidity. The main comorbidities are ODD (20%–60%), CD (20%–50%), and Anx-Dep disorders (10%–40%).^{6 12 22–25} We found that ODD affected 42.6% of all children and adolescents with ADHD, which is similar to the previously reported findings⁶; however, in our sample, the proportion of children and adolescents with ADHD accompanied by CD and Anx-Dep were only 6.3% and 12.4%, respectively, which were lower than previously reported.^{10 24 26}

The discrepant findings can be due to the following: rates of comorbidities reported in the literature vary widely due to different definitions of comorbid conditions, ages of the study cohorts and origin of samples; the participants in our study were evaluated from the Department of Child Health Care of the hospital setting for behavioural problems for the first time, so the severity of comorbidities of our participants may be less than those from paediatric psychiatric clinics; the scales were completed by their parents and symptoms, such as some internalising problems, may not have been exhibited or recognised by the parents, and the comorbidity assessments in our study were performed using a screening survey due to the large sample size. Nevertheless, our current findings support an emerging view that ADHD existed in the absence of comorbidities in only a minority of cases. In agreement with the literature, we found that among children and adolescents with ADHD, those with comorbidities had more problems compared with those without comorbidities across a wide range of daily life function indicators. The functional impairments in children and adolescents with ADHD and comorbidities were shown to differ depending on the comorbidity. Virring *et al*¹³ reported that internalising or autistic comorbid disorders are significantly associated with the degree of sleep problems in children with ADHD. The effect of ADHD and comorbidities on daily life functions was associated with the type of comorbidity and the number of comorbidities. Larson

*et al*⁸ showed that the majority (67%) of children with ADHD had at least one comorbidity, 16% had two comorbidities and 18% had ≥ 3 comorbidities. In this study, the overall detection rate of comorbidities in children and adolescents with ADHD (47.4%) was lower than reported in previous studies⁸; specifically, 10.4% of children and adolescents with ADHD had two comorbidities and 1.8% had three comorbidities. Despite the lower number, linear regression analysis indicated that the degree of impairment on several functional domains increased linearly with the number of comorbidities, which was consistent with the conclusion of the study conducted in the USA in 2007. Other studies have indicated that more comorbidities are predictive to ADHD continuing from childhood to adulthood,⁴ and the number of comorbid disorders, particularly anxiety disorders, was significantly related to long-term work disability.²¹

The third objective of the current study was to analyse the relationship between functional impairment in different types of ADHD. Although previous studies have shown that functional impairment in ADHD is related to core symptoms,^{17 18} the conclusions regarding the influence of different subtypes of ADHD were not consistent. For example, a study conducted in China found that the severity of core symptoms in ADHD influenced the occurrence of comorbidities and functional impairments, with the ADHD-C group having a significantly higher overall incidence of functional impairments than the ADHD-I or ADHD-H group.²⁷ Another study involving university students with ADHD showed that parent-reported anxiety symptoms were higher for students with ADHD-I than for those with the combined ADHD subtype.²⁸ Castagna *et al*²⁹ reported that youth diagnosed with ADHD-C had more frequent personal failures and hostile intent negative self-statements than those diagnosed with ADHD-I. In the current study, we found that the degree of impairment for all six functional domains in the ADHD-C group was higher than the ADHD-I or ADHD-H group.

Although previous studies have shown that in general, comorbidity and core symptoms can affect the daily life functions of children with ADHD, as far as different social functions are concerned, the specific factors that play

Table 5 Logistic regression analysis of risk factors associated with functional impairments in children with ADHD

	Family	Academic	Life skills	Self-concept	Social activities	Risky activities
Inattentiveness score, OR (95% CI)	1.04 (0.99 to 1.09)	1.10* (1.06 to 1.14)	1.06* (1.02 to 1.10)	1.19* (1.12 to 1.26)	0.99 (0.94 to 1.03)	1.11* (1.04 to 1.19)
Hyperactivity score, OR (95% CI)	1.08* (1.05 to 1.11)	1.06* (1.03 to 1.08)	1.08* (1.06 to 1.11)	1.01 (0.95 to 1.07)	1.08* (1.05 to 1.10)	1.11* (1.07 to 1.15)
ODD score, OR (95% CI)	1.21* (1.17 to 1.25)	1.01 (0.99 to 1.04)	1.06* (1.04 to 1.09)	1.08* (1.04 to 1.12)	1.03 (0.98 to 1.07)	1.05* (1.01 to 1.10)
CD score, OR (95% CI)	1.30* (1.21 to 1.39)	1.21* (1.15 to 1.28)	1.04 (0.98 to 1.10)	1.05 (0.96 to 1.15)	1.26* (1.18 to 1.36)	1.36* (1.26 to 1.47)
Anx-Dep score OR (95% CI)	1.28* (1.23 to 1.34)	1.15* (1.11 to 1.20)	1.21* (1.16 to 1.26)	1.78* (1.69 to 1.87)	1.18* (1.12 to 1.24)	1.25* (1.19 to 1.32)
No. of comorbid disorders OR (95% CI)	0.95 (0.79 to 1.15)	0.98 (0.83 to 1.15)	0.99 (0.85 to 1.17)	0.93 (0.76 to 1.13)	1.35* (1.19 to 1.53)	0.93 (0.73 to 1.18)
ADHD subtypes OR (95% CI)	1.05 (0.92 to 1.19)	1.02 (0.92 to 1.13)	0.97 (0.87 to 1.07)	0.94 (0.85 to 1.02)	1.04 (0.92 to 1.17)	0.99 (0.83 to 1.18)

Models include controls for child age, sex and IQ.

* $P < 0.05$.

ADHD, attention deficit hyperactivity disorder; Anx-Dep, anxiety and depression disorder; CD, conduct disorder; ODD, oppositional defiant disorder.

decisive roles in their impairment remain unclear. Therefore, the final objective of the current study was to analyse the risk factors associated with each functional domain in ADHD using logistic regression analysis. The results showed that the different comorbidities were related to specific functional domains. For the domains of family (OR=1.30), academic (OR=1.21) and risk activities (OR=1.36), CD symptom score had the most significant influence. In contrast, life skills (OR=1.21) and self-concept (OR=1.78) were most significantly influenced by Anx-Dep symptom score, and social activities (OR=1.35) was most influenced by the number of comorbidities. Therefore, we conclude that in most functional domains, the effect of comorbidities on functional impairment exceeded the effects of ADHD core symptoms.

The current study also showed that the incidence of CD, ODD or Anx-Dep in the N-ADHD group (2616 children) was 24.1%, and the main complaint of these children was multidomain functional impairments. Over the years, clinical efforts have been made to alleviate the core symptoms of children with ADHD, but there are still many patients in whom symptoms can persist into adolescence and adulthood. This is especially true when comorbidities and functional impairments have not been alleviated because functional impairments have an extensive and negative impact on learning, social interactions and daily life.^{19 21} Thus, although inattentiveness or hyperactivity symptoms in some children are not apparent and do not meet the diagnostic criteria for ADHD, clinicians should make efforts to screen and treat these other conditions because the persistence of CD, ODD and/or Anx-Dep may be the main reason social functioning does not improve.

In addition to different clinical significances and prognoses, responses to treatment also depend on the type of comorbidity, indicating that the existence of a comorbidity can affect the ADHD treatment strategy.¹¹ The Multimodal Treatment Study of Children with ADHD (MTA) reported the behaviour and the drug response of children with different types of ADHD comorbidities, finding that children with ADHD only or ADHD with ODD/CD, but without anxiety disorders, responded best to MTA medication treatments, with or without behavioural treatments.²⁴ Moreover, children with multiple comorbid disorders (anxiety and ODD/CD) responded optimally to combined (medication and behavioural) treatments.²⁴ The second edition of the Chinese ADHD Prevention and Treatment Guidelines³⁰ also pointed out that children with ADHD are often accompanied by a variety of psychological and developmental diseases. Thus, the diagnosis and treatment of ADHD comorbidities is essential. Specifically, given that stimulants may increase the risk of twitching, the second edition of the Chinese ADHD Prevention and Treatment Guidelines recommends atomoxetine and clonidine as preferred drugs for the treatment of ADHD when accompanied by a TD. In addition, nearly one-third of children with ADHD have anxiety, and stimulants may also increase anxiety

symptoms. Therefore, the second edition of the Chinese ADHD Prevention and Treatment Guidelines recommends atomoxetine as first-line treatment of ADHD when accompanied by anxiety.

This study had some limitations. First, participants were screened from the clinic of one children's hospital, and the cross-sectional design did not enable conclusions about causality. The N-ADHD group was not pure. There were >80 000 person-time per year visiting the Department of Child Health Care in our hospital. This was a limitation in our study, but we believe that it also gave us insight that children suspected of ADHD should receive close attention with respect to functional impairments. Fortunately, several results were consistent with those previously reported in multicentre studies conducted in other countries. Second, assessment from parents should be treated with caution due to possible recall bias. Because of the nature of the available data, the factors included in the logistic regression analysis and the family and social environmental factors were limited; however, the large sample size allowed meaningful results to be obtained.

CONCLUSIONS

ADHD should not be regarded as a single disease but as a comprehensive state comprising a group of diseases. The influence of comorbidities on social function in ADHD can exceed that of the core symptoms. Early clinical classification, comorbidity analysis and functional impairment assessment in children suspected of having ADHD are crucial for determining treatment and prognosis. Furthermore, the existence of a comorbidity can lead to changes in the ADHD treatment strategy. Additional studies about ADHD comorbidity problems are needed to further individualise interventions.

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REFERENCES

- Polanczyk GV, Salum GA, Sugaya LS, *et al*. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry* 2015;56:345–65.
- Li SM, Feng W, Fang F, *et al*. [Prevalence of attention deficit and hyperactivity disorder in children in China: a systematic review and Meta-analysis]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2018;39:993–8.
- Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet* 2016;387:1240–50.
- Lara C, Fayyad J, de Graaf R, *et al*. Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the world Health organization world mental health survey initiative. *Biol Psychiatry* 2009;65:46–54.
- Yoshimasu K, Barbaresi WJ, Colligan RC, *et al*. Childhood ADHD is strongly associated with a broad range of psychiatric disorders during adolescence: a population-based birth cohort study. *J Child Psychol Psychiatry* 2012;53:1036–43.
- Rimal H, Pokharel A. Prevalence of Attention Deficit Hyperactivity Disorder among School Children and Associated Co-morbidities - A Hospital Based Descriptive Study. *Kathmandu Univ Med J* 2016;14:226–30.
- Bishop C, Mulraney M, Rinehart N, *et al*. An examination of the association between anxiety and social functioning in youth with ADHD: a systematic review. *Psychiatry Res* 2019;273:402–21.
- Larson K, Russ SA, Kahn RS, *et al*. Patterns of comorbidity, functioning, and service use for us children with ADHD, 2007. *Pediatrics* 2011;127:462–70.
- Jerrell JM, McIntyre RS, Park Y-MM. Risk factors for incident major depressive disorder in children and adolescents with attention-deficit/hyperactivity disorder. *Eur Child Adolesc Psychiatry* 2015;24:65–73.
- Elia J, Ambrosini P, Berrettini W. ADHD characteristics: I. Concurrent co-morbidity patterns in children & adolescents. *Child Adolesc Psychiatry Ment Health* 2008;2:15.
- Jensen PS, Arnold LE, Richters JE. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 1999;56:1073–86.
- Reale L, Bartoli B, Cartabia M, *et al*. Comorbidity prevalence and treatment outcome in children and adolescents with ADHD. *Eur Child Adolesc Psychiatry* 2017;26:1443–57.
- Virring A, Lambek R, Jennum PJ, *et al*. Sleep problems and daily functioning in children with ADHD: an investigation of the role of impairment, ADHD presentations, and psychiatric comorbidity. *J Atten Disord* 2017;21:731–40.
- Ghanizadeh A. Conduct behaviors and oppositional defiant behaviors in children and adolescents with ADHD. *Postgrad Med* 2015;127:289–94.
- Wolraich ML, Lambert W, Doffing MA, *et al*. Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. *J Pediatr Psychol* 2003;28:559–68.
- Xiao Z-H, Wang Q-H, Luo T-T, *et al*. [Diagnostic value of Vanderbilt ADHD Parent Rating Scale in attention deficit hyperactivity disorder]. *Zhongguo Dang Dai Er Ke Za Zhi* 2013;15:348–52.
- Sasser T, Schoenfelder EN, Stein MA. Targeting functional impairments in the treatment of children and adolescents with ADHD. *CNS Drugs* 2017;31:97–107.
- Chiang H-L, Gau SS-F. Impact of executive functions on school and peer functions in youths with ADHD. *Res Dev Disabil* 2014;35:963–72.
- Al Ansari A, Hamadeh RR, Jahrami H, *et al*. Outcomes of children with attention deficit/hyperactivity disorder: global functioning and symptoms persistence. *East Mediterr Health J* 2017;23:589–93.



- 20 von Polier GG, Vloet TD, Herpertz-Dahlmann B. ADHD and delinquency—a developmental perspective. *Behav Sci Law* 2012;30:121–39.
- 21 Fredriksen M, Dahl AA, Martinsen EW, *et al.* Childhood and persistent ADHD symptoms associated with educational failure and long-term occupational disability in adult ADHD. *Atten Defic Hyperact Disord* 2014;6:87–99.
- 22 Gillberg C, Gillberg IC, Rasmussen P, *et al.* Co-Existing disorders in ADHD -- implications for diagnosis and intervention. *Eur Child Adolesc Psychiatry* 2004;13 Suppl 1:180–92.
- 23 Jensen PS, Martin D, Cantwell DP. Comorbidity in ADHD: implications for research, practice, and DSM-V. *J Am Acad Child Adolesc Psychiatry* 1997;36:1065–79.
- 24 Jensen PS, Hinshaw SP, Kraemer HC, *et al.* Adhd comorbidity findings from the MTA study: comparing comorbid subgroups. *J Am Acad Child Adolesc Psychiatry* 2001;40:147–58.
- 25 Jensen CM, Steinhausen H-C. Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. *Atten Defic Hyperact Disord* 2015;7:27–38.
- 26 Becker SP, Langberg JM, Evans SW, Stephen P, Becker JM, *et al.* Differentiating anxiety and depression in relation to the social functioning of young adolescents with ADHD. *J Clin Child Adolesc Psychol* 2015;44:1015-29.
- 27 Xiao Z-H, Wang Q-H, Luo T-T, *et al.* [Comorbidities and functional impairments in children with attention deficit hyperactivity disorder]. *Zhongguo Dang Dai Er Ke Za Zhi* 2013;15: 728–32.
- 28 Nelson JM, Liebel SW. Anxiety and depression among college students with attention-deficit/hyperactivity disorder (ADHD): Cross-informant, sex, and subtype differences. *J Am Coll Health* 2018;66:123–32.
- 29 Castagna PJ, Calamia M, Davis TE. Childhood ADHD and negative Self-Statements: important differences associated with subtype and anxiety symptoms. *Behav Ther* 2017;48:793–807.
- 30 Ching C, Eslick GD, Poulton AS. Evaluation of methylphenidate safety and Maximum-Dose titration rationale in attention-deficit/hyperactivity disorder: a meta-analysis. *JAMA Pediatr* 2019;173:630–9.