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Attention deficit hyperactivity disorder: Psychopathology, quality of life, multimodal therapy

PhD Thesis Abstract

ACKNOWLEDGEMENTS

1. BACKGROUND

1.1. Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is one of the most common child psychiatric disorders, affecting 3 to 6% of children (Brown et al., 2001; Costello et al., 1997; Mohammadi et al., 2021) and its symptoms persist into adulthood in 40 to 60% of cases (Simon et al., 2009). The core symptoms of ADHD include poor attention, hyperactivity, and impulsivity (APA, 2013; WHO, 2019). The prevalence rate is 3 times higher in boys than in girls (Willcutt, 2012), while the boy to girl ratio among those receiving treatment is 6 to 1 (Costello et al., 1997); the reason is that girls tend to have more attention deficit than hyperactive symptoms, which – despite their negative impact on the child's development – are less disturbing to the environment than hyperactivity-impulsivity disorder, and therefore girls are less likely to be referred to a specialist (Balázs & Miklósi, 2015). At the same time, more than 80% of children diagnosed with ADHD have at least one *comorbid*, or co-occurring, condition identified alongside ADHD, while 50% have at least two comorbid conditions (Gillberg et al., 2004). In boys, "externalising" comorbid disorders such as conduct disorder and oppositional defiant disorder are more prevalent, whereas with girls, especially adolescent girls, "internalising" comorbid disorders such as depression and anxiety are more prevalent (Rucklidge, 2008). Struggling in peer relationships is not a criterion for ADHD diagnosis, but children diagnosed with ADHD are, by the nature of their symptoms, most likely to have difficulty in peer relationships (Hoza, 2007). These symptoms may be manifested in their inability to pay adequate attention to peer cues when playing games or engaging in shared classroom activities (Selikowitz, 2010). They tend to be overactive and thus unable to participate effectively in quiet or patience-requiring games (Bacchini et al., 2008). During play, they can struggle to wait for their turn and disrupt the peer interactions of others (Nijmeijer et al., 2008), and they tend to behave more disruptively and wilfully than their peers, relying on more impulsive solutions to peer problems (Waschbusch et al., 2019; Wehmeier, 2010). Also, affected children tend to have relatively fewer friends and 80% experience significant rejection from others (Hoza, 2007). Since children diagnosed with ADHD often have impaired peer relationships (Hoza, 2007; Wehmeier, 2010), it is assumed that they also have difficulties with prosocial behaviour. Tengsujaritkul et al.

(2020) investigated functional impairment in children diagnosed and treated for ADHD and found that they had relatively lower prosocial scores and that associated comorbid conditions were linked with more peer problems. In a clinical study, children diagnosed with ADHD and treated with methylphenidate medication were compared with a control group in terms of peer relationship problems and prosocial behaviour (García et al., 2011). Their results showed that children diagnosed with ADHD had more peer relationship problems and were described by their teachers as less prosocial compared to the control group children. There are effective multimodal therapies for ADHD, including parent education, cognitive behavioural therapy, and medication (Hinshaw et al., 2015; NICE, 2018; Sonuga-Barke et al., 2013).

1.2. Quality of life

Health-related quality of life (HRQoL) is a multidimensional concept that encompasses the physical, social, and emotional components of health (Danckaerts et al., 2009). According to Agarwal et al. (2012), it refers primarily to "the personal assessment of an individual's life in terms of his or her overall health, impairments and everyday effectiveness" (p. 11). The HRQoL provides a picture of how the patient experiences their illness (Bastiaansen et al., 2004), whereas symptom scales do not provide a realistic picture (Jekkel & Magyar, 2007). Therefore, the HRQoL can be an important measure for understanding the impact of mental illnesses on individual functioning and for evaluating the effectiveness of therapy (Coghill, 2010). The study of HRQoL in children is still less common (Ravens-Sieberer et al., 2007) despite a recent increase in the number of children with chronic illnesses, including psychiatric conditions (Erskine et al., 2017; Ravens-Sieberer et al., 2014). A review by Polanczyk et al. (2015) found that the prevalence of psychiatric disorders in children and adolescents worldwide is 11.3 to 15.9%, which often go hand in hand with social and school functioning difficulties, showing significant continuity over time (Costello et al., 1999; Esser et al., 1990). Oppositional defiant disorder, specific phobias, and ADHD are among the most common syndromes in children aged 5 to 8 years (Rijlaarsdam et al., 2015). Mental disorders often remain unidentified or are diagnosed too late, which is considered a major public health problem worldwide (Belfer, 2008; Merikangas et al., 2009; Morris et al., 2011). The negative impact of psychiatric pathologies on HRQoL has been confirmed by several

studies (Dey et al., 2012; Radicke et al., 2021; Sawyer et al., 2002; Weitkamp et al., 2013), an impact that may be even more severe for children with chronic illnesses (Sawyer et al., 2002).

Over the last 2 decades, a number of studies have examined the impact of ADHD on HRQoL (Agarwal et al., 2012; Coghill et al., 2010; Danckaerts et al., 2009; Velő et al., 2013). The study of HRQoL per ADHD is important for several reasons: the high prevalence of the disorder (Brown et al., 2001; Costello et al., 1997), its chronicity (Simon et al., 2009), the functional impairments that the child may experience (Wehmeier et al., 2010), and the social impact on the child and their family (Swensen et al., 2003).

Danckaerts et al. (2009) reviewed 36 articles on HRQoL in children and adolescents with ADHD diagnoses published between 1988 and 2008 in a systematic review. They organised the literature into three major issues: the impact of ADHD on HRQoL, the relationship between ADHD symptoms and HRQoL mediators, and the impact of ADHD treatment on quality of life. The main findings were that children diagnosed with ADHD have lower HRQoL than their healthy peers, as reported by themselves and their parents, but children diagnosed with ADHD have fewer negative perceptions of their own HRQoL than their parents. The study suggests that ADHD has a greater impact on the psychosocial domains of HRQoL versus physical domains, like in the impacts of chronic somatic illnesses.

After a number of studies found that ADHD has a negative impact on HRQoL (Danckaerts et al., 2009; Velő et al., 2013), there has been a growing need to determine the impact of treatments on improving HRQoL while reducing ADHD symptoms. One aspect of the HRQoL studies of children and adolescents with ADHD diagnoses reviewed by Danckaerts et al. (2009) between 1988 and 2008 was to present studies that looked at changes in HRQoL as a result of treatment. Their review confirmed the positive effects of drug therapies on HRQoL, however, the majority of the studies incorporated relatively short follow-up periods, thus the authors pointed out that it is conceivable that changes in some aspects of HRQoL would require more time to be observed and thus would not be reflected in a short follow-up assessment.

2. OBJECTIVES AND HYPOTHESES

2.1. Objective of the first study

Research on HRQoL has aimed to compare clinical and non-clinical (healthy control) groups or assess differences within clinical groups. To our knowledge, there were no studies that had examined HRQoL in a group with mental disorders who are newly diagnosed and not yet receiving treatment. The first study of the present doctoral thesis aimed to assess the number and/or type of psychiatric diagnoses in primary school children and to evaluate the HRQoL (by parent and child) in children who were not receiving psychiatric or psychological treatment at the time of the study or had not previously received such treatment.

Our survey questions:

> - I/1. Is there a difference in the self-rated and parent-rated HRQoL of school children with and without psychiatric illness?
> - I/2. Is there a correlation between the number of psychiatric illnesses a child has and the HRQoL of the child and parent?
> - I/3. Is there a correlation between the age of the child and the HRQoL assigned by the child and parent?
> - I/4. Is the presence of psychiatric illness predicted by the HRQoL of the child's self and parent, the age of the child, and the gender of the child?

2.2. Objective of the second study

For children diagnosed with ADHD, functioning in peer relationships is a less-explored area, although there are some publications reporting difficulties in peer relationships (Hoza, 2007; Wehmeier, 2010). Clinical trials of functioning in peer relationships have less filtering of treatment efficacy (Booster et al., 2010; García et al., 2011; Tengsujaritkul et al., 2020), which is an important determinant in assessing functional impairment. Our second study aimed to assess the severity of peer relationship problems, the extent of prosocial behaviour, and their association with HRQoL in a clinical group of untreated but ADHD-diagnosed children. To our knowledge, no research had been conducted to explore prosocial behaviour and peer relationship problems among children with ADHD who had not received treatment, nor were we aware of any research that had examined

their relationship with HRQoL. In our second study, we also aimed to compare differences in prosocial behaviour and peer relationships between children with ADHD who had not yet received treatment but were diagnosed with ADHD and those who were diagnosed with ADHD versus those who were not.

Our hypotheses:

> II/1. Untreated children diagnosed with ADHD (clinical group) have lower prosociality and better peer relationships than children without ADHD (healthy controls).

> II/2. Higher levels of prosocial behaviour are associated with higher levels of HRQoL in the clinical and healthy control groups, as reported by both children and parents.

> II/3. Higher levels of peer relationship problems are associated with lower levels of HRQoL in the clinical and healthy control groups, as reported by both children and parents.

> II/4. Lower levels of prosocial behaviour are associated with higher levels of peer relationship problems in the clinical and healthy control groups.

> II/5. Children diagnosed with ADHD who have a comorbid externalising disorder (ADHD + CD and/or ODD group) have lower levels of prosocial behaviour than those who do not have an externalising disorder (ADHD group).

> II/6. Children diagnosed with ADHD who have a comorbid externalising disorder (ADHD + CD and/or ODD group) have higher levels of peer relationship problems than children who do not have an externalising disorder (ADHD group).

2.3. The objective of our third study

Mainly available was information on the effectiveness of drug therapies in evaluating the impact of ADHD therapy on quality of life (Danckaerts et al., 2009; Coghill et al., 2009; Coghill et al., 2017), but even for these we found short-term follow-up studies, and the studies relied mostly on parent perceptions of HRQoL. The aim of the third study in the present PhD thesis was to assess the long-term (36 months) effects of multimodal therapy (drug and non-pharmacological) on psychopathology (ADHD and comorbid symptoms) and parent and child judgements of HRQoL in children and adolescents diagnosed with ADHD.

Our hypotheses:

- ➢ III/1. At the end of the study (Time [T] 2 at 36 months), children diagnosed with ADHD will show fewer psychopathological symptoms (ADHD and comorbid symptoms) than at the beginning of the study (T1).
- ➢ III/2. At the end of the study (T2; 36 months), children diagnosed with ADHD have better HRQoL, both self and parent-rated, than at baseline (T1).

3. METHOD

This doctoral research was conducted in collaboration with the Childhood Psychiatric Disorders Research Group at ELTE. Our research was approved by the Ethics Committee of the Health Research Council (ETT-TUKEB licence number: 26182/2011-EKU; 50723-2/2013/EKU; 5046-1/2014/EKU).

3.1. Sample

The *clinical group* consisted of children admitted to the Vadaskert Child and Adolescent Psychiatric Hospital and Special Outpatient Clinic, Budapest, either as inpatients or outpatients. For the clinical group, the following inclusion criteria were applied: 1. the child was diagnosed with ADHD by a treating physician but not yet involved in therapy; 2. there was no intellectual disability or suspicion of intellectual disability; 3. a structured diagnostic interview (see below) confirmed the diagnosis of ADHD; and 4. there was no history of psychological and/or psychiatric treatment (neither psychotherapy nor medication).

To create the *control group,* 12 schools were randomly selected from a list of public primary schools in Budapest. In addition, two rural schools were included in our study by convenience sampling. Only public primary schools with children of average intelligence were included, and those with children with special educational needs were excluded. The criteria for inclusion in the study were: 1. the child was not under psychological or psychiatric treatment at the time of the study and had not been previously, and 2. the presence/absence of psychiatric disorders was confirmed by a structured psychiatric interview (see below).

This doctoral research consisted of three study parts, which I separated and refer to as Study 1, Study 2, and Study 3.

Study 1:

In our first study, we split the control group into two separate groups according to whether the diagnostic interview established a diagnosis: Group 1: the diagnostic interview established one or more psychiatric diagnoses (diagnosed control), and Group 2: the diagnostic interview did not establish a psychiatric diagnosis (healthy control).

Study 2:

In our second study, we included the clinical group of our study sample as well as children from the control group for whom the diagnostic interview (see below) did not reveal any psychiatric diagnosis (healthy controls). We created two different groups from the clinical group, including 1. Comorbid externalising disorder with ADHD (ADHD + CD and/or ODD group), and 2. comorbid externalising disorder without ADHD (ADHD group).

Study 3:

In our third study, we followed up the clinical group with the ADHD diagnosis who had been admitted to the Vadaskert Child and Adolescent Psychiatric Hospital and Special Outpatient Clinic and the healthy control group, as well. For the clinical group, we excluded from the follow-up study those children whose treating physician (child psychiatrist) did not recommend further medication (due to ineffectiveness or side effects) or did not participate in the "nest" programme in the ward (see below). The reasons for not being included in the follow-up are presented in Results.

3.2. Study measurement

The instruments and their inclusion were the same in all three test phases. For instruments not used in all three studies, the instrument is indicated in parentheses in the presentation of the instrument to indicate the trial in which it was used.

➢ *Demographic characteristics*

A demographic data sheet completed by parents/guardians was compiled for this study. We asked questions about gender, age, pregnancy, birth, perinatal history of the child, number of siblings, number of siblings in the siblings' order, parents' age, education, and more.

➢ *Psychopathology: Symptoms and diagnoses*

To measure psychopathological symptoms and diagnoses, we used a modified version of the Mini-International Neuropsychiatric Interview 2.0 for Children and Adolescents (MINI; Balázs et al., 2004; Sheehan et al., 1998; Sheehan et al., 2010; Lecubrier et al., 1997). The MINI for Children is a structured psychiatric interview that assesses 25 child and adolescent psychiatric disorders according to DSM-IV criteria.

➢ *Prosocial behaviour and contemporary relationship problems (Study 2)*

To assess prosocial behaviour and peer relationship problems, we used the Hungarian parent version of the Strengths and Difficulties Questionnaire (SDQ) (Goodman et al., 1998) (Birkás et al., 2008; Turi et al., 2013). The items of the questionnaire are classified into five subscales: emotional symptoms, behavioural problems, hyperactivity, peer relationship problems, and prosocial behaviour.

➢ *Quality of life*

Quality of life was assessed using the Hungarian version of the German self-completion questionnaire Inventar zur Erfassung der Lebensqualität bei Kindern und Jugendlichen (ILK: Measure of QoL for Children and Adolescents) (Mattejat et al., 1998; Mattejat & Remschmidt, 1998). In Hungary, the ILK questionnaire is a quality of life instrument used in child psychiatric clinics that is suitable for assessing the quality of life of both healthy children and adolescents with psychiatric or somatic illness (Kiss et al., 2007). In addition to the child's subjective self-completion (i.e., self-report) version, there is also a parent version in which the parent assesses the quality of life of their child.

3.3. Procedure

The research for this PhD thesis was a multi-stage process between 2011 and 2017. The baseline survey (T1) was conducted between 2011 and 2014, which included studies 1 and 2 of this dissertation. The follow-up of the study sample (T2) was carried out between 2014 and 2017, the results of which are presented in Study 3.

➢ *Baseline assessment (T1):* After the adolescents and their parents were informed about the study and gave verbal and written consent, we checked whether the criteria for inclusion in the study were met. For both groups (clinical and control), we first administered a modified version of the Children's MINI to assess psychopathological symptoms. After the diagnostic interview was recorded, the

ILK and SDQ questionnaires were administered. After the diagnostic interviews and questionnaires were completed, the children in the clinical group received an optimal dose of methylphenidate, which was prescribed according to the instructions of their child psychiatrist independently of our study and administered according to the treatment protocol. In addition to drug therapy, the children in the clinical group participated in "nest" (Kis et al., 2017), a programme based on cognitive behavioural therapy at the Vadaskert Children's Psychiatric Hospital. In addition, parents of children diagnosed with ADHD participated in four suitable parent training sessions linked to nest. The optimal dose of medication and behavioural therapy interventions were checked and, if necessary, fine-tuned at regular check-ups at the Outpatient Clinic of Vadaskert Hospital. The healthy control group did not receive any intervention.

➢ *Follow-up (T2):* Thirty-six months after the start of the study, all children from the clinical and non-clinical groups were contacted again and invited to participate in a follow-up study. During the follow-up, a modified version of the Children's MINI and the ILK and SDQ were completed again.

4. RESULTS

4.1. Results of Study 1

➢ *I/1: HRQoL of diagnosed control and healthy control school children*

A significant difference in HRQoL between the two groups was found when comparing the self-rated HRQoL of the control group with diagnoses and healthy control groups (Table 1). The control group with diagnoses had significantly lower HRQoL than the healthy control group. When HRQoL was broken down into dimensions, we found significant differences in four HRQoL domains: school, peer relationships, time spent alone, and mental health. In these dimensions, the HRQoL scores of the control group with psychiatric diagnoses were lower than those of the healthy control group.

Table 1: *Comparison of diagnosed and healthy control group based on child-rated quality of life*

	Control group with diagnoses (*n* = 26)			Healthy control group (*n* = 53)			
	M (*SD*)	Median	IQR	*M* (*SD*)	Median	IQR	Mann-Whitney *U* test
HRQoL	28.95(2.49)	29	4.00	32.10(2.32)	33.00	3.00	U=206.5; $p<0.001$***
HRQoL1	3.62(0.76)	4.00	1.00	4.44(0.61)	4.50	1.00	*U*=284.5; $p<0.001$***
HRQoL2	4.50(0.72)	5.00	1.00	4.76(0.47)	5.00	0.00	*U*=533.5; $p=0.135$
HRQoL3	4.45(0.88)	5.00	1.00	4.87(0.37)	5.00	0.00	*U*=496.00; $p<0.05$*
HRQoL4	3.25(1.29)	4.00	2.00	4.04(0.98)	4.00	2.00	*U*=432.00; $p<0.05$*
HRQoL5	4.50(0.72)	5.00	1.00	4.64(0.59)	5.00	1.00	*U*=588.00; $p=0.327$
HRQoL6	3.95(1.16)	4.00	1.75	4.70(0.50)	5.00	1.00	*U*=402.00; $p<0.001$***
HRQoL7	4.66(0.48)	5.00	1.00	4.68(0.51)	5.00	1.00	*U*=584.5; $p=0.575$

ADHD = attention deficit hyperactivity disorder; HRQoL = health-related quality of life; HRQoL 1 to 7: 1 – school, 2 – family, 3 – peer relationships, 4 – time spent alone, 5 – somatic health, 6 – mental health, 7 – general; M = mean; SD = standard deviation; IQR = interquartile range. Levels of significance: *p < 0,05; **p < 0,01; ***p < 0,001.

There was also a significant difference between the HRQoL of the two groups according to parents' perceptions: Children in the control group with diagnoses also had a lower HRQoL than the healthy control group according to parents' perceptions (Table 2). Disaggregated by domains of HRQoL based on parents' perceptions, the diagnosed control group showed lower HRQoL scores than the healthy control group on five dimensions: school, peer relationships, somatic health, mental health, and general health.

Table 2: *Comparison of diagnosed and healthy control group by parents*

	Control group with diagnoses (*n* = 26)			Healthy control group (*n* = 53)			
	M (SD)	Median	IQR	*M (SD)*	Median	IQR	Mann-Whitney U test
HRQoL	29.75(2.98)	30.00	4.75	33.04(2.20)	33.50	3.00	*U*=285.00; $p<0.001$***
HRQoL1	3.83(0.70)	4.00	1.00	4.58(0.57)	5.00	1.00	*U*=347.00; $p<0.001$***
HRQoL2	4.50(0.78)	5.00	1.00	4.80(0.40)	5.00	0.00	*U*=574.00; $p=0.155$
HRQoL3	4.33(0,76)	4.50	1.00	4.78(0.41)	5.00	0.00	*U*=470.00; $p<0.05$*
HRQoL4	4.37(0,71)	4.50	1.00	4.70(0.54)	5.00	1.00	*U*=525.00; $p=0.051$
HRQoL5	4.54(0,65)	5.00	1.00	4.86(0.45)	5.00	0.00	*U*=811.00; $p<0.05$*
HRQoL6	3.83(0,81)	4.00	0.75	4.60(0.60)	5.00	1.00	*U*=353.00; $p<0.001$***
HRQoL7	4.33(0,70)	4.00	1.00	4.72(0.45)	5.00	1.00	*U*=473.00; $p<0.01$**

ADHD = attention deficit hyperactivity disorder; HRQoL = health-related quality of life; HRQoL 1 to 7: 1 – school, 2 – family, 3 – peer relationships, 4 – time spent alone, 5 – somatic health, 6 – mental health, 7 – general; M = mean; SD = standard deviation; IQR = interquartile range. Levels of significance: *p < 0,05; **p < 0,01; ***p < 0,001.

> ➤ *I/2: Correlation between number of diagnoses and HRQoL*

Based on the children's perceptions, there was a medium negative relationship between HRQoL and the number of diagnoses. When examining HRQoL by domain, there was a medium negative relationship between HRQoL regarding school and number of diagnoses. Also found were a significant negative weak/medium correlation between the: number of diagnoses and the peer relationships HRQoL domain; number of diagnoses and time spent alone (HRQoL); and the number of diagnoses and mental health (HRQoL) (Table 3).

Table 3: *Spearman rank correlations between child's quality of life and diagnosis rate*

	HRQoL							
	HRQoL sum	HRQoL 1	HRQoL 2	HRQoL 3	HRQoL 4	HRQoL 5	HRQoL 6	HRQoL 7
Number of diagnoses	-0.556[**]	-0.522[**]	-0.175	-0.301[**]	-0.297[**]	-0.114	-0.397[**]	-0.074

HRQoL 1 to 7: 1 – school, 2 – family, 3 – peer relationships, 4 – time spent alone, 5 – somatic health, 6 – mental health, 7 – general; M = mean; SD = standard deviation; IQR = interquartile range. Levels of significance: *p < 0,05; **p < 0,01.

Moreover, a medium negative correlation between the number of diagnoses and HRQoL was found according to parent perception. Disaggregating HRQoL by domains, a medium negative correlation was found between the number of diagnoses and school (HRQoL) and between the number of diagnoses and mental health (HRQoL). Significant weak correlations were found between the number of diagnoses and overall HRQoL in peer relationships, number of diagnoses and time spent alone, number of diagnoses and somatic health, and between the number of diagnoses and general HRQoL domains (Table 4).

Table 4: *Spearman rank correlations between parent-rated quality of life and diagnosis rate*

	HRQoL							
	HRQoL sum	HRQoL1	HRQoL2	HRQoL3	HRQoL4	HRQoL5	HRQoL6	HRQoL7
Number of diagnoses	-0.512^{**}	-0.448^{**}	-0.194	-0.304^{**}	-0.280^{*}	-0.311^{**}	-0.475^{**}	-0.301^{**}

HRQoL 1 to 7: 1 – school, 2 – family, 3 – peer relationships, 4 – time spent alone, 5 – somatic health, 6 – mental health, 7 – general. Levels of significance: $*p < 0{,}05$; $**p < 0{,}01$.

> ➢ *I/3: Correlation between age and HRQoL*

Age showed a significant weak negative correlation only with the time spent alone domain, indicating that reduced HRQoL among adolescents was only observed for time spent alone (Table 5).

Table 5: *Spearman rank correlations between child's quality of life and age*

	HRQoL							
	HRQoL sum	HRQoL1	HRQoL2	HRQoL3	HRQoL4	HRQoL5	HRQoL6	HRQoL7
Age	-0.33	-0.128	-0.115	0.007	0.280^{*}	-0.110	-0.154	-0.151

HRQoL 1 to 7: 1 – school, 2 – family, 3 – peer relationships, 4 – time spent alone, 5 – somatic health, 6 – mental health, 7 – general. Level of significance: $*p < 0{,}05$.

Age did not show a significant correlation with parent-rated HRQoL (Table 6).

Table 6: *Spearman rank correlations between parental quality of life and age*

	HRQoL							
	HRQoL sum	HRQoL1	HRQoL2	HRQoL3	HRQoL4	HRQoL5	HRQoL6	HRQoL7
Age	-0.139	-0.199	-0.095	-0.059	0.100	-0.011	-0.213	-0.166

HRQoL 1 to 7: 1 – school, 2 – family, 3 – peer relationships, 4 – time spent alone, 5 – somatic health, 6 – mental health, 7 – general.

> *I/4: Predicting diagnoses in terms of HRQoL, age, and gender*

Our logistic regression model was significant (χ2[9] = 35.527, p < 0.001) for the child's judgement of HRQoL, gender, and age variables (Table 7). The model explained 55.4% of the variance in group membership (Nagelkerke R^2) and correctly classified 81.7% of cases (cut off point = 0.5). The diagnosed control group was 8.11 times more likely to have low HRQoL in school and 2.49 times more likely to have low HRQoL during time alone than the healthy control group. The effect of gender and age was not significant.

Table 7: *Effect of the child's HRQoL, age, and gender on the presence of a diagnosis*

	B	*SE*	Wald	*df*	*p*	Exp(B)	95% CI Lower	95% CI Upper
HRQoL1	-2.09	0.71	8.67	1	.003	8.11	2.01	32.69
HRQoL2	0.10	0.85	0.01	1	.908	0.91	0.17	4.75
HRQoL3	0.43	0.80	0.29	1	.590	0.65	0.14	3.11
HRQoL4	-0.91	0.40	5.13	1	.023	2.49	1.13	5.48
HRQoL5	0.52	0.61	0.72	1	.395	0.60	0.18	1.96
HRQoL6	-1.08	0.73	2.21	1	.137	2.95	0.71	12.28
HRQoL7	0.93	0.73	1.65	1	.199	0.39	0.09	1.64
Age	-0.02	0.21	0.01	1	.943	1.00	0.65	1.49
Gender	-1.71	0.94	3.34	1	.068	0.18	0.03	1.13

B = Beta SE = standard error of Beta; Wald = Wald value; df = degree of freedom; p = p value; Exp(B) = odds ratio; 95% CI = 95% confidence interval. HRQoL 1 to 7: 1 – school, 2 – family, 3 – peer relationships, 4 – time spent alone, 5 – somatic health, 6 – mental health, 7 – general.

With parent-rated HRQoL, gender, and age variables, our logistic regression model was significant, indicating that the predictors reliably discriminated between the diagnosed control and healthy control groups (χ2[9] = 29.043, p = 0.001) (Table 8). A Nagelkerke's R^2 of 0.45 indicated a moderate relationship between prediction and grouping. The overall prediction success was 84% of the diagnosed control group and 62.5% of the healthy control group (cut off point = 0.5). The diagnosed control group was 4.11 times more likely to have low HRQoL than the healthy control group. An increasing age was associated with a decrease in the probability of several diagnoses (B = -0.41).

Table 8: *The impact of the parent's quality of life, age, and gender on the existence of a diagnosis*

	B	*SE*	Wald	*df*	*p.*	Exp(B)	95% CI Lower	95% CI Upper
HRQoL1	-1.41	0.60	5.59	1	.018	4.11	1.27	13.26
HRQoL2	-0.52	0.62	0.71	1	.398	1.69	0.50	5.69
HRQoL3	-0.74	0.64	1.35	1	.246	2.10	0.60	7.35
HRQoL4	0.43	0.63	0.46	1	.496	0.65	0.19	2.25
HRQoL5	0.13	0.66	0.04	1	.848	0.88	0.24	3.19
HRQoL6	-0.84	0.71	1.40	1	.237	2.32	0.58	9.29
HRQoL7	0.09	0.89	0.01	1	.915	0.91	0.16	5.16
Age	-0.41	0.19	4.72	1	.030	0.66	0.46	0.96
Gender	-1.12	0.71	2.45	1	.118	0.33	0.08	1.33

B = Beta SE = standard error of Beta; Wald = Wald value; df = degree of freedom; p = p value; Exp(B) = odds ratio; 95% CI = 95% confidence interval. HRQoL 1 to 7: 1 – school, 2 – family, 3 – peer relationships, 4 – time spent alone, 5 – somatic health, 6 – mental health, 7 – general.

4.2. Results of Study 2

> *II/1: Prosocial behaviour and peer relationship problems in the clinical and healthy control groups*

The clinical group scored significantly lower on the prosocial behaviour scale and significantly higher on the peer relationship problems scale than the healthy control group (Table 9).

Table 9: *Differences between clinical and healthy control groups in prosocial behaviour and peer relationship problems*

	Clinical group (*n* = 79)			Healthy control group (*n* = 54)			Mann-Whitney U test
	M (SD)	Median	IQR	*M (SD)*	Median	IQR	
Prosocial behaviour	6.66 (2.40)	7	4	8.31 (1.84)	9	3	*U*=1114,50; *p*<0,0001[***]
Peer relationship problems	4.05 (2.47)	4	4	0.73 (0.90)	0	1	*U*=3244,00; *p*<0,0001[***]

ADHD = attention deficit hyperactivity disorder; M = mean; SD = standard deviation; IQR = interquartile range; *p < 0.05; **p < 0.01; ***p < 0.001

> *II/2-4: Relationships between contemporary relationship problems, prosocial behaviour, and HRQoL*

Results on the relationships between peer relationship problems, prosocial behaviour, and HRQoL are presented in Table 10.

Table 10: *Exploring the links between contemporary relationship problems, prosocial behaviour, and quality of life in the clinical and healthy control groups*

	Peer relationship problems		Prosocial behaviour	
Group	**Clinical**	**Healthy control**	**Clinical**	**Healthy control**
	rho; *p*		rho; *p*	
HRQoL by parents	−0.658; 0.001***	−0.470; 0.001***	0.341; 0.004**	0.374; 0.007**
HRQoL by children	−0.349; 0.003**	−0.132; 0.361	0.024; 0.840	0.202; 0.163
Peer relationship problems	-		−0.289; 0.016*	−0.439; 0.001***

HRQoL = health-related quality of life; ADHD = attention deficit hyperactivity disorder; *p < 0.05; **p < 0.01; ***p < 0.001.

Prosocial behaviour showed a weak positive relationship with parent-rated HRQoL in both the clinical and healthy control groups. Parent-rated HRQoL and peer relationship problems also showed a significant medium negative association in the clinical and healthy control groups.

A weak negative relationship was found between prosocial behaviour and peer relationship problems in the clinical group and a medium negative relationship in the healthy control group. Furthermore, the children's HRQoL score in the clinical group showed a significant weak negative relationship with peer relationship problems, but no significant relationship with prosocial behaviour. In the healthy control group, the children's HRQoL results showed no significant relationship with the other variables.

> *II/5: Comorbid externalising disorders and prosocial behaviour in the clinical group*

Within the clinical group, the ADHD group – children without a comorbid externalising disorder – and the ADHD + CD and/or ODD group – children with an externalising comorbid disorder – showed no significant difference in prosocial behaviour (Table 11).

Table 11: *Prosocial behaviour in the ADHD group with and without a comorbid externalising disorder*

	ADHD group (*n* = 29)			ADHD + CD and/or ODD group (*n* = 49)			
	M (SD)	Median	IQR	*M (SD)*	Median	IQR	Mann-Whitney U test
Prosocial behaviour	7.14 (2.28)	7	4.75	6.38 (2.45)	7	3	U=539.00; *p*=0.279

M = mean; SD = standard deviation; IQR = interquartile range; ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; ODD = oppositional defiant disorder; *p < 0.05; **p < 0.01; ***p < 0.001.

> *II/6: Comorbid externalising disorders and contemporary relationship problems in the clinical group*

The two groups (ADHD group and ADHD + CD and/or ODD) showed significant differences in peer relationship problems. The ADHD + CD and/or ODD group showed higher scores on peer relationship problems than the ADHD group without externalizing disorders (Table 12).

Table 12: Peer relationship problems among children diagnosed with ADHD and among children diagnosed with ADHD and externalizing comorbid diagnoses

|	ADHD group (*n* = 29)			ADHD + CD and/or ODD group (*n* = 49)			
	M (SD)	Median	IQR	*M (SD)*	Median	IQR	Mann-Whitney U test
Peer relationship problems	3.08 (2.59)	2	4	4.58 (2.25)	4.5	3	*U*=771.50; *p<0.05**

M = mean; SD = standard deviation; IQR = interquartile range; ADHD = attention deficit hyperactivity disorder; CD = conduct disorder; ODD = oppositional defiant disorder; *p < 0.05; **p < 0.01; ***p < 0.001

4.3. Results of Study 3

> ➤ *III/1: Psychopathology (ADHD and comorbid symptoms) at T2*

Of the 13 scales in the Children's MINI, six scales showed a significant Time main effect and/or a Time × Group interaction. Scores on these scales indicated statistically significant changes between T1 and T2, regardless of the group (clinical vs. healthy control). Scale scores showed a significant decrease in the group regardless of time.

There was also a significant Time main effect and Time × Group interaction on the scales for major depressive episode ($F[1, 51] = 7.294$, $p = 0.010$, $\eta2p = 0.15$) and dysthymic disorder ($F[1, 5]) = 6.434$, $p = 0.015$, $\eta2p = 0.13$), and the change was different between groups (Figure 1). Scores on the scales for the Time main effect and the Time × Group interaction were constant or increased non-significantly in the healthy control group, whereas these scores decreased significantly in the clinical group.
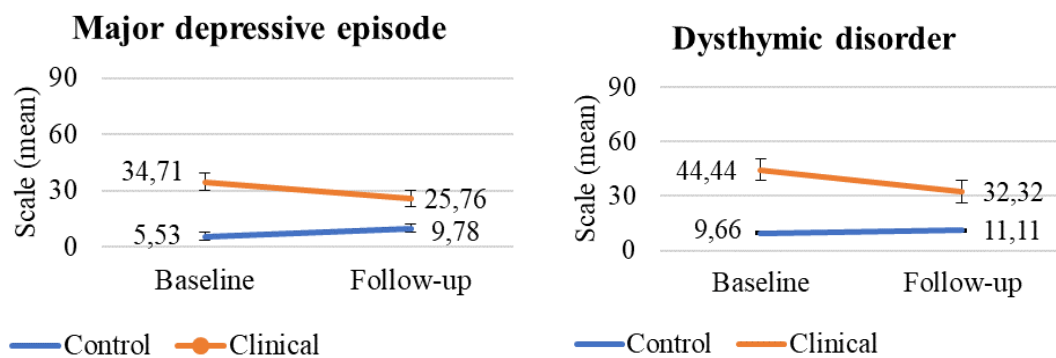

Figure 1: *Time main effect and Time × Group interaction scales of the Children's MINI Questionnaire for major depressive episode and dysthymic disorder*

A Time × Group interaction effect was a significant result for the other four scales, including ADHD ($F[1, 54] = 12.314$, $p = 0.001$, $\eta2p = 0.22$), social phobia ($F[1, 51] = 4.824$, $p = 0.034$, $\eta2p = 0.10$), oppositional defiant disorder ($F[1, 54] = 7.592$, $p = 0.009$, $\eta2p = 0.15$) and conduct disorder ($F[1, 54] = 11.034$, $p = 0.002$, $\eta2p = 0.22$). See Figure 2. Scores on the Time × Group interaction scales were constant or did not increase

significantly in the healthy control group, whereas they decreased significantly in the clinical group.

There were no significant effects for the remaining seven scales: (hypo)manic episode, panic disorder, separation anxiety disorder, specific phobia, obsessive-compulsive disorder, tic disorder, and generalized anxiety disorder. Based on the mean scores from these scales, the scores remained constant or increased in the healthy control group and did not significantly decrease in the clinical group, except for obsessive-compulsive disorder, for which the scores remained constant in the healthy control group and did not significantly increase in the clinical group.
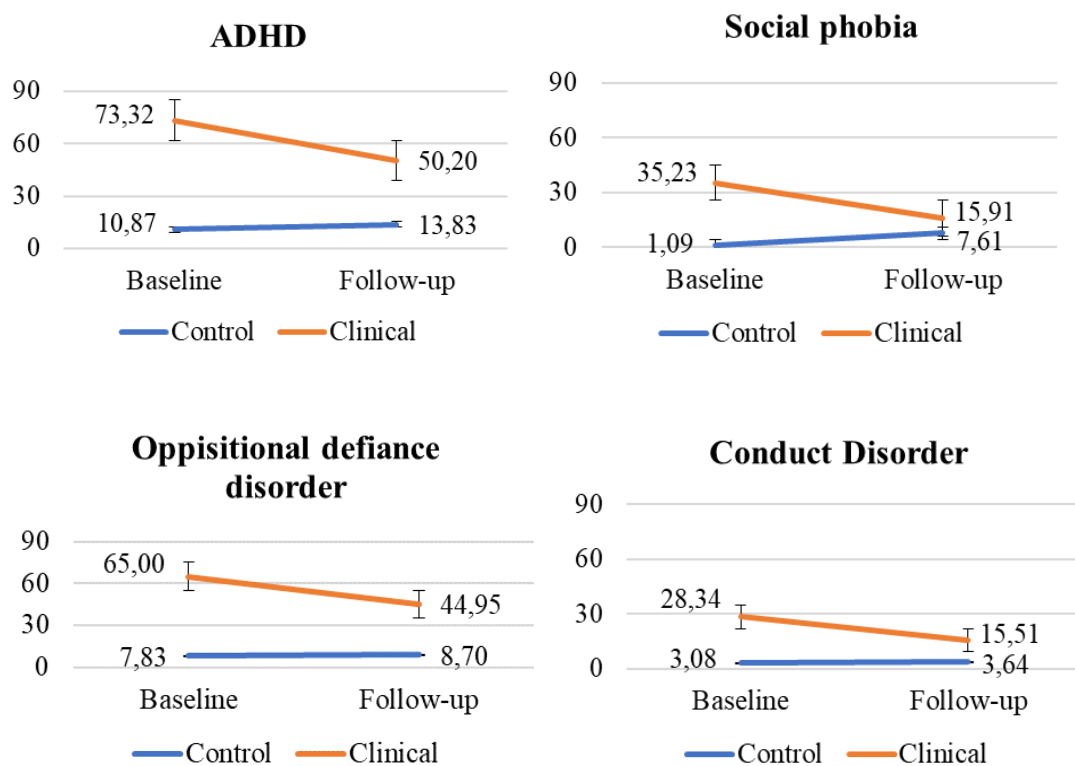
Figure 2: *Time × Group interaction scales of the Children's MINI Questionnaire for attention deficit hyperactivity disorder, social phobia, oppositional defiant disorder, and conduct disorder*

➢ *III/2. Parent and child-rated HRQoL at T2*

HRQoL rated by parents indicated a statistically significant Time × Group interaction (F[1, 41] = 11.264, p = 0.002, η2p = 0.22) (Figure 3). In the clinical group, HRQoL was significantly higher at T2 than at T1, indicating a higher HRQoL. In the healthy control group, there was no significant change, with HRQoL scores decreasing on average, but this change – indicating a worse HRQoL – was not significant. The HRQoL as judged by children showed a less significant Time × Group interaction (F[1, 38] = 3.570, p = 0.066, η2p = 0.09). The changes showed a similar pattern to the HRQoL scores as judged by parents.
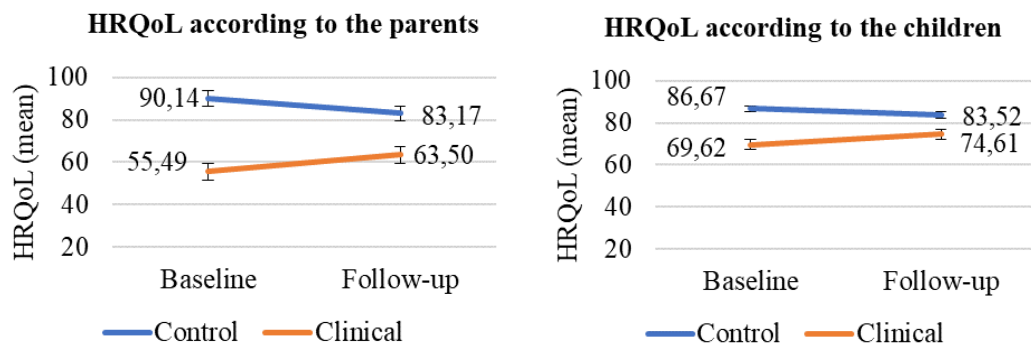
Figure 3: *Parent- and child-rated HRQoL scales' Time × Group interaction*

5. DISCUSSION

The studies conducted for this doctoral thesis address the topic of ADHD and HRQoL from three perspectives: first, in the case of untreated psychiatric disorders in school-age children; second, in terms of the functional outcomes of children diagnosed with ADHD who have not yet received treatment; and third, in exploring the impact of multimodal therapy for ADHD on HRQoL. All three studies have important clinical relevance. In many cases, mental disorders are either unidentified or diagnosed too late (Belfer, 2008; Merikangas et al., 2009; Morris et al., 2011), so that accumulated frustration as a result of undiagnosed or untreated mental disorders contributes to poor grades and negative

feedback from family members, peers, and authority figures (Koppelman, 2004). The negative effect of psychiatric pathologies on HRQoL has been confirmed (Dey et al., 2012; Sawyer et al., 2002; Radnicke et al., 2021, Weitkamp et al.,2013), but there was no information on the impact of undetected pathologies on the HRQoL of affected children, and our Study 1 aimed to answer this question. Primary school children in the control group of our clinical trial – then-currently and previously untreated – were diagnosed in one third of the study group, which were in most cases had ADHD and ODD. Our findings suggest that undiagnosed and untreated pathologies have a negative impact on several aspects of HRQoL and that school HRQoL is a strong predictor of the presence of a psychiatric disorder. Based on these findings, we believe that it is important to screen students in-school for mental health to both identify as soon as possible the pathologies that cause difficulties in the daily lives of affected children and prevent the development of comorbid conditions.

Our second study explored the prosociality and peer relationships of untreated children diagnosed with ADHD and their association with quality of life. In the case of ADHD, difficulties at school had been discussed in several prior studies, and in most cases the symptoms of ADHD were the reasons why parents sought help. However, functioning in peer relationships had received less attention even though children diagnosed with ADHD have many difficulties in this area (Écsi, 2018; Hoza, 2007). The present study confirmed that children diagnosed with ADHD can have lower prosociality and experience more problems in peer relationships than a healthy control group. From a clinical point of view, an important finding is that peer relationship problems are negatively related to HRQoL such that targeted support for the functioning of affected children in peer relationships should be an aspect of ADHD treatment, and thus an improvement in their quality of life might be achieved.

Our third study explored the long-term effects of multimodal therapy for ADHD on symptoms and HRQoL. Most previous studies had incorporated relatively short follow-up periods and mainly explored the effectiveness of drug therapy (Coghill et al., 2017; Coghill, 2010) despite the fact that ADHD treatment guidelines (EMMI, 2020; NICE, 2018) consider *complex treatment* (drug therapy and cognitive behavioural therapy) to be the most effective. Although the benefits of treatment are explained in detail by clinicians during psychoeducation, there is still a lot of fear and misconception among parents regarding drug therapies (Dosreis et al., 2003), which often leads to refusal of therapies

(Demidovich et al., 2011). Our study results support that multimodal therapy can be effective in the long term, leading to a reduction in ADHD and comorbid psychiatric symptoms as well as an improvement in HRQoL.

Overall, the results of this doctoral thesis provide important information on the HRQoL in children diagnosed with psychiatric disorders, especially ADHD. Our findings are the first to address: the negative impact of untreated psychiatric comorbidities on HRQoL; the exploration of prosocial behaviours and peer relationships and their impact on quality of life in children diagnosed with untreated ADHD; and the impact of comorbid disorders on peer relationships. The study is unique in that it investigated the effects of multimodal treatment of ADHD over the long term, with a follow-up of several years. The findings presented in this dissertation ideally contribute to a better understanding of the impact of psychiatric comorbidities on children's HRQoL, hopefully helping professionals to develop targeted prevention and intervention procedures.

6. LIMITATIONS

Limitations of this doctoral research:

- The clinical sample in our study consisted of children diagnosed but not treated at the Vadaskert Child and Adolescent Psychiatric Hospital and Special Outpatient Clinic. There was relatively little time between the diagnosis and the involvement in treatment to conduct a 1.5-hour interview and questionnaire with the child and parent. This difficult study circumstance is reflected in the low number of study items.

- For our control group, the study sample was collected mainly from schools in Budapest. Although we tried to include students from rural schools, their presence in the study sample was low.

- There was a gender difference between the clinical and control groups, with a significantly higher proportion of boys in the clinical group, reflecting the gender distribution in the clinical group (Biederman et al., 2000). This was accounted for in statistical analyses, where necessary. Gender differences could not be examined in the present sample.

- We aimed to include children of average intelligence in the study but did not test the subjects' intelligence (IQ). This is because the duration of an IQ test can be

90 minutes, which would have increased subjects' total assessment time to 150 minutes, which is too long for children, especially those diagnosed with ADHD. In the case of the clinical group, only children with no history of mental retardation or no suspicion of mental retardation were recommended by the treating physician for inclusion in the study. Only schools for children of average intelligence were targeted as a control group, and schools for children with special educational needs were excluded. In the test situation, children were asked to indicate if they did not understand a question. A mentor (parent or researcher) was present during the completion of the self-assessment questionnaire, allowing children to ask for information if needed.

- The study included a demographic questionnaire that collected information on parents' educational attainment and earnings status (active, passive, etc.), but no precise information on socioeconomic status (SES). Based on educational attainment and earnings status, we tried to investigate the impact or influence of SES on our findings, but due to our low number of items we could not calculate a suitable statistical test.

- We also did not measure the physical health of the children, which may also have had an impact on HRQoL scores.

- The MINI Children's diagnostic interview used in the study was based on DSM-IV rather than DSM-5 criteria. This was because the DSM-5-based version of the Children's MINI was not available at the start of the present study. However, it is thought that the differences between the two versions are not significant for the ADHD diagnosis in children (Epstein & Loren, 2013). While the number of required ADHD symptoms changed from six to five and the onset of symptoms and impairments from 7 to 12 years over the age of 17, recent studies have shown that these changes do not affect ADHD's prevalence in children (Thomas et al., 2015).

- The Children's MINI is able to assess a wide range of DSM-IV psychiatric diagnoses in childhood and adolescence, but it would also be important to assess comorbidities such as learning disabilities, which are present in almost 25% of ADHD cases (Pliszka, 1998) and affect quality of life (Tárnokiné Törő, 2017).

- For the SDQ, only the parent version was used, but the questionnaire also has a version for children to complete. The data from children would have provided

important information – especially in terms of prosocial behaviour and peer relationship problems – but due to the length of the study period, we were not able to collect additional information from the children.

Each study's limitations:

- Regarding the study design, it should be noted that our first two studies were cross-sectional, which does not allow us to draw causal conclusions.

- In the first study, a psychiatric diagnosis could have been made for a significant proportion of the control group, but this result should be treated with caution if one wanted to make any conclusions about the mental health of primary school children. In this dissertation we presented a study based on volunteer participation, so it is possible that a greater number of parents who experience difficulties with their children's mental health agreed to participate in the study. Furthermore, the lack of significance of gender in our regression model is due to weak collinearity even at appropriate VIF values (see Dissertation tables 2–4 in the Appendix), which makes it likely that the effect of gender in a regression model will tend to diminish.

- In the second study, there was a difference in the gender distribution between the clinical and control groups. However, this difference reflects the overall difference in the sex ratio of children diagnosed with ADHD, especially in clinical practice (Pastor et al., 2015) and between healthy children (KSH, 2017). In addition, it is important to note that the results of the current study were not affected by gender. One of the aims of our study was to assess peer relationship problems and explore their association with quality of life. In our sample, the internal consistency of the SDQ's Peer Relationship scale was found to be poor (see Dissertation Table 1 in the Appendix), presumably due to testing with a low number of items. This possibly influenced our results.

- For the third study, it is important to note first that the research focused only on children who were able to participate in the follow-up portion of the study (i.e., no drug side effects occurred, and a psychiatrist's therapeutic recommendations were followed). However, we compared the study completer and non-completer groups at baseline in several domains, such as age, gender, self- and parent-rated HRQoL, and symptom severity, and found no significant differences between them.

- Due to the low number of items in our sample, a post-hoc power analysis was performed, which showed low power values except for the major depressive episode and dysthymia scales. The effect of multimodal treatment should definitely be investigated with a larger number of items, as we found promising effects even with our low power sample with a limited number of items.

- A further limitation of Study 3 is that for ethical reasons we could not further randomise children with ADHD not-yet-diagnosed to treatment into two groups: 1) children with ADHD not-yet-diagnosed to treatment who receive treatment for a longer period of time versus 2) children with ADHD not-yet-diagnosed to treatment who receive no further treatment. The group of children not previously receiving treatment included all children who received further combined treatment as indicated by their psychiatrist at the hospital.

- Finally, even though parents had attended parent training and consulted with professionals on the effective use of behavioural interventions, our study did not include whether parents actually and consistently used these interventions with their children. Interpreters of our results should consider that not only multimodal treatment but also other factors (such as family functioning) and additional therapeutic support may have contributed to the improvement in quality of life of children diagnosed with ADHD.

7. FUTURE RESEARCH DIRECTIONS

The results of this doctoral research have raised several questions that might be addressed in future research. In the context of our first study, the high number of psychiatric diagnoses in the control group raises the question of why the parents of these children had not sought help to that point. Did stigma associated with psychiatric care play a role in their failure to seek help? There is a clinical case for exploring this to remove barriers to help-seeking for children.

Per our second study we were not able to establish causal relationships due to the study design, but it would be important to explore which factors lead to problematic functioning in areas of prosocial behaviour and peer relationships. A longitudinal study could answer whether these areas are still functioning well in preschool or whether children with ADHD symptoms are already starting from a disadvantaged position.

Our third study found an improvement in HRQoL because of multimodal treatment, but the quantitative data did not allow us to determine which components had the greatest impact. We wonder what role the reduction in symptoms, support from professionals, and possible positive changes in family-friend relationships played in this, and what the child experienced from these changes. A more accurate picture of the improvements caused by therapy would be obtained by using content analysis to examine the HRQoL of the children affected. The necessary ethical approval for this study has already been obtained by our research team, and we plan to launch this study soon.

8. NEW RESULTS

New results from this doctoral work:

- ➢ Psychiatric pathologies among primary school children can result in lower HRQoL in several domains. The number of diagnoses was negatively related to HRQoL, and reduced HRQoL in the school domain was the best predictor of having a diagnosis in this study.
- ➢ For children diagnosed with ADHD but not yet receiving treatment, problems in peer relationships can be negatively associated with HRQoL. More peer relationship problems may be expected in the presence of comorbid conditions, in addition to ADHD.
- ➢ Multimodal therapy for ADHD might also lead to both a long-term reduction in ADHD and comorbid symptoms and improvement in HRQoL.

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