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Comorbidities and quality of life in children with intellectual disability

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Statement of contributions:
Dinah Reddihough - conception and design of the work AND interpretation of data for the work AND drafting the work and revising it critically for important intellectual content.
Helen Leonard - conception and design of the work AND acquisition and interpretation of data for the work AND revising it critically for important intellectual content.
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Comorbidities and quality of life in children with intellectual disability

ABSTRACT (224 words)

Background: Many children with intellectual disability live with medical comorbidities. This study examined the impacts of comorbidities on quality of life (QOL) of children with intellectual disabilities and whether impacts varied with caregiver perceptions that medical needs had been met.

Methods: Primary caregivers of 447 children (aged 5-19 years) with an intellectual disability reported on their child's medical comorbidities and the extent to which they perceived their child's medical needs had been met in a cross-sectional observational study. The Quality of Life Inventory-Disability was used to measure QOL on a 100-point scale. Linear regression models including interaction terms were used to evaluate their associations.

Results: Parent-reported recurrent child pain (-4.97 95%CI -8.21, -1.72), night-time sleep disturbances (-4.98, 95%CI -7.23, -2.73), daytime somnolence (-8.71, 95%CI -11.30, -2.73), seizures that occurred at least weekly (-7.59, 95%CI -13.50,-1.68) and conservatively-managed severe scoliosis (-7.39, 95%CI -12.97, -1.81) were negatively associated with child

QOL. Despite the majority of parents (~70%) perceiving that their child's medical needs had been met to a great extent, this did not significantly moderate the association between any comorbidities and QOL.

Conclusions: Comorbidities were common and had marked associations with QOL. Evaluation and management of pain and sleep disturbance continue to be high priorities in improving QOL of young people with intellectual disabilities. Further research on the optimal methods of managing these comorbidities is warranted.

Keywords: Quality of life, comorbidity, intellectual disability, children, adolescents

Key messages

- Medical comorbidities, particularly pain and sleep disturbance, were associated with poorer quality of life in children with intellectual disability.
- Parent perception of excellent medical care had no influence on the impact of sleep disturbance or pain on the child's quality of life.

INTRODUCTION

Children with intellectual disability have difficulties in the conceptual, social and practical skills necessary for everyday living, and many also live with medical comorbidities (Oeseburg *et al.* 2011). Comorbidities associated with severe intellectual disability are well-recognised and may vary with the underlying cause of intellectual disability,(Colver *et al.* 2014, Leonard *et al.* 2017, Muskens *et al.* 2017, Roizen and Patterson 2003) each diagnosis conferring complex health care needs for many children. For example, about 45% of children with cerebral palsy have epilepsy (Reid *et al.* 2016, Reid *et al.* 2018) and all have some degree of motor impairment. Children with Down syndrome have lower rates of epilepsy (approximately 6%) (Smigielska-Kuzia *et al.* 2009) and whilst they have hypotonia, most walk independently (Foley and Killeen 2019). The average prevalence of epilepsy in the autism spectrum disorders is 30% (Viscidi *et al.* 2013) and whilst there may be hypotonia and gross motor delays, these are not universal and there is often improvement with age (Ming *et al.* 2007); and epilepsy is more frequent in Rett syndrome (50-90%) (Bao *et al.* 2013) with usually poorer gross motor skills with increasing age (Downs *et al.* 2016a) and if unable to walk, many are vulnerable to progressive spinal deformity (Downs *et al.* 2016b). Comorbidities such as sleep disturbance (Surtees *et al.* 2018) and mental health/behavioural problems (Buckley *et al.* 2020) are common regardless of the diagnosis associated with the underlying intellectual disability. These health conditions each have capacity to influence quality of life (QOL), but there is surprisingly little research on how these medical issues impact QOL in children with intellectual disability.

Comorbidities require ongoing medical surveillance and care to optimise health and wellbeing. Family-centred models of care and care coordination in children with special needs have been associated with high family satisfaction, and these models are also associated with less use of hospital services (Turchi *et al.* 2009). It is feasible that well-targeted, family-centred medical care could reduce the impacts of comorbidities on child QOL and be associated with parental perceptions that medical needs had been met. For this reason, we were interested to explore whether caregiver perceptions of excellent medical care could moderate any adverse impacts of comorbidities on QOL.

Using large available datasets describing children with an intellectual disability, this study aimed to evaluate the associations between physical and mental health comorbidities and child QOL. We also aimed to explore whether variation in parental perception that medical needs had been met influenced associations between comorbidities and QOL.

METHODS

A cross-sectional observational study design was used. Families were recruited if they had a child (aged 5-19 years and still at school) with confirmed intellectual disability and a diagnosis of either autism spectrum disorder (ASD), cerebral palsy, Down syndrome or Rett syndrome. Families were contacted through population-based registers available to the investigators and other data sources, including the Western Australian Autism Biological Registry (Taylor *et al.* 2013), the Western Australian Autism Register (Glasson 2002), the Victorian Cerebral Palsy Register (Reid *et al.* 2016), and the Australian Rett Syndrome

Database (Downs *et al.* 2016b). Caregivers of children with Down syndrome born from 1980 to 2004 who had previously participated in our research(Bourke *et al.* 2008) were invited to participate, and additional families were contacted through community organizations such as Developmental Disability WA, social media advertisements on the facebook page for Telethon Kids Institute and network sampling.

Ethics approval for this study was provided by Human Research Ethics Committees at The University of Western Australia (RA/4/20/4276) and the Child and Adolescent Health Services (RGS2390). Primary caregivers provided informed consent to participate in the study.

Procedure

Following recruitment, a parent-report questionnaire was administered using the Research Electronic Data Capture (REDCap) tool (Harris *et al.* 2009) or, if preferred, using a paper format or telephone interview. Paper questionnaire were posted to the respondent and returned to the research team by post. Trained psychologists (AE, NM) were available to complete some questionnaires during a telephone interview if needed with the primary caregiver.

Independent variables

The following data were collected as comorbidity variables: Parents observed their child's experiences of pain over the previous month as "not at all", "occasionally" or "recurrently".

The Sleep Disturbance Scale for Children (Bruni *et al.* 1996). comprising 26 items rated on a 5-point Likert scale, was used to describe sleep. As well as giving an overall score, the instrument derives five subdomains by summing the relevant items. For this study, only the "Disorders of Initiating and Maintaining Sleep" (DIMS) and the "Disorders of Excessive Somnolence" (DOES) subscales were used. Scores were compared with normative data reported in the initial validation paper,(Bruni *et al.* 1996) to calculate z-scores and then t-scores based on the normative DIMS or DOES dataset (Bruni *et al.* 1996). This scale was developed for typically developing children but some satisfactory validation data are available for children with neurodevelopmental disorders (Esbensen and Hoffman 2017, Marriner *et al.* 2017). A diagnosis of epilepsy was classified as "yes" or "no", and if yes, the frequency of seizures was described as "controlled", "fewer than once per month", "monthly" or "daily or weekly". Scoliosis was classified as "no scoliosis", "mild or moderate scoliosis", "severe scoliosis treated with surgery" or "severe scoliosis managed conservatively". Primary caregivers reported "yes" responses for the presence or treatment of constipation and gastroesophageal reflux to document gastrointestinal problems. As a proxy measure of respiratory health, primary caregivers reported the number of courses of antibiotics prescribed for respiratory infections in the previous 12 months with data coded as "none, "less than four" and "four or more". Primary caregivers reported all psychiatric diagnoses that the child had received and from whom (eg, physician) as well as their child's prescribed medications and the reason for use. From these data, children with mental health/behavioural problems were identified if the caregiver reported a physician-diagnosed mental health or

attention deficit and hyperactivity disorder, or their child had been prescribed a psychotropic medication.

A novel item was constructed to measure the primary caregiver's perception that the child's medical needs had been met overall during the previous 12 months. Responses were provided on a 7-point Likert scale and data were coded into a binary variable representing perceptions of needs being met to a "great extent" or a "moderately or less" extent.

Potentially confounding variables included diagnostic group, sex and age classified as 5 to 12 years or 13 to 19 years. Our choice of age cut point corresponds to an important transition between primary and secondary school.

Dependent variable

QOL was measured using the Quality of Life Inventory-Disability (QI-Disability), a 32-item parent-report measure based on extensive qualitative data(Davis *et al.* 2017, Epstein *et al.* 2016, Epstein *et al.* 2019a, Murphy *et al.* 2017) and developed for children with intellectual disability (Downs *et al.* 2019). The questionnaire comprises six domains: Social Interaction (7 items), Positive Emotions (4 items), Negative Emotions (7 items), Physical Health (4 items), Leisure and the Outdoors (5 items) and Independence (5 items). Parents are asked to rate their observations of their child's well-being and enjoyment of life over the past month for each item on a 5-point Likert scale. Item scores are linearly transformed to a scale of 0 to 100, with higher scores representing better QOL. Good internal consistency (Cronbach alpha

values 0.72-0.90), test-retest reliability and validity of QI-Disability has been demonstrated (Downs *et al.* 2019, Epstein *et al.* 2019b, Jacoby *et al.* 2020).

Statistical analysis

Multivariate linear regression models were used to examine associations between comorbidities and total and domain QOL scores, adjusting for confounding factors. The regression models were then extended to include interaction effects between whether medical needs were strongly met and the comorbidity variables. Significant interactions would indicate that the association between the comorbidity and QOL was different for children whose primary caregiver perceived that medical needs were strongly met compared to those with lesser satisfaction. The small amount of missing data was considered to be missing at random. Estimates and their confidence intervals were reported for each model and a p value smaller than 0.05 was considered statistically significant. Statistical analyses were performed using Stata 16.0 (StataCorp 2019).

RESULTS

Between March 2018 and October 2019, a questionnaire was completed by 447 of 585 invited parents/primary caregivers, including 133/162 (82.1%) with a child with ASD, 151/229 (65.9%) with a child with cerebral palsy, 90/98 (91.8%) with a child with Down syndrome and 74/96 (77.1%) with a child with Rett syndrome. Five (5.6%) children with Down syndrome and 10 (6.6%) with cerebral palsy had a co-occurring diagnosis of ASD; and 28 (21.0%) children with ASD and five (3.3%) with cerebral palsy had a co-occurring

diagnosis of attention deficit and hyperactivity disorder. Most (90.6%) respondents were biological mothers, 54.7% worked full- or part-time and 76.5% were dual parent families. The mean age of the children was 11.8 years (SD 3.9, range 5-19). Distributions for child functioning, comorbidity and QOL variables are presented in Table 1.

Associations between comorbidities and QI-Disability total scores

Compared to each reference category, abnormal DOES scores (-8.71, 95%CI -11.30, -6.11) and conservatively managed severe scoliosis (-7.39, 95%CI -12.97, -1.81) were associated with lower QOL scores. Surgically managed scoliosis (-5.17, 95%CI -9.42,-0.92), abnormal DIMS scores (-4.98, 95%CI -7.23, -2.73), recurrent pain (-4.97, 95%CI -8.21, -1.72), seizures that occurred at least weekly (-3.57, 95%CI -7.08, -0.06) and use of four or more courses of antibiotics for respiratory illness during the previous 12 months (-3.41 95%CI -7.25, 0.44 were associated with smaller reductions in scores. The presence of constipation, reflux and mental health/behavioural problems had small negative associations with child QOL that were not statistically significant (Table 2).

Associations between comorbidities and QI-Disability domain scores

Abnormal DIMS and DOES scores each had negative and significant associations with most of the QOL domain scores (Table 3). The presence of recurrent pain was associated with lower Physical Health (-5.74, 95%CI -10.12, -1.36) and Leisure and the Outdoors (-5.83, 95%CI -11.45, -0.22) domain scores and a very large reduction in the Negative Emotions (-12.04, 95%CI -17.17, -6.91) domain scores indicating more challenging behaviours (Table

3). Seizures that occurred more than weekly and severe scoliosis that was managed conservatively were each associated with reduced scores in the Physical Health and the Independence domains, with the severe scoliosis groups also having higher scores in the Negative Emotions domain (fewer challenging behaviours) (Table 3). The presence of mental health/behaviour problems was associated with lower Negative Emotions domain scores (-9.36, 95%CI -14.06, -4.66). Frequent antibiotic use was associated with lower Physical Health domain scores with the most frequent antibiotic use also associated with lower Leisure and the Outdoors domain scores. Otherwise, constipation and reflux were associated with small coefficient values which were non-significant (Table 3).

Moderating effects of satisfaction with medical care on QI-Disability total scores

More than 80% of children had four or more medical appointments over the previous 12 months, including 90% for cerebral palsy, 87.8% for Rett syndrome, 77.9% for ASD and 71.1% for Down syndrome. High levels of satisfaction that the child's medical needs had been greatly met reduced the negative association between mental health/behavioural problems (5.49, 95%CI -0.37, 11.36), frequent seizures (5.47, 95%CI -1.60, 12.55) and conservatively managed scoliosis (5.35, 95%CI -6.68, 17.38) and total QOL scores but these increases in scores did not quite reach statistical significance (Figure 1). The effects of recurrent pain and abnormal DIMS and DOES scores and frequent antibiotic use for respiratory illness persisted despite perceptions that medical care needs had been greatly met (Table 2).

DISCUSSION

In this study, the presence of recurrent pain, sleep abnormalities, frequent seizures and severe scoliosis were significantly associated with challenges to the child's QOL. Many children with intellectual disability are not able to self-report and, accordingly, observations are an important component of assessment of pain (Valkenburg *et al.* 2010). In this study, nearly one fifth of primary caregivers reported that their child had recurrent pain over the previous month, associated with lower total QOL scores and lower Negative Emotions domain scores, suggesting that pain has implications for the child's behaviours. Consistent with these findings, reports of pain by children (Dickinson *et al.* 2007) and adolescents (Rapp *et al.* 2017) with cerebral palsy have been associated with poorer scores in KIDSCREEN domain scores, a generic QOL measure (Ravens-Sieberer *et al.* 2007). There is some evidence that identification and active management of pain is not routinely undertaken for children with cerebral palsy (Fehlings 2017). The application of systematic pathways for early identification, investigation of cause and management of pain in intellectual disability more broadly could provide capacity for better child QOL, consistent with recent calls for stronger and more coordinated action to combat paediatric pain (Eccleston *et al.* 2020), an important need because high satisfaction with medical care did not reduce the negative effect of recurrent pain on QOL.

Almost half of the children had poor initiation and maintenance of sleep and nearly one quarter experienced excess diurnal sleepiness, as might be expected in this population (Surtees *et al.* 2018). Poor sleep is associated with poorer daytime behaviours, alertness and

energy levels and has marked impacts on children with intellectual disability and carers alike (Heussler 2016). It is not surprising that poor sleep was associated with reduced QOL for total and all of the domain scores. Behavioural and sleep hygiene strategies are the first line in therapy followed by pharmacological treatment (Heussler 2016, Spruyt and Curfs 2015). For example, prolonged-release melatonin is associated with improved sleep when behavioural strategies have not been effective (Gringras *et al.* 2017). Again, we observed that high satisfaction with medical care was not associated with attenuation of the impacts of poor night-time sleep on child QOL. We do not know if sleep problems were refractory despite evidence-based management, including the management of other comorbid conditions that influence sleep (Heussler 2016). Although sleep assessment is recommended at every paediatric consultation (Waters *et al.* 2013), it is also possible that care could have been perceived as good even though sleep was simply not addressed, as has been observed in paediatric care for attention deficit and hyperactivity disorder (Efron *et al.* 2016). Our findings underscore the consequences of poor sleep, the need for systematic clinical approaches and further research to resolve difficult sleep problems.

More children with cerebral palsy or Rett syndrome were unable to walk, inferring additional vulnerability for scoliosis and subsequent restrictive lung disease (Downs *et al.* 2016b, Persson-Bunke *et al.* 2012). Larger proportions of the children in these diagnostic groups also had frequent seizures and had been prescribed multiple courses of antibiotics for respiratory illnesses. Each of these comorbidities impacted upon the child's QOL. Gastroesophageal reflux was commonly reported for children with cerebral palsy while constipation was

distributed evenly across the diagnostic groups but with less impact on QOL, possibly because of availability of consensus management statements (Kahrilas *et al.* 2008, Locke *et al.* 2000) including specific guidelines for Rett syndrome (Baikie *et al.* 2014).

Child behavioural and emotional problems are associated with carer psychosocial stress that exhausts physical and mental resources over time (Gray *et al.* 2011). In the current study, mental health/behavioural problems, identified by the presence of a psychiatric diagnosis or medications for a psychiatric diagnosis, were observed in 40% of children with ASD and in 4.4-9.9% for the other diagnoses. There was no independent effect on Total QOL scores. Having a diagnosis or management could have afforded some protection to the child's QOL more generally, although challenging behaviours persisted as observed in the Negative Emotions subscale scores. Challenging behaviours were an expression of poor quality of life in the qualitative studies on which QI-Disability is based (Davis *et al.* 2017, Epstein *et al.* 2016, Epstein *et al.* 2019a, Murphy *et al.* 2017) and are included as items in the Negative Emotions subscale. As such, it would not be informative to evaluate challenging behaviours as an independent variable also. The evidence base for psychosocial interventions for mental health problems in intellectual disability is surprisingly poor, with most evidence focused on the preschool period (Kok *et al.* 2016). Medical care that was perceived to strongly meet the child's needs was associated with some improvement in QOL but this effect did not reach statistical significance.

Confidence intervals for the moderation effect of caregiver satisfaction were wide and mostly non-significant, due in part to small numbers in the more severe categories of some comorbidities but also suggesting that caregiver satisfaction with medical care had little relationship between the comorbidities and the child's QOL. We did not measure the ingredients of medical care and we do not know if problems were reduced when care was perceived as highly satisfactory. We do know that the majority of families across the diagnostic groups had multiple medical encounters for their child's medical needs over the previous 12 months indicating complex health needs. We recommend that further studies investigate how interventions and support based on child needs such as mental health, chronic pain and poor sleep, as well as other identified medical priorities such as respiratory infections, scoliosis and seizures, can influence the child's QOL. Further research on the characteristics of medical care for children with intellectual disability, including the ratio of primary and hospital service use, use of screening protocols and care coordination, might identify how to reduce the adverse effects of comorbidities on QOL in this complex group of children.

Strengths of our study include the opportunity to recruit from established population databases of children with ASD, cerebral palsy, Down syndrome and Rett syndrome, together representing a range of characteristics observed in intellectual disability. A comprehensive questionnaire was used to evaluate relationships between comorbidities, a select moderator variable and QOL, using a QOL measure validated for children with intellectual disability (Downs *et al.* 2019). There was a high completion rate for each of the four populations

studied. We acknowledge some limitations. The proportion of children with pain, scoliosis and epilepsy is likely higher in our group. This indicates important associations where they exist but that would be less relevant to other groups. With the relatively large number of participants, we believe that our results have applicability across the range of intellectual disability. We were reliant on proxy report for all the variables studied, which has particular relevance for issues such as pain which could be over- or under-estimated. We measured parent caregiver satisfaction with medical care using a single item rated on a seven-point Likert scale and this should be interpreted with caution because it is a novel item without supporting validity data. The moderating effects of medical care observed in this study may not be transferrable to other jurisdictions with different management systems for children with intellectual disability.

CONCLUSIONS

We recently reported that for children with intellectual disability, participation in the community is independently associated with QOL and that this represents one potential avenue for intervention (Williams *et al.* 2021). Building on this platform to understand the determinants of QOL for these children and using the same validated measure of QOL, we now report associations between comorbidities and QOL in this population of children. There were strong negative associations between recurrent pain, sleep dysfunction and QOL. Building on our cross-sectional study, further longitudinal research is warranted including how best to manage these problematic comorbidities to improve QOL.

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Table 1: Frequency distribution (%) of categorical and mean (SD) values for continuous variables describing the children in the study (n=447)

		All (n=447)	Autism spectrum disorder (n=132)	Cerebral palsy (n=151)	Down syndrome (n=90)	Rett syndrome (n=74)
		n (%)				
Age	5 to 12 years	230 (51.5)	76 (57.6)	65 (43.0)	52 (57.8)	37 (50.0)
	13 to 19 years	217 (48.6)	56 (42.2)	86 (57.0)	38 (42.2)	37 (50.0)
Sex	Female	223 (49.9)	35 (26.5)	60 (39.7)	54 (60.0)	74 (100)
Mobility	Able to walk fair distances (at least 500m)	134 (30.0)	91 (68.9)	12 (8.0)	31 (34.4)	0 (0.0)
	Walks independently but < 500m	160 (35.8)	39 (29.6)	41 (27.2)	58 (64.4)	22 (29.7)
	Needs assistance to walk	35 (7.8)	2 (1.5)	19 (12.6)	0 (0.0)	14 (18.9)
	Unable to walk	118 (26.4)	0 (0.0)	79 (52.3)	1 (1.1)	38 (51.4)
Verbal communication (n-446)	Speaks well and understood	46 (10.3)	25 (18.9)	13 (8.6)	6 (6.7)	2 (2.7)
	Some difficulty speaking such as lack of clarity	134 (30.0)	52 (39.3)	32 (21.2)	43 (47.8)	7 (9.6)
	Only understood by those who know him/her well	87 (19.5)	29 (22.0)	18 (11.9)	34 (37,8)	6 (8.2)
	Nonverbal communication	119 (26.7)	19 (14.4)	49 (32.5)	6 (6.7)	45 (61.6)
	Unable to communicate nonverbally	60 (13.5)	7 (5.3)	39 (25.8)	1 (1.1)	13 (17.8)
Epilepsy (n=441)	None	267 (60.5)	110 (83.3)	62 (41.1)	85 (94.4)	10 (14.7)
	Under control	45 (10.2)	6 (4.6)	25 (16.6)	4 (4.4)	11 (16.2)
	Less than once a week	66 (15.0)	9 (6.8)	35 (23.2)	1 (1.1)	22 (32.4)
	Daily or weekly	63 (14.3)	7 (5.3)	29 (19.2)	0 (0.0)	25 (36.8)
Scoliosis (n=439)	None	334 (76.1)	129 (97.7)	96 (63.6)	84 (94.4)	24 (36.4)
	Mild or moderate	50 (11.4)	2 (1.5)	23 (15.2)	4 (4.5)	21 (31.8)
	Severe scoliosis managed surgically	36 (8.2)	1 (0.8)	19 (12.6)	1 (1.1)	15 (22.7)
	Severe scoliosis managed conservatively	19 (4.3)	0 (0.0)	13 (8.6)	1 (0.0)	6 (9.1)
Observed pain (n=446)	Not observed	167 (37.4)	58 (43.9)	44 (29.3)	36 (40.0)	29 (39.2)
	Observed occasionally	202 (45.3)	63 (47.7)	69 (46.0)	46 (51.1)	24 (32.4)
	Observed recurrently	77 (17.3)	11 (8.3)	37 (24.7)	8 (8.9)	21 (28.4)

DIMS (n-440)	Abnormal	210 (47.7)	69 (52.7)	77 (52.7)	31 (34.8)	33 (44.6)
DOES (n=443)	Abnormal	103 (23.3)	24 (18.3)	36 (24.3)	15 (16.7)	28 (37.8)
Constipation	Yes	191 (42.7)	48 (36.4)	74 (49.0)	35 (38.9)	34 (46.0)
Reflux	Yes	86 (19.2)	11 (8.3)	54 (35.8)	9 (10.0)	12 (16.2)
Mental health/behavioural problems	Yes	77 (17.2)	54 (40.9)	15 (9.9)	4 (4.4)	4 (5.4)
Courses of antibiotics over the past 12 months (n=445)	None	240 (53.9)	87 (65.9)	63 (41.7)	52 (57.8)	38 (52.8)
	1-3	162 (36.4)	41 (31.1)	62 (41.1)	34 (37.8)	25 (34.7)
	>=4	43 (9.7)	4 (3.0)	26 (17.2)	4 (4.4)	9 (12.5)
Number of consultations with general practitioners or specialists over past 12 months (n=445)	0	11 (2.5)	9 (6.9)	1 (0.7)	1 (1.1)	0 (0)
	1-3	68 (15.3)	20 (15.3)	14 (9.3)	25 (27.8)	9 (12.2)
	>=4	366 (82.2)	102 (77.9)	135 (90.0)	64 (71.1)	65 (87.8)
Perceived extent to which medical needs were met (n=425)	To a great extent	282 (68.3)	82 (66.1)	99 (66.9)	60 (71.4)	41 (71.9)
	To a moderate or lesser extent	136 (32.0)	42 (34.2)	49 (33.1)	25 (29.4)	20 (29.0)
		Mean (SD)				
Quality of life	Total score	69.2 (12.7)	68.3 (10.9)	66.6 (13.5)	77.5 (11.7)	66.4 (11.2)
	Physical Health	69.9 (16.7)	74.5 (15.6)	67.2 (16.6)	71.7 (16.5)	65.5 (17.0)
	Positive Emotions	77.2 (17.8)	73.8 (16.3)	75.2 (19.2)	86.7 (14.6)	75.6 (17.1)
	Negative Emotions	65.4 (18.7)	57.7 (18.4)	67.6 (19.8)	70.9 (16.4)	67.8 (15.6)
	Social Interaction	70.6 (19.0)	61.3 (17.6)	70.9 (20.1)	80.1 (15.9)	74.7 (15.1)
	Variety of Activities	70.5 (20.1)	72.4 (18.6)	64.5 (21.2)	78.2 (17.4)	69.9 (20.1)
	Independence	61.8 (24.0)	69.9 (16.3)	54.2 (26.0)	77.8 (17.6)	44.4 (20.0)

DIMS: Disorders of Initiating and Maintaining Sleep

DOES: Disorders of Excessive Somnolence

Mental health/behavioural problems: 35 children diagnosed or taking medications for ADHD; 28 children diagnosed or taking medications for anxiety; 9 children diagnosed with or taking medications for both anxiety and ADHD; two children with depression; and two children with anxiety and obsessive compulsive disorder. one child diagnosed or taking medications for anxiety and depression

Table 2: Base multivariate model of association between comorbidity variables and the quality of life total score, and multivariate models including interactions between each independent variable by level of the moderator variables

		Base multivariate model (main effects)		**Moderation by level of satisfaction**	
		Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Pain	No	Ref		Ref	
	Occasional	-0.51 [-2.78,1.76]	0.659	-3.16 [-7.29,0.98]	0.134
	Recurrent	-4.97 [-8.21,-1.72]	0.003	-3.62[-9.66,2.43]	0.240
Pain*Level of satisfaction	No pain			Ref	
	Occasional* High satisfaction			3.96 [-1.02,8.95]	0.119
	Recurrent* High satisfaction			-1.50 [-8.73,5.72]	0.682
Sleep - DIMS	Normal	Ref		Ref	
	Abnormal	-4.98 [-7.23,-2.73]	<0.001	-4.18 [-8.23,-0.12]	0.044
DIMS*Level of satisfaction	Abnormal* High satisfaction			-0.97 [-5.92,3.99]	0.701
Sleep - DOES	Normal	Ref		Ref	
	Abnormal	-8.71 [-11.30,-6.11]	<0.001	-10.92 [-15.25,-6.59]	<0.001
DOES*Level of satisfaction	Abnormal* High satisfaction			3.51 [-1.93,8.94]	0.205
Seizures	None	Ref		Ref	
	Controlled	-0.47 [-4.25,3.30]	0.806	-0.51 [-8.37,7.34]	0.898
	<Weekly	-0.25 [-3.64,3.15]	0.886	-2.19 [-8.50,4.11]	0.494
	>=Weekly	-3.57 [-7.08,-0.06]	0.046	-7.59 [-13.50,-1.68]	0.012
Seizures* Level of satisfaction	No seizures			Ref	
	Controlled* High satisfaction			-0.51 [-8.37,7.34]	0.898
	<Weekly* High satisfaction			2.30 [-5.06,9.65]	0.540
	>=Weekly* High satisfaction			5.47 [-1.60,12.55]	0.129
Scoliosis	None	Ref		Ref	
	Mild/moderate	-3.77 [-7.37,-0.16]	0.041	-1.01 [-8.17,6.15]	0.781
	Severe - surgery	-5.17 [-9.42,-0.92]	0.017	-5.47 [-12.52,1.57]	0.127
	Severe - No surgery	-7.39 [-12.97,-1.81]	0.010	-10.52 [-20.58,-0.47]	0.040
Scoliosis* Level of	Mild/mod* High			-2.80 [-11.06,5.46]	0.505

satisfaction	satisfaction				
	Severe with surgery* High satisfaction			0.74 [-8.00,9.48]	0.867
	Severe with no surgery* High satisfaction			5.35 [-6.68,17.38]	0.383
Constipation	No	Ref		Ref	
	Yes	1.15 [-0.94,3.24]	0.281	2.94 [-1.08,6.96]	0.151
Constipation* Level of satisfaction	Yes* High satisfaction			-2.97 [-7.77,1.84]	0.226
Reflux	No	Ref		Ref	
	Yes	1.27 [-1.65,4.20]	0.392	2.33 [-2.88,7.54]	0.380
Reflux*Level of satisfaction	Yes* High satisfaction			-1.57 [-7.82,4.67]	0.620
Mental health/behavioural problems	No	Ref		Ref	
	Yes	-1.40 [-4.38,1.58]	0.356	-5.14 [-9.95,-0.34]	0.036
Mental health/behavioural problems * Level of satisfaction	Yes* High satisfaction			5.49 [-0.37,11.36]	0.066
Antibiotics (respiratory in last year)	Never	Ref		Ref	
	<4	-1.55 [-3.77,0.67]	0.171	-0.38 [-4.53,3.76]	0.855
	>=4	-3.41 [-7.25,0.44]	0.082	-3.01 [-9.38,3.37]	0.354
Antibiotics* Level of satisfaction	<4*High level			-1.17 [-6.14,3.80]	0.644
	>=4* High satisfaction			-0.30 [-8.29,7.69]	0.941
Level of satisfaction	Low			Ref	
	High			0.71 [-4.16,5.58]	0.774
Sex	Male	Ref		Ref	
	Female	0.21[-2.14,2.56]	0.862	-0.19 [-2.59,2.21]	0.876
Age group	Primary	Ref		Ref	
	Secondary	-0.64 [-2.72,1.44]	0.544	-1.39 [-3.55,0.76]	0.205
Diagnostic group	Autism spectrum disorder	Ref		Ref	
	Cerebral palsy	1.96 [-1.04,4.96]	0.200	2.15 [-0.95,5.25]	0.173
	Down syndrome	7.43 [4.30,10.55]	<0.001	7.76 [4.54,10.99]	<0.001
	Rett syndrome	2.93 [-1.39,7.26]	0.183	3.32 [-1.27,7.92]	0.156

* denotes testing for an interaction between the two named variables
DIMS: Disorders of Initiating and Maintaining Sleep
DOES: Disorders of Excessive Somnolence

Table 3: Multivariate relationships between the comorbidity variables and each of the quality of life domain scores, taking into account the effects of confounding variables*

		Physical Health	Positive Emotions	Negative Emotions	Social Interaction	Leisure	Independence
Pain	No	Ref	Ref	Ref	Ref	Ref	Ref
	Occasional	-0.15 (-3.20, 2.90) 0.924	-0.71 (-4.22, 2.80) 0.691	-6.46 -10.05, -2.88) <0.001	1.40 (-2.31, 5.11) 0.459	1.40 (-2.51, 5.32) 0.482	2.06 (-2.08, 6.20) 0.328
	Recurrent	-5.74 (-10.12, -1.36) 0.010	-3.97 (-9.00, 1.07) 0.122	-12.04 (-17.17, -6.91) <0.001	-2.24 (-7.57, 3.07) 0.407	-5.83 (-11.45, -0.22) 0.042	0.79 (-5.16, 6.73) 0.795
Sleep - DIMS	Normal	Ref	Ref	Ref	Ref	Ref	Ref
	Abnormal	-8.46 (-11.48, -5.44) <0.001	-3.09 (-6.57, 0.38) 0.080	-6.06 (-9.60, -2.51) 0.001	-4.24 (-7.91, -0.57) 0.024	-2.27 (-6.14, 1.60) 0.249	-5.43 (-9.54, -1.33) 0.010
Sleep - DOES	Normal	Ref	Ref	Ref	Ref	Ref	Ref
	Abnormal	-8.77 (-12.25, -5.29) <0.001	-10.81 (-14.81, -6.81) <0.001	-6.07 (-10.16, -1.98) 0.004	-8.16 (-12.39, -3.93) <0.001	-11.43 (-15.91, -6.95) <0.001	-6.34 (-11.06, -1.62) 0.009
Seizures	None	Ref	Ref	Ref	Ref	Ref	Ref
	Controlled	-0.12 (-5.18, 4.95) 0.964	3.47 9-2.36, 9.30) 0.243	1.02 (-4.92, 6.96) 0.735	1.49 (-4.67. 7.66) 0.634	-2.28 (-8.78, 4.22) 0.491	-5.69 (-12.61, 1.23) 0.107
	<Weekly	-0.73 (-5.30, 3.84)	1.61 (-3.64, 6.86)	-0.76 (-6.13, 4.62)	3.37 (-2.18, 8.93)	-2.00 (-7.86, 3.85)	-3.32 (-9.51, 2.87)

		0.754	0.548	0.782	0.233	0.502	0.292
	>=Weekly	-5.67 (-10.42, -0.92) 0.019	-2.00 (-7.46, 3.46) 0.471	1.60 (-3.96, 7.16) 0.572	-2.62 (-8.39, 3.15) 0.373	-2.57 (-8.65, 3,52) 0.407	-10.40 (-16.83, -3.98) 0.002
Scoliosis	None	Ref	Ref	Ref	Ref	Ref	Ref
	Mild/moderate	-3.32 (-8.20, 1.55) 0.180	-2.66 (-8.27, 2.94) 0.350	0.62 (-5.10, 6.34) 0.832	-2.42 (-8.34, 3.51) 0.423	-5.90 (-12.15, 0.347) -12.15	-9.45 (-16.05, -2.85) 0.005
	Severe - surgery	-2.86 (-8.59, 2.87) 0.327	-2.50 (-9.09, 4.09) 0.457	8.82 (2.09, 15.55) 0.01	-6.43 (-13.40, 0.54) 0.070	-10.09 (-17,44, -2.74) 17.44	-18.99 (-26.76, -11.22) <0.001
	Severe – No surgery	-11.23 (-18.63, -3.85) 0.003	-1.51 (-10.01, 6.98) 0.726	9.48 (0.82, 18.15) 0.032	-2.95 (-11.93, 6.03) 0.519	-8.80 (-18.28, 0.67) 0.068	-27.43 (-37.64, -17.22) <0.001
Constipation	No	Ref	Ref	Ref	Ref	Ref	Ref
	Yes	-0.60 (-3.40, 2.20) 0.675	2.99 (-0.23, 6.22) 0.068	-1.39 (-4.68, 1.91) 0.409	3.78 (0.37, 7.19) 0.030	3.96 (0.36, 7.56) 0.031	-2.01 (-5.82, 1.79) 0.299
Reflux	No	Ref	Ref	Ref	Ref	Ref	Ref
	Yes	0.15 (-3.80, 4.09) 0.942	2.54 (-1.99, 7.08) 0.270	4.44 (-0.17, 9.07) 0.059	1.96 (-2.83, 6.76) 0.421	0.83 (-4.22, 5.89) 0.746	-2.1o (-7.45, 3.15) 0.441
Mental health/behavioural problem	No	Ref	Ref	Ref	Ref	Ref	Ref
	Yes	1.30 (-2.68, 5.29) 0.52	-2.67 (-7.25, 1.91) 0.253	-9.36 (-14.06, -4.66) <0.001	-2.93 (-7.78, 1.91) 0.234	4.51 (-0.61, 9.64) 0.084	1.51 (-3.88, 6.91) 0.582

Antibiotics for respiratory causes in previous 12 months)	Never	Ref	Ref	Ref	Ref	Ref	Ref
	<4	-4.68 (-7.67, -1.69) 0.002	1.07 (-2.37, 4.50) 0.542	-1.12 (-4.69, 2.34) 0.511	-1.96 (-5.96, 1.67) 0.289	-0.36 (-4.19, 3.48) 0.855	-1.72 (-5.77, 2.33) 0.404
	>=4	-6.97 (-12.16, -1.77) 0.009	0.42 (-5.67, 6.39) 0.892	-2.86 (-8.95, 3.23) 0.356	-4.74 (-11.06, 1.58) 0.141	-7.78 (-14.45, -1.11) 0.022	1.40 (-5.64, 8.44) 0.696
Sex	Male	Ref	Ref	Ref	Ref	Ref	Ref
	Female	0.79 (-2.36, 3.94) 0.624	-0.60 (-4.22, 3.02) 0.747	0.29 (-3.40, 3.98) 0.878	-0.32 (-4.15, 3.50) 0.868	1.94 (-2.12, 6.00) 0.348	-0.44 (-4.72, 3.83) 0.838
Age group	Primary	Ref	Ref	Ref	Ref	Ref	Ref
	Secondary	0.49 (-2.31, 3.29) 0.730	-2.61 (-5.83, 0.61) 0.112	2.61 (-0.68, 5.90) 0.120	-1.81 (-5.22, 1.59) 0.296	-4.61 (-8.21, -1.02) 0.012	2.84 (-0.96, 6.63) 0.142
Diagnostic group	Autism spectrum disorder	Ref	Ref	Ref	Ref	Ref	Ref
	Cerebral palsy	-1.66 (-5.70, 2.38) 0.419	1.75 (-2.90, 6.39) 0.460	5.88 (1.14, 10.62) 0.015	10.95 (6.03, 15.86) <0.001	-0.07 (-5.25, 5.11) 0.979	-5.13 (-10.62, 0.36) 0.067
	Down syndrome	-4.33 (-8.54, -0.14) 0.043	11.15 (6.32, 15.98) <0.001	8.87 (3.94, 13.81) <0.001	17.18 (12.08, 22.29) <0.001	5.52 (0.13, 10.92) 0.45	6.81 (1.10, 12.51) 0.019
	Rett syndrome	-2.65 (-8.43, 3.13) 0.369	2.93 (-3.72, 9.58) 0.387	4.79 (-2.03, 11.61) 0.168	16.64 (9.61, 23.67) <0.001	6.82 (-0.60, 14.24) 0.072	

* confounding variables include sex, age group and diagnostic group

DIMS: Disorders of Initiating and Maintaining Sleep
DOES: Disorders of Excessive Somnolence

Figure 1 - Adjusted mean QID total scores for comorbidity levels stratified by degree of satisfaction with medical care. Error bars denote 95% confidence intervals