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Finnish children who experienced narcolepsy after receiving the Pandemrix vaccine during the 2009-2010 H1N1 pandemic demonstrated high level of psychosocial problems.

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ABSTRACT

Aim: We assessed psychosocial burdens in children who developed narcolepsy after receiving the Pandemrix H1N1 vaccine during the 2009-2010 pandemic. Parental quality of life was also assessed.

Methods: This multicentre study covered four of the five Finnish University Hospital Districts, which dealt with about 90% of the paediatric narcolepsy cases after the Pandemrix vaccination. The medical records of children diagnosed from 2010-2014 were reviewed. The questionnaires included the Youth Self Report (YSR), Children´s Depression Inventory (CDI), the Child Behaviour Checklist (CBCL) and questions on parental resources, stress and quality of life.

Results: We obtained the medical records of 94 children who were aged 5-17 years at the time of their narcolepsy diagnosis and questionnaire data for 73 of those children. Most children had strong narcolepsy symptoms 25% had CDI scores that suggested depression. In addition, 41% had total CBCL problem scores above the clinically significant limit and 48% were anxious, withdrawn and had somatic complaints. Sleep latency was weakly associated with the CBCL total problem score. Half of the children needed psychiatric interventions and parental stress was common.

Conclusion: Depression and behavioural problems were common in children with narcolepsy after the Pandemrix vaccination and their parents frequently reported feeling stressed.

Keywords: children, narcolepsy, physical symptoms, psychosocial symptoms, vaccination

Keynotes:

- This multicentre Finnish study assessed any psychosocial burdens in children diagnosed with narcolepsy after the Pandemrix vaccine during the H1N1 influenza pandemic in 2009-2010.
- We studied the medical records of 94 children who were aged 5-17 years at the time of their narcolepsy diagnosis and questionnaire data were collected for 73 of the subjects.
- Depression and behavioural problems were common in children with narcolepsy and half needed psychiatric interventions.

INTRODUCTION

From 2009-2010 Finland carried out a vaccination programme to protect its residents against the H1N1 influenza pandemic. The country used Pandemrix (GlaxoSmithKline, London, UK) and the coverage was 75% in children and adolescents.[1] All the doses of the vaccines that were delivered were recorded in electronic primary healthcare databases, which are linked to the Population Information System. The vaccines were given to children older than 6 months of age. The vaccine campaign was followed by a sudden outbreak of type 1 narcolepsy in children under 17 years of age and the incidence rate rose from 0.3 to 5.3 per 100,000 during 2010.[1-3] This included 54 cases of narcolepsy under the age of 17 years.[4] Earlier studies have suggested that the symptoms of this Pandemrix-related narcolepsy did not differ from cases before the vaccine was administrated.[5]

The main symptoms of type 1 narcolepsy are excess daytime sleepiness, attacks suddenly falling asleep without warning and cataplexy. Other common symptoms are weight gain leading to obesity, fragmented sleep, hypnagogic and hypnopompic hallucinations, nightmares, and sleep paralyses.[6] Narcolepsy may also induce precocious puberty.[7]

Narcolepsy can make children feel very ill.[8] Children diagnosed with type 1 narcolepsy after the Pandemrix vaccination had a high prevalence of psychosocial problems and decreased quality of life. Previous studies reported that these children show high rates of emotional problems, anxiety disorders and low self-esteem: 16-29% presented with depression, 14-29% with attention deficit hyperactivity disorder, and as many as 1.8% with schizophrenia.[8-13] These comorbidities strongly affected their quality of life. In addition, adaptive behaviour was often impaired and this had an impact on the relationships between children and their parents.[8-14] Younger children had more psychosocial problems, anxiousness, withdrawal, social problems, attention problems, somatic complaints, and aggressive behaviour than older children.[15-17] Attention problems, aggressive behaviour and attention deficit hyperactivity disorder were somewhat alleviated by time and by medication.[15]

Clinicians became very aware of the high frequency of psychiatric symptoms in children and adolescents affected by narcolepsy outbreak after the Pandemrix vaccination program. The aim of this study was to describe any psychosocial symptoms in children with type 1 narcolepsy, the impact

of narcolepsy into the family life and the factors that influenced the severity of the patients' symptoms.

MATERIALS AND METHODS

This multicentre study was conducted in four of the five University Hospital Districts in Finland. The Helsinki, Tampere, Oulu and Kuopio university hospital districts covered approximately 90% of the diagnosed paediatric narcolepsy cases after the Finnish Pandemrix vaccination campaign in Finland (Figure 1). The study was approved by the Ethics Committee of the Hospital for Children and Adolescents, which is part of Helsinki University Hospital.

Patients

The study was carried out in two parts (Figure 1). First, we reviewed the medical records of all 50 children diagnosed with type 1 narcolepsy in the Helsinki University Hospital District between January 2010 and June 2014 in Helsinki University Hospital District. We approached all the families and sent them questionnaires. Second, we widened the study to cover all type 1 narcolepsy patients in university hospital districts of Tampere, Oulu and Kuopio. We collected data on narcolepsy symptoms and the results from the neurological examinations that were performed on all the children when they visited a neurologist at the time of their diagnosis. Information about medication, growth, date and age at diagnosis and the findings of the Multiple Sleep Latency Test (MSLT) were collected from the medical records of the 94 patients.

The questionnaire study was conducted in 2013 and 2015, which was 3-5 years after the onset of narcolepsy. The narcolepsy diagnoses fulfilled the criteria of the International Classification of Sleep Disorders, version 2 or version 3. Diagnoses were confirmed by polysomnography and the MSLT. Cerebrospinal fluid orexin quantification was performed in 24 (25%) borderline or unclear cases. The children who did not present with cataplexy all had low cerebrospinal orexin levels. All the children were clinically examined and followed up by paediatric neurologists.

Questionnaires

The psychosocial symptoms and emotional, behaviour and social difficulties were assessed by a questionnaire survey. Parents filled in the Child Behaviour Checklist (CBCL) for all of the children. Parents also filled in a questionnaire on parental resources and stress together with a simple Likert scale measure from 1-7 that quantified the amount of stress they felt and their quality of life. Children who were at least 11 years of age filled in the Youth Self-Report (YSR) [19]and the Children´s Depression Inventory (CDI).

The CBCL and YSR are standardized questionnaires, which cover a broad range of problems including total, internalizing problems, such as anxiety, withdrawal, depressive and somatic symptoms and externalizing problems, such as rule-breaking and aggressive behaviour. Raw scores were projected onto a normal distribution and transformed into T-scores that represented standard deviations from the normal mean. T-scores of at least 63 (≥98th percentile) were considered as being in the clinical range, scores between 60- 63 (93rd - 98th percentile) were considered borderline and scores below 60 (<93rd percentile) were considered normal. The YSR and CBCL questionnaires also defined eight narrow band symptom domains, including withdrawn, somatic complaints, anxious or depressed, social problems, thought problems, attention problems, rule-breaking and aggressive behaviour.[18]

Depressive mood traits were assessed by using the Children´s Depression Inventory (CDI) questionnaire and the children were asked whether they had symptoms of depression during the last 2 weeks. The CDI has been reported to be reliable for assessing depressive symptoms, with a cut score of 13 more indicating depression.[19]

Parental quality of life was estimated using both a simple Likert scale measure from 1-7, where 1 stands for low quality and 7 for good quality of life (Figure 5) and a more complex questionnaire of on parental resources and stress. We used a Finnish adaptation of the Questionnaire on Resources and Stress for Families with Chronically Ill or Handicapped Members.[20] This questionnaire contains 35 yes or no statements about stressful factors in the family life.

Statistical analysis

Statistical analyses were performed using SPSS version 25 (IBM Corp, New York, USA). Nonparametric tests were used: the Wilcoxon Signed Rank test for paired comparisons and the Mann-Whitney test for unpaired group comparisons. A bivariate linear regression analysis was used to analyse correlations between factors and symptoms.

Instead of using the child´s body mass index (BMI), we used BMI-for-age which is more stable as the child grows.[21] BMI-for-age is calculated by using coefficients related to age to obtain numeric values that are equivalent to adult BMI. We had the length and weight values before the onset of narcolepsy and 1, 2 and 3 years after the onset of symptoms.

The socioeconomic status of the family was divided into four categories for analysis purposes. Class I included people with an academic degree, business managers, and professionals; class 2 included administrative personnel, owners of small businesses, and minor professionals. Class 3 included skilled manual employees and Class 4 included unskilled employees.

RESULTS

We approached 123 families whose child developed narcolepsy after receiving a Pandemrix vaccination and received permission to inspect the medical records of 94 children (Figures 1 and 2). The response rates to the main elements of the questionnaire survey were 59% (73/123) for the parental questionnaire, 51% (63/123) for the CDI and 52% (64/123) for the YSR. The medical record data and questionnaire results are presented in Figures 2-5, and the correlated results are in Table 1. We also present the MSLT results (Figure S1) and details of the socioeconomic distribution (Figure S2) and children's medication (Figure S3).

Medical records

The narcolepsy-related symptoms experienced by the children were: excessive daytime sleepiness (100%), cataplexy (91%), interrupted sleep (84%), nightmares (60%), hallucinations in 58% and sleep paralyses in 19% of included children (Figure 2).

The simple routine clinical neurological examination results were normal in all of the children we studied. Helsinki University Hospital carried out a more precise examination on 27 children using a modified version of the Touwen examination.[22]This revealed some minor aberrations: a minor tremor in nine children, cataplectic faces in four children and truncal hypotonia in 11 children. The diagnostic delay was shorter in younger children up to the age of 10 years than children children aged 10 years plus (R^2 0.14, $p < 0.001$).

At the time of questionnaire survey, 98% of children were on medication, 91% were using stimulants, 39% used antidepressant to treat cataplexy, 12% were on sodium oxybate and 39% were on more than one medication (Figure S3).

BMI

Weight gain started soon after the onset of narcolepsy, but was only significant during the first year (Figure 3). The median BMI-for-age changed from 21.7 kg/m^2 before the onset of narcolepsy to 24.0 kg/m^2 three years after the first symptoms. After the three-years follow-up 31/72 (43%) children were overweight with BMI-for-age scores of more than 25.

Questionnaires

The responses to the questionnaires indicated that psychiatric symptoms were common in the cohort (Figure 4). The CBCL total problems score exceeded the limit of clinical significance in 41% of the children. The internalizing problems score, which comprised anxious, withdrawal, depressive and somatic symptoms exceeded the limit in in 48% of cases. The respective figure was 27% for the externalizing problems score, which comprised rule-breaking and aggressive behaviour. When it came to the YSR questionnaire, 28% had total problems scores in the clinical range and it was 23% for the internalizing problems score (Figure 4). The median CDI value was 7 interquartile range (IQR) of 4-14 while 16 children (25%) scored 13 or more which suggested depression.

There were 70 responses to the Questionnaire on Resources and Stress for Families with Chronically Ill or Handicapped Members and the median value was 15 out of maximum of 35 points. In the Likert

where 1 stands for the lowest value and 7 for the highest values. The median score for the 69 parents who scored their quality of life on a (1-7) Likert scale was 4.8 (IQR 4 - 6) at the time of the questionnaire survey. The parents of children under 10 years of age reported a lower quality of life than the lower than the parents of children aged 10 years plus ($p = 0.046$). The median value for parental concerns in the beginning was 7 (IQR 6 - 7) and by the time of the study it had fallen to 5 (IQR 4-6). This indicated that parental concerns about the child's future, participation and behaviour was high at the beginning and declined over time. The median score for parental stress at the time of the study was 4 (IQR 3 – 5) while the median value for the wellbeing of the siblings was 4 (IQR 4 - 5) (Figure 5).

Correlations between factors and symptoms

We used the CDI and the CBCL total and internalizing problem scores as markers for psychosocial problems and compared them to the risk factors we had identified (Figure 4, Table 1). There was a positive correlation between BMI-for-age before the onset of narcolepsy and BMI-for-age three years after disease onset. The age at diagnosis correlated to the BMI-for-age at three years after onset of narcolepsy indicating that younger children gained more weight. The BMI-for-age three years after onset of narcolepsy correlated to CBCL internalizing and total problem scores. Children who had a higher BMI after three years of onset of narcolepsy had more psychosocial problems.

The child's age at the onset of symptoms and their age at diagnosis correlated to the CBCL internalizing and total problem scores. Younger children had more psychosocial problems. the MSLT scores correlated to CBCL total problem scores: the shorter the MSLT sleep latency the higher the CBCL total score. CBCL total and internalizing problems correlated to the quality of life and stress felt by the parents and to their siblings´ wellbeing.

The parental resources and stress questionnaire scores correlated to CBCL total problems score (R^2 0.52, $p = 0.00$) and the Likert scale scores for both quality of life (R^2 0.37, $p = 0.005$) and parental stress (R^2 0.36, $p = 0.013$).

DISCUSSION

The Pandemrix vaccination campaign during the 2009-2010 was followed by an abrupt outburst of type 1 narcolepsy in Finland, which lasted for approximately four years. We studied a large cohort of 94 children with narcolepsy type 1. The questionnaires indicated that, 25% of the children scored results suggesting depression. In addition 41% of children had psychosocial problems scores above the clinically significant limit and 48% had complaints scores for being anxiety, withdrawn or having somatic complaints that exceeded this limit. Despite medication and psychosocial support, half of the children needed psychiatric intervention. Narcolepsy increased family stress and decreased family quality of life. Parental stress alleviated over time. Children under 10 years of age gained more weight and had more psychosocial problems than children older than 10 years of age. The amount of weight gain correlated with psychosocial problems and internalizing problems, namely scores for being anxious, withdrawn, depressed and having somatic symptoms.

CDI, CBCL and quality of life test results

We found high rates of psychosocial symptoms in this cohort of children with narcolepsy. The findings were similar to the results of eight cohorts ranging from 6 to 117 children.[11,23]

When we used the recommended CDI cut-off of score 13, we found that 25% of children with narcolepsy had depressive symptoms at clinical range. The prevalence of depression ranged from 0.2 to 13%.[24] According to 2015 recommendations issued by the National Institute for Health and Care Excellence,[25] the prevalence for depression in children under the age of 13 years was 2.8% and it was 5.6% for children aged between 13 to 18 years. Finnish data for 2012 showed that the cumulative incidence of diagnosed depression by the age of 15 years was 2.9% for girls and 1.6% for boys.[26] In our cohort of children with narcolepsy, clinically significant level of CBCL total T-score values were observed 2.5 to 4 times more often than in a normal cohort (n = 470) of Finnish children in Helsinki, who took part in a study to assess sleep disturbances in children.[27]

The reason for the psychosocial symptoms seen in our study group is not known, but there could be a number of explanations. One potential explanation is sleep disturbance and daytime

hypersomnia. We know from previous studies that children with persistent sleep problems do have high levels of psychosocial, somatic and medical problems.[28] However, the children with narcolepsy were more likely to have high CBCL total scores (60%) and internalizing problems scores (56%) above the clinically significant level of 60 than Finnish children with other sleep disturbances (16% and 22%, respectively).[27]

One potential reason for high levels of psychosocial problems could be the disturbance of orexin regulation system by itself. Orexin is part of complex system, that comprises interactions between wake and sleep-promoting neuronal systems[6] but it is also linked to moods, anxiety, eating disorders and addiction.[28]

At the time of questionnaire survey, there was no disease-specific quality of life questionnaire available for children with narcolepsy. The validated questionnaires for children with chronic illnesses, and their parents, did not seem to be appropriate for this study. That is why we used a Finnish modification of the Questionnaire on Resources and Stress for Families with Chronically Ill or Handicapped Members. This fulfilled our requirements for an acceptable level of validity.[21] We found that the degrees of behavioural, emotional and adaptive challenges in the child were reflected in the parental and family quality of life in line with the earlier studies.[12]

Almost half of the parents scored the maximum Likert scale score of 7 soon after the onset of narcolepsy when asked about how concerned they were about their child. However, their concerns decreased significantly over time. Parents of children under 10 years of age were more concerned than parents of children aged 10 plus (Figure 5).

Age and weight

In this study cohort, children under 10 years of age were more likely to have more severe symptoms leading to shorter diagnostic delays than children over 10 years of age. The younger children gained weight faster and ended up with a heavier weight than the older children. This weight gain was also accompanied by more psychosocial problems.

The weight gain in our study correlated to young age and weight before the onset of the disease. Similar correlations have been reported by Inocente et al.[29] who stated that more than 50% of 117 children were obese, and that it affected younger children more often than teenagers. When we carried out the three-year follow up, 43% children were overweight, with BMI-for-age scores above 25 and 31% had scores above 30 that indicated obesity. As 2018 study by the Finnish Institute of Health and Welfare found that 29% of Finnish boys and 18-
21% of girls aged 7-16 years had BMI-for-age scores above 25. Scores above 30 were observed in 9-10% of boys and 3-5% of girls aged 7-16 years.[30]

On the other hand, young age and BMI-for-age after three years of onset of narcolepsy correlated to CBCL total and internalizing problems scores and thus to the level of social problems scores. This result echoed the finding of a study by Shelton et al.[16] They studied 25 children with narcolepsy and correlated young age to a higher frequency of emotional, behavioural and attention problems.

Strengths and limitations

The strength of this study was the large cohort of 94 children. At the time of study, many of the affected families showed negative attitude towards public authorities, including healthcare providers. It is likely that this negative attitude was reflected in the participation rate and the number of responses to the questionnaires. The medical records of the responders and non-responders in the Helsinki University Hospital District, was similar when we considered gender, the age at the time of diagnosis, mean sleep latency, as measured by the MSLT and the need for psychiatric treatment.

This study has also had some limitations including the fact that it was carried out when the children with narcolepsy were on medication. It is likely that their medications alleviated some of their symptoms and improved their condition. Therefore, the results may have underestimated the influence that untreated narcolepsy would have had on their symptoms. We did not have a matched control group or access to normative data about quality of life measures. We used normative data as

a reference for the questionnaire scores whenever available. The results were adjusted against the parents´ socioeconomical status but, not to other factors.

CONCLUSION

Children diagnosed with narcolepsy after the Pandemrix vaccination campaign presented with a highly variable symptoms ranging from mild to highly disabling. Depression and behavioural problems were common and half the children needed psychiatric intervention. Psychosocial problems led to high levels of parental concerns and stress and reduced the quality of life families.

ABBREVIATIONS

YSR, Youth Self Report

CDI, Children's Depression Inventory

CBCL, Child Behaviour Checklist

MSLT, Multiple Sleep Latency Test

BMI, body mass index

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CONFLICTS OF INTEREST: The authors have no conflicts of interest to declare.

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Table 1

Factors and linear correlations associated with severity of symptoms. Significant correlations are bolded.

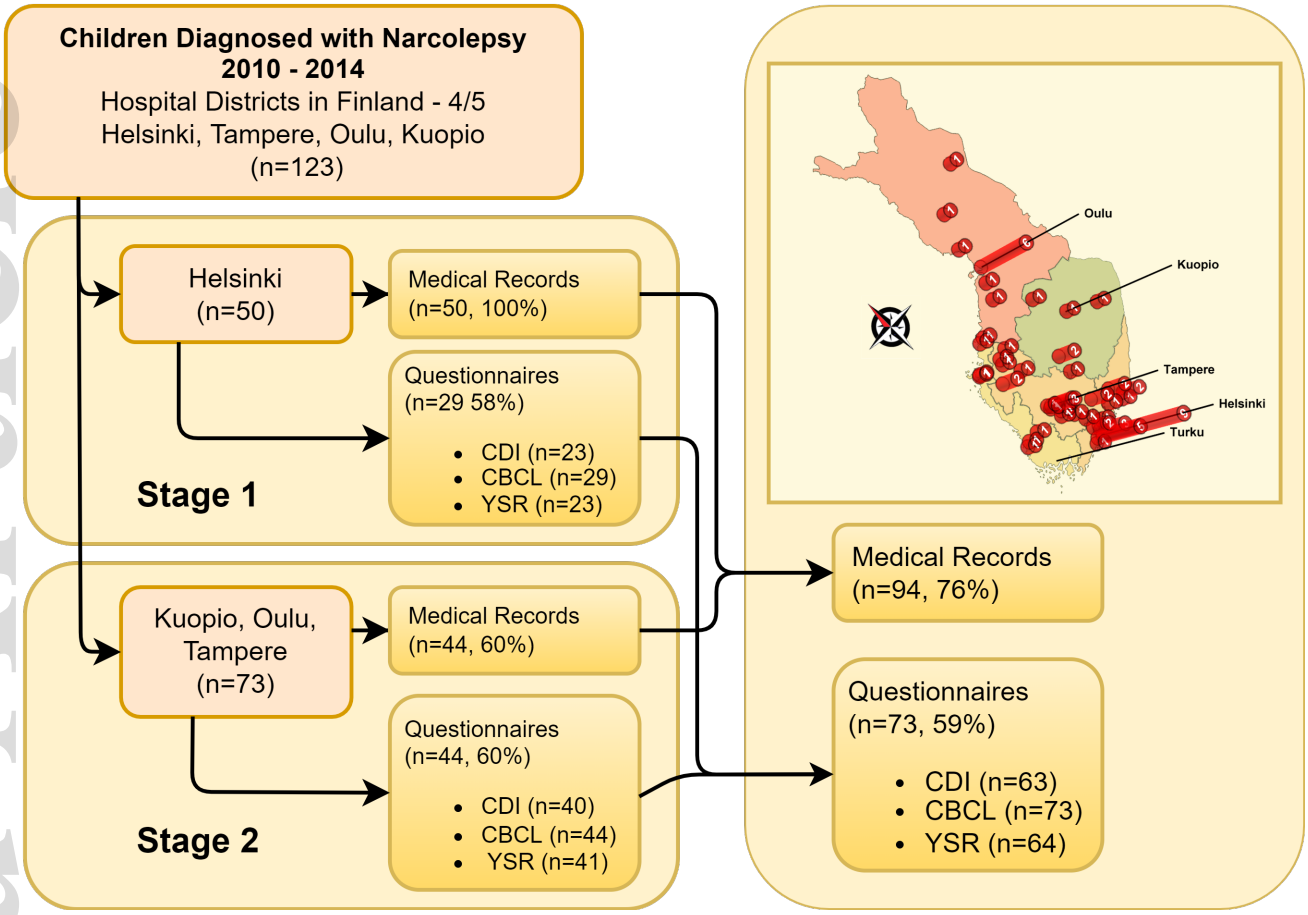
Symptom correlations		R^2	P
Symptoms in children with narcolepsy			
BMI-for-age at 3y[a]	BMI-for-age at onset	**0.64**	**< 0.001**
	Age at diagnosis	**0.06**	**0.04**
	Age at onset	0.04	0.09
Mean sleep latency	Internalizing problems [c]	0.04	0.10
Psychosocial problems[b]	BMI-for-age at 3y [a]	**0.09**	**0.03**
	Age at onset	**0.09**	**0.01**
	Age at diagnosis	**0.09**	**0.01**
	MSLT	**0.08**	**0.02**
Internalizing problems[c]	BMI -for-age at 3y [a]	**0.11**	**0.01**
	Age at onset	**0.09**	**0.01**
Depression (CDI)	BMI-for-age at 3y [a]	**0.09**	**0.04**
	Mean sleep latency	0.06	0.06
	Change in BMI	0.02	0.46
	Age at onset	0.00	0.73
	Age at diagnosis	0.00	0.58
Socioeconomic status	Psychosocial problems[b]	0.00	0.92
	Internalizing problems[c]	0.03	0.16
	CDI	0.01	0.54
Parental symptoms			
Parental QOL	Psychosocial problems [b]	**0.27**	**< 0.001**
	Internalizing problems [c]	**0.24**	**< 0.001**
	Depression (CDI)	**0.11**	**0.01**
Parental Stress	Psychosocial problems [b]	**0.26**	**< 0.001**
	Internalizing problems [c]	**0.08**	**0.02**
	CDI	**0.11**	**0.01**
	Age at diagnosis	0.01	0.43

	Age at onset	0.01	0.52
Symptoms in siblings			
Siblings well-being	Psychosocial problems [b]	**0.07**	**0.05**
QOL of siblings	Psychosocial problems [b]	0.01	0.45

[a] BMI-for-age 3 years after onset of narcolepsy.

[b] Psychosocial problems = CBCL total problem T-score.

[c] Internalizing problems = CBCL internalizing problems T-Score



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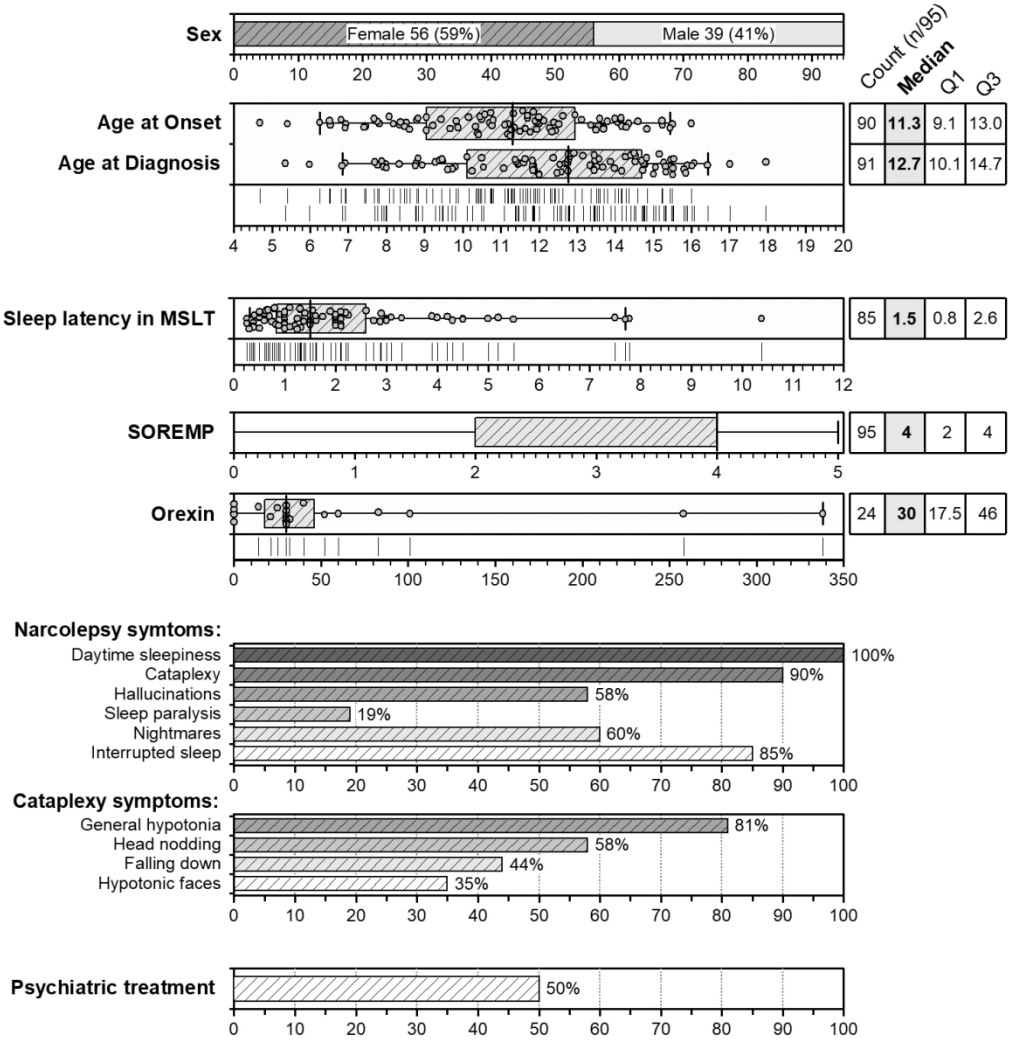

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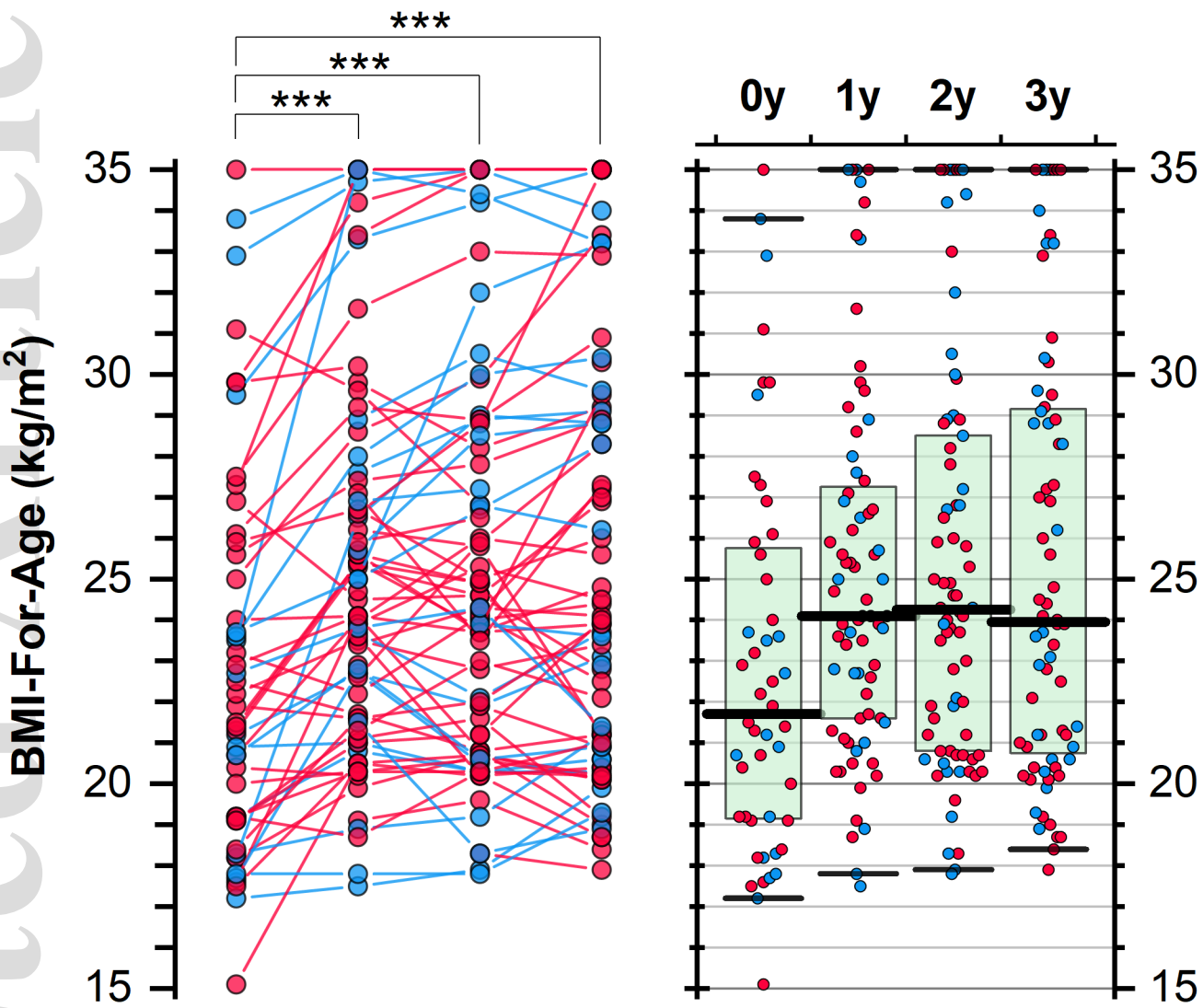
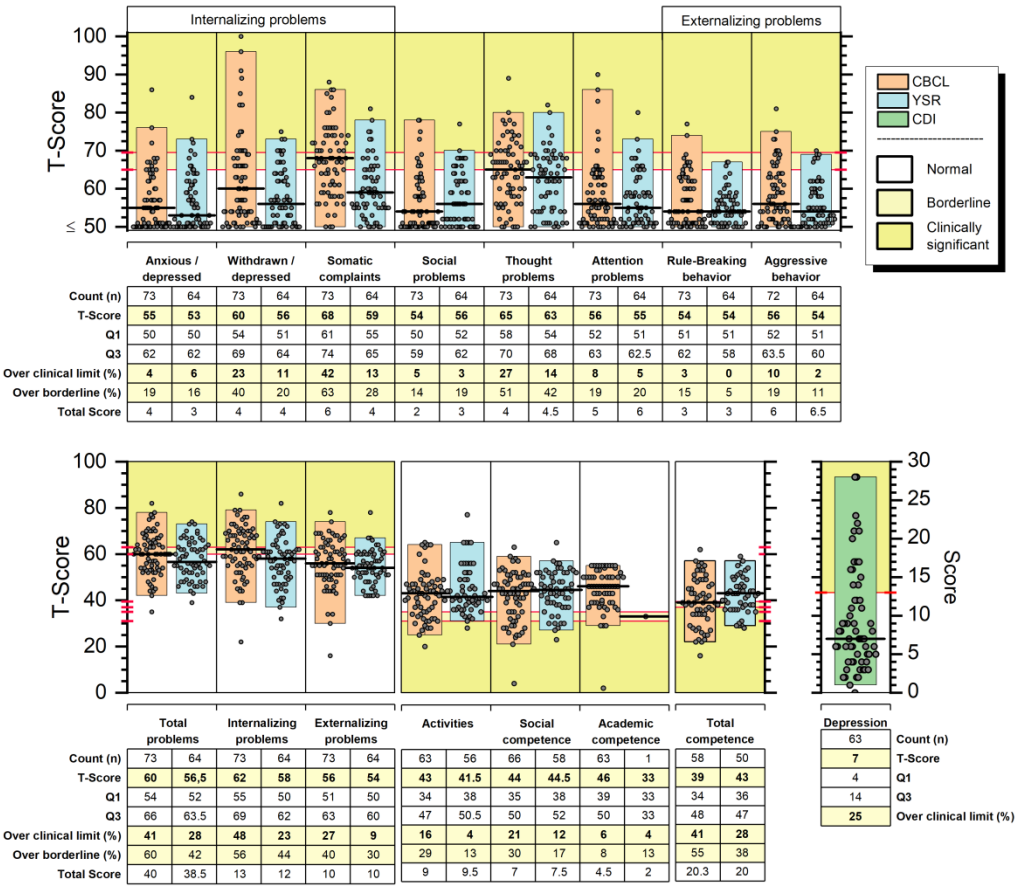


Time	0y	1y	2y	3y
Count	48	72	74	72
Median	21.7	24.1	24.3	24.0
Q1	19.2	21.6	20.8	20.8
Q3	25.8	27.3	28.5	29.2

apa_16233_f3.png

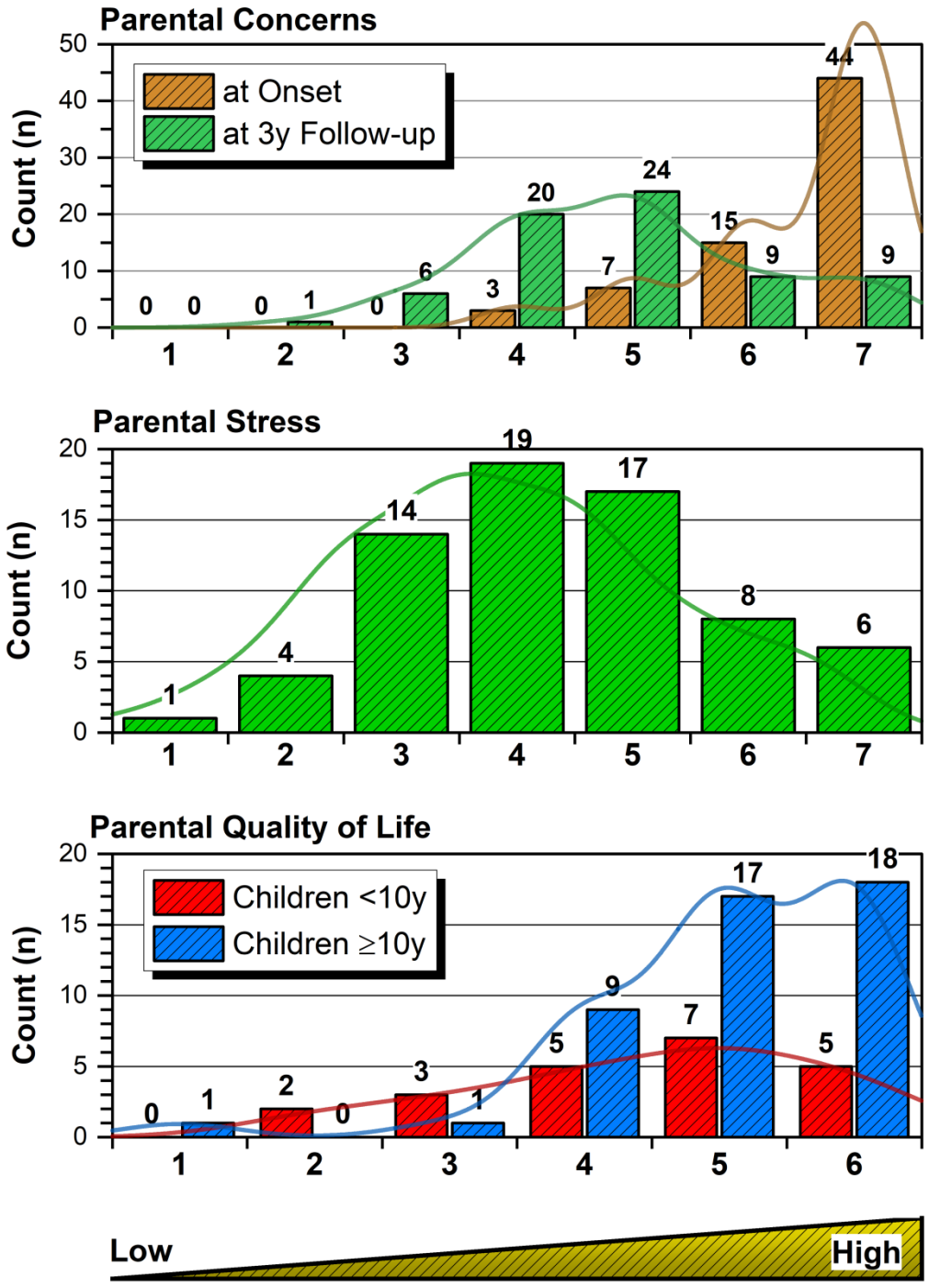


	Anxious / depressed		Withdrawn / depressed		Somatic complaints		Social problems		Thought problems		Attention problems		Rule-Breaking behavior		Aggressive behavior	
Count (n)	73	64	73	64	73	64	73	64	73	64	73	64	73	64	72	64
T-Score	**55**	**53**	**60**	**56**	**68**	**59**	**54**	**56**	**65**	**63**	**56**	**55**	**54**	**54**	**56**	**54**
Q1	50	50	54	51	61	55	50	52	58	54	52	51	51	51	52	51
Q3	62	62	69	64	74	65	59	62	70	68	63	62.5	62	58	63.5	60
Over clinical limit (%)	**4**	**6**	**23**	**11**	**42**	**13**	**5**	**3**	**27**	**14**	**8**	**5**	**3**	**0**	**10**	**2**
Over borderline (%)	19	16	40	20	63	28	14	19	51	42	19	20	15	5	19	11
Total Score	4	3	4	4	6	4	2	3	4	4.5	5	6	3	3	6	6.5

	Total problems		Internalizing problems		Externalizing problems		Activities		Social competence		Academic competence		Total competence	
Count (n)	73	64	73	64	73	64	63	56	66	58	63	1	58	50
T-Score	**60**	**56,5**	**62**	**58**	**56**	**54**	**43**	**41.5**	**44**	**44.5**	**46**	**33**	**39**	**43**
Q1	54	52	55	50	51	50	34	38	35	38	39	33	34	36
Q3	66	63.5	69	62	63	60	47	50.5	50	52	50	33	48	47
Over clinical limit (%)	**41**	**28**	**48**	**23**	**27**	**9**	**16**	**4**	**21**	**12**	**6**	**4**	**41**	**28**
Over borderline (%)	60	42	56	44	40	30	29	13	30	17	8	13	55	38
Total Score	40	38.5	13	12	10	10	9	9.5	7	7.5	4.5	2	20.3	20

Depression	
63	Count (n)
7	T-Score
4	Q1
14	Q3
25	Over clinical limit (%)

apa_16233_f4.png



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