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Relationship between parent-reported gastrointestinal symptoms, sleep problems, autism spectrum disorder symptoms, and behavior problems in children and adolescents with 22q11.2 deletion syndrome

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ABSTRACT

Background: 22q11.2 deletion syndrome (22q) is a chromosome disorder, where a segment of chromosome 22, located at q11.2, is missing. This study aims to investigate the relationship between a number of parent-reported comorbid conditions including gastrointestinal symptoms, sleep problems, autism spectrum disorder (ASD) symptoms and behavior problems in children and adolescents with 22q deletion syndrome.

Method: The Gastrointestinal Symptom Inventory, Children's Sleep Habits Questionnaire, Behavior Problem Inventory-Short Form and the Social Communication Questionnaire were completed by parents of 149 children and adolescents aged 3–18 years with a diagnosis of 22q.

Results: A series of correlations and hierarchical multiple regressions were conducted to examine the relationships between GI symptoms, sleep problems and behavior problems in children and adolescents with 22q deletion syndrome. A significant moderate relationship was found between GI symptoms and sleep problems. Gender and ASD symptoms predicted GI symptoms. Significant small relationships were found between GI symptoms and self-injurious behavior. Significant small to moderate relationships were found between sleep problems and self-injurious behavior, aggressive/destructive behavior, and sterotyped behavior. Sleep problems predicted challenging behavior.

Conclusions: This research demonstrated the importance of studying the relationship between comorbidities, including gastrointestinal symptoms, sleep problems, and behavior problems and how they shape the phenotype of 22q deletion syndrome.

What this paper adds?

The current study investigates the relationship between a number of parent-reported comorbid conditions including gastrointestinal symptoms, sleep problems, autism spectrum disorder (ASD) symptoms and behavior problems in 149 children and adolescents

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with 22q.11.2 Deletion Syndrome (22q). 22q is a rare, genetic condition. A significant moderate association was found between GI symptoms and sleep problems. Further analysis revealed that higher rates of GI symptoms and sleep problems significantly predicted each other. This study found a significant small relationship between GI symptoms and behavior problems, in particular the frequency and severity of self-injurious behavior (SIB). Significant moderate relationships were found between sleep problems and behavior problems indicating that higher rates of sleep problems in the sample were related to more behavior problems such as the frequency and severity of SIB, the frequency and severity of aggressive/destructive behavior, as well as the frequency of stereotyped behavior. Sleep problems predicted the frequency of SIB, aggressive/destructive behavior and stereotyped behavior. This study adds to the literature by providing data on the relationship between these comorbid conditions, such as (1) GI symptoms and sleep problems, (2) GI symptoms and self-injurious behavior, and (3) sleep problems and SIB, aggressive/destructive behavior and stereotyped behavior. It also provides evidence of the predictors of comorbid conditions in 22q deletion syndrome, including the predictive relationship between GI symptoms and sleep problems, as well as sleep problems being a predictor of behavior problems.

1. Introduction

1.1. 22q11.2 Deletion syndrome

22q11.2 deletion syndrome (22q) is a complex chromosome disorder caused by a deletion in the chromosome region q11.2. The estimated prevalence rates for 22q vary between 1 in every 2000/4000 live births (Fung et al., 2015; Grati et al., 2015; Mcdonald-Mcginn et al., 2001), although it is hard to determine exact prevalence rates, as not every child born is screened. It is likely that only the more severely affected children and a small portion of the adults with 22q are diagnosed (Habel, McGinn, Zackai, Unanue, & McDonald-McGinn, 2012).

The syndrome presents phenotypic variability, which at first led it to be misidentified as several different syndromes such as DiGeorge, velocardiofacial syndromes, and conotruncal anomaly face (Kirkpatrick & DiGeorge, 1968; Shprintzen et al., 1978). Following numerous investigations of the genetic basis for these syndromes it was discovered that they were all caused by the same chromosome deletion (Carey et al., 1992). The syndrome is now known to have a wide variety of symptoms ranging from mild to severe that includes multiple congenital and neurodevelopmental anomalies. Common facial features include hooded/swollen eyelids, tubular nose, broad nose tip, small mouth, hypertelorism and mild ear abnormalities (Oskarsdóttir, Holmberg, Fasth, & Strömland, 2008).

Other common manifestations include heart defects, palate abnormalities, endocrine, autoimmune and gastrointestinal symptoms, as well as cognitive delays and psychiatric comorbidities such as attention deficit hyperactivity disorder (AD/HD), autism spectrum disorder (ASD), anxiety disorder, major depressive disorder, and obsessive-compulsive disorders (Habel et al., 2012; McDonald-McGinn et al., 1999; Schneider et al., 2014). Given advances in paediatric care and treatment over the past decade, research suggests that there is a 90–95 % survival rate beyond infancy, with most individuals surviving into adulthood (Bassett et al., 2011; Fung et al., 2015; McDonald-McGinn & Sullivan, 2011).

1.2. 22q11.2 Deletion syndrome and comorbidity

Comorbidity is the presence of two or more disorders in the same individual at the same time (Matson & Nebel-Schwalm, 2007). With a comorbid disorder, the symptoms of the second diagnosis must differ from the symptoms of the primary diagnosis (Matson & Nebel-Schwalm, 2007). Assessing and treating comorbidities can be difficult, and symptoms of disorders can overlap. Comorbidities can result in a more complex diagnosis and treatment, leading to higher levels of stress and burden to caregivers (Lecavalier, Leone, & Wiltz, 2006). Having a greater understanding of the relationships between comorbidities in 22q could help clinicians with diagnosing, assessing and treating core symptoms.

ASD is characterized by persistent impairments in social interaction and communication, in conjunction with restrictive or repetitive patterns of behavior or interests (American Psychiatric Association, 2013). Prevalence rates of ASD comorbid with 22q have been reported in 14–58 % of individuals (Fiksinski et al., 2017; Schneider et al., 2014). ASD has been shown to co-occur with many different disorders, including behavior problems, gastrointestinal symptoms, AD/HD, anxiety, toileting problems, epilepsy, and sleep problems (Leader & Mannion, 2016b; Devlin, Healy, Leader, & Reed, 2008; Francis, Mannion, & Leader, 2017; Leader & Mannion, 2016a; Mannion & Leader, 2014a; Mannion & Leader, 2014b, 2014c; Williams, Leader, Mannion, & Chen, 2015). Research has identified comorbidities in other rare genetic conditions such as Fragile X Syndrome (Newman, Leader, Chen, & Mannion, 2015). Due to the overlap between ASD and 22q, it can be hypothesized that comorbid conditions common in ASD may also be common in 22q.

Research has shown that gastrointestinal symptoms (Campbell et al., 2018; Cancrini et al., 2014; Giardino et al., 2014; Kotcher et al., 2019), sleep problems (Kennedy et al., 2014; Moulding et al., 2019), and behavior problems (Briegel, Schneider, & Schwab, 2008; Golding-Kushner, Weller, & Shprintzen, 1985; Klaassen et al., 2013) are commonly comorbid with 22q.

1.3. 22q11.2 Deletion syndrome and gastrointestinal symptoms

Gastrointestinal (GI) disorders are disorders that involve issues with the oesophagus, stomach, the intestines, the rectum and organs associated with digestion; symptoms could include constipation, nausea, diarrhea, or abdominal pain (Talley, Weaver, Zinsmeister, & Melton III, 1992). GI disorders are over three times more likely to occur in children with a developmental delay than in typically developing children (Chaidez, Hansen, & Hertz-Picciotto, 2014). Kotcher et al. (2019) investigated GI symptoms in individuals with

22q and found that chronic GI symptoms were prevalent across all age groups, indicating its lifelong prevalence in individuals with 22q.

GI congenital abnormalities are often reported in patients with 22q deletion syndrome. These include esophageal atresia, jejunal atresia, umbilical hernia, diaphragmatic herniation, intestinal malrotation, congenital megacolon, and anorectal malformations (atresia, anterior displacement) (Giardino et al., 2014). Giardino et al. (2014) found that 58 % of 22q patients have GI dysfunction, and found abdominal pain to be most common, occurring in 34 % of individuals. Common GI symptoms included vomiting (30 %), chronic constipation (26 %), gastroesophageal reflux disease (23 %), and feeding disorders (15 %). Campbell et al. (2018) reviewed the medical records of 1,421 patients with molecularly confirmed 22q deletion syndrome from 1992 to 2018 and identified that 65 % presented with GI abnormalities. Chronic constipation was the most commonly reported GI abnormality with 35 % of patients affected (Campbell et al., 2018). Cancrini et al. (2014) found 41 % of patients with 22q had a history of GI problems, highlighting its prevalence in 22q.

1.4. 22q11.2 Deletion syndrome and sleep problems

Some of the most common sleep disorders include insomnia, sleep apnea, restless legs syndrome and narcolepsy. Symptoms include trouble falling to sleep, night waking, nights terrors, or wetting the bed (Zuckerman, Stevenson, & Bailey, 1987). Comparison studies have found that children and adolescents with 22q have a higher prevalence of sleep problems at 60 % compared to 23 % of sibling controls (Moulding et al., 2019). Previous research has identified sleep-related breathing disorders such as obstructive sleep apnea as a common comorbidity as a result of the airway obstruction caused by craniofacial dysmorphia of the syndrome (Crockett, Goudy, Chinnadurai, & Wootten, 2014; Heike et al., 2007; Kennedy et al., 2014). Sleep apnea has been reported in 10 % of children and adolescents with 22q, compared to only 2–4 % of typically developing controls (Kennedy et al., 2014). Common sleep problems reported in children with 22q include restless sleep and insomnia, affecting 43 % and 30 % of patients, respectively (Moulding et al., 2019). Restless sleep in 22q has been linked to increased anxiety, AD/HD symptoms and impaired cognitive function which commonly occur with the syndrome, while insomnia in 22q has been associated with anxiety and conduct disorder symptoms (Moulding et al., 2019).

1.5. 22q11.2 Deletion syndrome and behavior problems

Behavior problems are described as “culturally abnormal behavior(s) of such intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy, or behavior which is likely to seriously limit use of, or result in the person being denied access to, ordinary community facilities” (Emerson, 1995, p.44). Children and adolescents with 22q have been known to have an increased risk of behavioral and emotional challenges (Briegel et al., 2008; Jansen et al., 2007; Niklasson, Rasmussen, Óskarsdóttir, & Gillberg, 2009). Briegel et al. (2008) found 60 % of participants with 22q met the criteria for at least one form of challenging behavior based on the Child Behavior Checklist (Achenbach, 1991), while 34 % presented with social problems, 30 % had internalising problems, 23 % had attention problems and 23 % engaged in externalising behavior.

1.6. Current study

This study aimed to investigate the possible relationships that exist between parent-reported comorbid conditions and how they shape the phenotype of 22q deletion syndrome. The comorbid conditions that were examined were GI symptoms, sleep problems, behavior problems and ASD symptoms. This study examined the predictors of GI symptoms, sleep problems, and behavior problems in children and adolescents with 22q deletion syndrome.

2. Method

2.1. Participants

The study sample comprised of 149 children and adolescents with an independent diagnosis of 22q11.2 Deletion Syndrome. Most participants received a formal diagnosis from a doctor ($n = 121$, 81.2 %) or a geneticist ($n = 19$, 12.8 %), while 6% ($n = 9$) received diagnosis from other sources. The mean age of the sample was 9 years ($SD = 4.75$), with a range from 3 to 18 years. Of the participants, 50.3 % ($n = 75$) were male and 49.7 % ($n = 74$) of participants were female. A total of 72.5 % ($n = 108$) of participants presented with an intellectual disability (ID). In the total sample, 45 % presented with a mild ID ($n = 67$), 23.5 % with moderate ID ($n = 35$), and 4% with severe ID ($n = 6$). Most participants were from the United States of America (USA; $n = 81$, 54.4 %), while 9.4 % ($n = 14$) were from the United Kingdom (UK), 10.7 % ($n = 16$) were from Australia, 8.1 % ($n = 12$) were from Ireland and 17.5 % ($n = 26$) were from other countries.

2.2. Informants and procedure

Informants were parents or guardians of children and adolescents diagnosed with 22q deletion syndrome. Parents competed the rating scales independently according to the instructions printed on top of the questionnaires. Parents and guardians were recruited through social media, 22q deletion syndrome worldwide organizations, online forums, and parenting support groups. If parents wished

to participate in the study, they were provided with a participant information sheet and a consent form to complete. Once consent was obtained, the informants were provided with the battery of the above questionnaires to complete in their own time. Every questionnaire was completed by all informants.

2.3. Measures

2.3.1. Demographic information

A questionnaire devised by the authors and completed by each parent acting as an informant provided information on participants' age, gender, and resident country. Information was also provided on age and source of diagnosis, current educational intervention, current comorbid diagnosis, and presence of ID, AD/HD, anxiety disorders, and any other medical or psychological disorders. The presence of early GI symptoms such as constipation, diarrhea, abdominal pain or nausea was assessed. Parents were asked to indicate what, if any, medication their child was taking and what condition the medication was used to treat.

2.3.2. Gastrointestinal Symptom Inventory

The Gastrointestinal Symptom Inventory (GSI; Autism Treatment Network, 2005) is a 35-item questionnaire developed by the Autism Treatment Network. The GSI consists of 35 questions, however, there are additional items dependent on each participant's symptomology, and therefore consists of 77 items in total. This measure includes questions about the presence, duration, and nature of various GI symptoms over the past three months. The inventory is scored dichotomously (i.e. whether or not the child has any GI symptoms). Although to date the inventory has not been validated, it has been used in published research as a measure for GI symptoms (Mannion & Leader, 2016; Leader, Francis, Mannion, & Chen, 2018; Leader, Tuohy, Chen, Mannion, & Gilroy, 2020; Mannion & Leader, 2013; Mazefsky, Schreiber, Olino, & Minshew, 2014; Mazurek et al., 2013; Williams, Christofi, Clemmons, Rosenberg, & Fuchs, 2012; Williams et al., 2012b).

2.3.3. Children's Sleep Habits Questionnaire (CSHQ)

The CSHQ (Owens, Spirito, & McGuinn, 2000) is a 52-item parental-report questionnaire used to screen for children's' sleep habits. The child's sleep habits are divided into eight different sub-scales: bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety, night-waking, parasomnias, sleep disordered breathing, and daytime sleepiness. This scale asks respondents to report the frequency with which their child has engaged in certain sleep-related behaviors over the last typical week. A total CSHQ score of 41 has been reported to be a sensitive clinical cut-off for identification of probable sleep problems (Owens et al., 2000). The CSHQ has demonstrated good internal consistency, ranging from 0.68 to .78, and good test-retest reliability between .62 and .79 (Shahid, Wilkinson, Marcu, & Shapiro, 2012).

2.3.4. Social Communication Questionnaire (SCQ)

The SCQ (Rutter, Le Couteur, & Lord, 2003) is a 40-item parent-report questionnaire used to evaluate communication skills and social functioning in children who may have ASD. Each item requires a dichotomous yes/no answer and each scored item receives a value of 1 point for abnormal behavior and 0 points for absence of abnormal behavior/normal behavior. Total scores can range from 0 to 39 and a total SCQ raw score of $\geq$15 is highly suggestive of the presence of ASD symptoms. The SCQ demonstrates varying degrees of specificity in the differentiation between ASD and non-ASD cases (0.58–0.88), and so is used to assist clinicians in diagnosis, but is not appropriate as a sole diagnostic tool (Allen, Silove, Williams, & Hutchins, 2007; Chandler et al., 2007). It has shown high convergent validity (70 %) with the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Bailey et al., 2003) and high factor-based reliability, based on the Social-Communication, and Stereotyped Behaviors and Unusual Interest scales (83 %–96 % respectively, measured on a sample of children with Down Syndrome; Magyar, Pandolfi, & Dill, 2012).

2.3.5. Behavior Problems Inventory-Short Form (BPI-S)

The BPI-S (Rojahn, Matson, Lott, Esbensen, & Smalls, 2001) is a shortened version of the BPI-01, an assessment instrument developed to measure frequency and severity of challenging behaviors. It consists of a 30-item questionnaire and is made up of three behavior subscales: Self-Injurious Behavior (SIB; 8items), Aggressive/Destructive Behavior (10 items), and Stereotyped Behavior (12 items). Each item is rated by frequency (0 = never, to 4 = hourly) and severity (0 = no problem, to 3 = severe problem) using a Likert-Scale. Previous studies have confirmed the validity and reliability of the BPI-S in assessing maladaptive behaviors (Rojahn et al., 2012a, 2012b). Cronbach's α ranges from 0.68 to 0.92 for the subscales within the BPI-S (Rojahn et al., 2012a).

3. Results

3.1. Analyses

A series of Pearson's correlations were conducted to examine the relationship between GI symptoms (as measured by total GSI scores), sleep problems (as measured by total CSHQ scores), ASD symptoms (as measured by total SCQ scores) and behavior problems (as measured by total subscale scores of the BPI-S; SIB frequency and severity, aggressive/destructive behavior frequency and severity and stereotyped behavior frequency) in children and adolescents with 22q. A series of hierarchical multiple regression analyses were conducted in order to determine the predictors of GI symptoms, sleep problems and behavior problems while controlling for age, gender and ASD symptoms.

3.2. Descriptive statistics

3.2.1. Demographic information

As shown in Table 1, AD/HD was the most common psychological disorder ($n = 31$, 20.8 %). Within the sample of 3–6 year olds, 5% ($n = 3$) had AD/HD. Within the 7–12 year olds, 33.3 % ($n = 19$) had AD/HD and 28.1 % ($n = 9$) aged 13–18 years had a diagnosis of AD/HD. The most common educational intervention received was 'Other' interventions ($n = 34$, 22.8 %). These included home schooling, one-to-one tutoring, special education, physical therapy, social skills training, educational aide, modified school curriculum, social thinking, early childhood intervention, case management, 504 learning plan, psychopedagogical intervention, small group instruction, and special needs classes. These interventions were received by 26.7 % ($n = 16$) aged 3–6 years, 21.1 % ($n = 12$) aged 7–12 years and 18.8 % ($n = 6$) aged 13–18 years.

Medication usage was most commonly used to treat GI symptoms ($n = 44$, 29.5 %). Thirty-five percent of 3–6 year olds received medication to treat GI symptoms, 22.8 % ($n = 13$) aged 7–12 years received medication to treat GI symptoms and 31.3 % ($n = 10$) aged 13–18 years.

3.2.2. Sleep problems, behavior problems, ASD symptoms and GI symptoms

The mean total score on the CSHQ was 52.14 ($SD = 9.18$). Sleep problems were present in 91.3 % ($n = 136$) of the sample, whereby a sleep problem was classified if a child obtained a score of 41 or more on the CSHQ. As can be seen in Table 2, daytime sleepiness ($M = 14.94$, $SD = 3.06$) was the highest reported sleep problem total score in 3–6 years ($M = 14.48$, $SD = 3.04$), 7–12 years ($M = 14.93$, $SD = 3.11$) and in 13–18 years ($M = 15.84$, $SD = 2.89$)

Ninety one percent ($n = 135$) of children and adolescents with 22q presented with a score of 15 or more on the SCQ, indicating the presence of ASD symptoms. Social interaction ($M = 10.17$, $SD = 3.73$) was the highest reported subscale in 3–6 years ($M = 10.90$, $SD = 3.71$), 7–12 years ($M = 15.84$, $SD = 2.89$) and in 13–18 years ($M = 9.63$, $SD = 3.85$) (See Table 2). The presence of aggressive/destructive behavior was reported as the highest with 91.9 % ($n = 137$), followed by stereotyped behavior ($n = 121$, 81.2 %) and SIB ($n = 99$, 66.4 %). Stereotyped behavior was the most common reported behavior problem ($M = 7.09$, $SD = 6.94$), in 3–6 years ($M = 6.30$, $SD = 5.99$), 7–12 years ($M = 7.75$, $SD = 8.10$) and in 13–18 years ($M = 7.41$, $SD = 6.39$). It was found that 88 % ($n = 131$) of participants presented with GI symptoms with constipation being the most common ($n = 98$, 65.8 %). Constipation was the most common symptom among 3–6 years ($n = 41$, 68.3 %). Abdominal pain was the most common symptom among 7–12 years ($n = 41$, 71.9 %), while constipation and abdominal pain were both the most prevalent symptom among 13–18 years ($n = 22$, 68.8 %) (See Table 2). Correlations between behavior problems and GI symptoms and sleep problems are presented in Table 3.

Table 1
Percentages and frequencies of comorbid psychological disorders, type of interventions currently received and medication usage of participants in the total sample and across age groups within the sample.

	Total ($N = 149$)		Toddler/Preschool 3–6 Years ($n = 60$)		School-Aged Children 7–12 Years ($n = 57$)		Adolescents 13–18 Years ($n = 32$)	
	n	%	*n*	%	*n*	%	*n*	%
Psychological Disorder								
Generalized Anxiety Disorder	19	12.8	3	5.0	11	19.3	5	15.6
Social anxiety	4	2.7	1	1.7	1	1.8	2	6.3
Separation anxiety	4	2.7	1	1.7	3	5.3	0	0
Obsessive Compulsive Disorder	3	2.0	0	0	1	1.8	2	6.3
AD/HD	31	20.8	3	5.0	19	33.3	9	28.1
Other	17 [a]	11.4	4	6.7	3	5.3	10	31.3
Educational Intervention								
Applied Behaviour Analysis	13	8.7	6	10.0	6	10.5	1	3.1
Eclectic	26	17.5	11	18.3	6	10.5	9	28.1
Individualised Education Plan	27	18.1	6	10.0	13	22.8	8	25.0
Speech Therapy	18	12.1	10	16.7	7	12.3	1	3.1
Mainstream School	31	20.8	11	18.3	13	22.8	7	21.9
Other	34 [b]	22.8	16	26.7	12	21.1	6	18.8
Medication								
Treatment for GI Symptoms	44	29.5	21	35.0	13	22.8	10	31.3
Treatment for Sleep Problems	20	13.4	4	6.7	11	19.3	5	15.6
Treatment for Thyroid Problems	19	12.8	6	10.0	4	7.0	9	28.1
Treatment for Heart Problems	11	7.4	4	6.7	1	1.8	6	18.8
Treatment for Psychological Disorders	23	15.4	1	1.7	12	21.1	10	31.3

[a] Includes post traumatic stress disorder, selective mutism, depression, and unspecified anxiety disorder.
[b] Includes home schooling, one-to-one tutoring, special education, physical therapy, social skills training, educational aide, modified school curriculum, social thinking, early childhood intervention, case management, 504 learning plan, psychopedagogical intervention, small group instruction, and special needs classes.

Table 2
Means and Standard Deviations for Study Measures.

Scale	Total ($N = 149$)		Toddler/Preschool 3–6 Years ($n = 60$)		School-Aged Children 7–12 Years ($n = 57$)		Adolescents 13–18 Years ($n = 32$)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
CSHQ								
Bedtime Resistance	9.48	3.58	10.00	3.56	10.08	3.84	7.44	2.26
Sleep Onset Delay	1.72	0.77	1.60	0.76	1.72	0.77	1.97	0.74
Sleep Duration	5.02	2.00	5.05	2.11	4.98	1.94	5.06	2.00
Sleep Anxiety	6.91	2.27	6.75	2.17	7.77	2.30	5.72	1.82
Night Waking	5.20	1.80	5.68	1.64	4.82	1.85	5.00	1.88
Parasomnias	11.06	2.59	11.53	2.65	10.93	2.64	10.40	2.30
Sleep Disordered Breathing	4.38	1.55	4.33	1.45	4.19	3.11	4.84	1.99
Daytime Sleepiness	14.94	3.06	14.48	3.04	14.93	3.11	15.84	2.89
SCQ								
Social Interaction	10.17	3.73	10.90	3.71	7.90	3.62	9.63	3.85
Communication	8.14	2.89	7.92	3.04	7.98	2.94	8.84	2.44
Repetitive/Stereotypic Behavior	3.11	2.32	2.93	2.14	3.21	2.42	3.28	2.50
BPI-S								
SIB Frequency	2.59	2.88	2.58	3.02	2.53	2.82	2.72	2.82
SIB severity	1.72	1.98	1.60	1.83	1.77	2.15	1.88	1.98
Aggressive/destructive behavior frequency	4.60	5.60	4.70	5.15	5.75	6.64	2.28	3.44
Aggressive/destructive behavior severity	3.23	4.21	3.00	3.04	4.21	5.30	1.94	3.60
Stereotyped behavior frequency	7.09	6.94	6.30	5.99	7.75	8.10	7.41	6.39
	n	%	*n*	%	*n*	%	*n*	%
Presence of early GI symptoms								
Constipation	63	42.3	24	40.0	26	45.6	13	40.6
Abdominal Pain	34	22.8	12	20.0	13	22.8	9	28.1
Bloating	28	18.8	10	16.7	13	22.8	5	15.6
Nausea	15	10.1	5	8.3	5	8.8	5	15.6
Diarrhea	13	8.7	4	6.7	7	12.3	2	6.3
Other	21	14.1	6	10.0	11	19.3	4	12.5
Gastrointestinal Symptom Inventory								
Constipation	98	65.8	41	68.3	35	61.4	22	68.8
Abdominal Pain	97	65.1	34	56.7	41	71.9	22	68.8
Bloating	63	42.3	24	40.0	24	42.1	15	46.9
Nausea	55	36.9	15	25.0	21	36.8	19	59.4
Diarrhea	55	36.9	23	38.3	20	35.1	12	37.5
Other	25	16.8	10	16.7	9	15.8	6	18.8

3.3. Gastrointestinal symptoms

A hierarchical multiple regression was conducted to examine if these variables predicted GI symptoms. Age, gender and ASD symptoms were entered in the first block. Sleep problems, as measured by total CSHQ scores, was entered in the second block. Behavior problems, as measured by the BPI-S subscale scores (SIB frequency, SIB severity, aggressive/destructive behavior frequency, aggressive/destructive behavior severity and stereotyped behavior frequency) was entered into the third block. GI symptoms, as measured by total GSI scores was the criterion variable.

Step one, including age, gender and ASD symptoms significantly contributed to the model ($F_{(3,145)} = 7.14$, $p = .001$, $R^2 = .13$; *Adj* $R^2 = .11$), explaining 11 % of the variance for total GI symptoms. The only significant predictors in this model were gender ($p < .001$) and ASD symptoms ($p = .03$). In Step two, total sleep problems significantly contributed to the model ($F_{(4,144)} = 13.11$, $p = .001$, $R^2 = .27$; *Adj* $R^2 = .25$), explaining an additional 14 % of the variance. At Step three, the model including the BPI-S subscales; SIB frequency, SIB severity, aggressive/destructive behavior frequency, aggressive/destructive behavior severity and stereotyped behavior frequency significantly contributed to the model ($F_{(9,139)} = 7.36$, $p = .001$, $R^2 = .32$; *Adj* $R^2 = .28$), explaining 28 %. The addition of the BPI-S subscales to the model did not significantly predict total GI symptoms (See Table 4).

Table 3
Pearson's correlations between BPI-S subscale scores and GSI total scores, CSHQ total scores and SCQ total scores.

	SIB Frequency	SIB Severity	Aggressive/destructive behavior Frequency	Aggressive/destructive behavior Severity	Stereotyped Behavior Frequency
Total GSI	.19*	.18*	−.09	−.07	.10
Total CSHQ	.38**	.39**	.24**	.22**	.24**
Total SCQ	−.01	−.03	.07	.03	−.05

* $p < .05$.
** $p < .001$.

3.4. Sleep problems

A hierarchical multiple regression was conducted to analyse the predictive relationship between behavior problems and sleep problems. Age, gender and ASD symptoms were entered in the first block. GI symptoms were entered into the second block. Behavior problems were entered into the third block. Sleep problems was the criterion variable. At Step one, the model including age, gender, and ASD symptoms did not predict sleep problems ($F_{(3,145)} = .04$, $p = .990$, $R^2 = .00$; $Adj\ R^2 = -.02$). At Step two, with the addition of total GI symptoms, the model was statistically significantly ($F_{(4,144)} = 6.83$, $p = .001$, $R^2 = .16$; $Adj\ R^2 = .14$), explaining an additional 12 % of the variance. At Step three, the model including the BPI-S subscales significantly contributed to the model ($F_{(9,139)} = 6.02$, $p = .001$, $R^2 = .28$, $Adj\ R^2 = .23$), explaining 23 % of the variance. The addition of the BPI-S subscales to the model did not significantly predict total sleep problems (See Table 5).

3.4.1. Sleep problems and gastrointestinal symptoms

Of the sample, 81.9 % ($n = 122$) had both comorbid GI symptoms and a comorbid sleep problem. There was a significant relationship between total GI symptoms and sleep problems ($r = .37$, $p < .001$).

3.5. Behavior problems

A series of hierarchical multiple regressions were conducted to examine if sleep problems and GI symptoms predicted the frequency of SIB, aggressive/destructive behavior and stereotyped behavior, while controlling for age, gender, and ASD symptoms.

3.5.1. Predictors of SIB frequency

At Step one, the model including age, gender and ASD symptoms, as measured by total scores on the SCQ was not significant in predicting SIB frequency ($F_{(3,145)} = 1.60$, $p = .19$, $R^2 = .03$ $Adj\ R^2 = .01$). Total GI symptoms were entered in Step two and the model became statistically significant ($F_{(4,144)} = 3.85$, $p = .005$, $R^2 = .10$, $Adj\ R^2 = .07$). The addition of total GI symptoms as a predictor explained an additional 5.9 % of the variance. At Step three, total sleep problems significantly contributed to the model ($F_{(5,143)} = 6.49$, $p = .001$, $R^2 = .19$, $Adj\ R^2 = .16$), explaining an additional 9% of the variance. As can be seen in Table 6, gender ($p = .01$) and total CSHQ score ($p = .001$) were significant predictors in Step three. The entire model explained 16 % of the variance in the frequency of SIB.

3.5.2. Predictors of aggressive/destructive behavior frequency

At Step one, the model including age, gender and ASD symptoms, as measured by total scores on the SCQ, did not predict the frequency of aggressive/destructive behavior ($F_{(3,145)} = 1.21$, $p = .308$, $R^2 = .02$ $Adj\ R^2 = .00$). The addition of total GI symptoms as measured by the GSI was not significant ($F_{(4,144)} = 1.10$, $p = .360$, $R^2 = .03$ $Adj\ R^2 = .00$). Total sleep problems were entered in Step three ($F_{(5,143)} = 3.63$, $p = .004$, $R^2 = .11$ $Adj\ R^2 = .08$), explaining 8% of the variance. The significant predictors in step three were total GI symptoms ($p = .02$) and total sleep problems ($p = .001$), whereby higher levels of each predicted higher frequencies of aggressive/destructive behavior.

3.5.3. Predictors of stereotyped behavior frequency

At Step one, the model including age, gender and ASD symptoms, as measured by total scores on the SCQ did not predict the frequency of stereotyped behavior ($F_{(3,145)} = 1.06$, $p = .37$, $R^2 = .02$ $Adj\ R^2 = .00$). The addition of total GI symptoms as measured by the GSI was not significant ($F_{(4,144)} = 1.54$, $p = .20$, $R^2 = .04$ $Adj\ R^2 = .01$). Total sleep problems were entered in Step three ($F_{(5,143)} = 2.54$, $p = .03$, $R^2 = .08$ $Adj\ R^2 = .05$), explaining 5% of the variance. Total sleep problems was the only significant contributor to the variance explained ($p = .01$).

Table 4
Summary of Hierarchical Regression Model for Predictors of GI Symptoms.

Step		*B*	*SE B*	*β*
1	Age	.00	.00	.12
	Gender	−.94	.25	−.29**
	Total SCQ	.05	.02	.17*
2	Total CSHQ Score	.07	.01	.37**
3	SIB Frequency	.06	.09	.00
	SIB Severity	.04	.14	.04
	Aggressive/destructive Behavior Frequency	−.08	.05	−.07
	Aggressive/destructive Behavior Severity	.01	.07	.03
	Stereotyped Behavior Frequency	.02	.02	.08

* $p<.05$.
** $p<.001$.

Table 5
Summary of Hierarchical Regression Model for Predictors of Sleep Problems.

Step		*B*	*SE B*	*β*
1	Age	.00	.01	.01
	Gender	.45	1.52	.03
	Total SCQ	.00	.13	.00
2	Total GSI Score	2.45	.47	.43**
3	SIB Frequency	.25	.52	.08
	SIB Severity	.92	.80	.20
	Aggressive/destructive Behavior Frequency	.51	.32	.21
	Aggressive/destructive Behavior Severity	−.31	.42	−.14
	Stereotyped Behavior Frequency	−.03	.12	−.03

** $p<.001$.

Table 6
Summary of Hierarchical Regression Model for Predictors of BPI-S Subscales.

Criterion Variables										
Predictor		SIB Frequency			Aggressive/destructive Behavior Frequency			Stereotyped Behavior Frequency		
		B	*SE B*	*B*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Step 1	Age	.00	.00	.05	−.01	.01	−.13	.01	.01	.07
	Gender	1.00	.47	.17*	.55	.92	.05	1.68	1.14	.12
	Total SCQ	−.01	.04	.−.01	.06	.08	.06	−.06	.10	−.05
Step 2	Total GSI Score	.49	.15	.27*	−.27	.31	−.08	.65	.38	.15
Step 3	Total CSHQ Score	.10	.03	.32**	.19	.05	.31**	.17	.07	.22*

* $p < .05$.
** $p<.001$.

4. Discussion

This study investigated the relationship between parent-reported comorbid conditions, such as gastrointestinal symptoms, sleep problems, ASD symptoms and behavior problems and how they shape the phenotype of 22q deletion syndrome. Significant relationships were found between comorbid conditions, which provides novel data on the relationship between comorbid conditions in children and adolescents with 22q deletion syndrome.

Similar to previous published research (Campbell et al., 2018; Giardino et al., 2014), the current study found that GI symptoms are extremely common in 22q deletion syndrome. Constipation was the most common reported GI symptom among all participants and among each of the age groups (3−6 years, 7−12 years and 13−18 years), followed by abdominal pain. This finding is similar to Giardino et al. (2014) who found abdominal pain and constipation are the most common GI symptoms in those with 22q deletion syndrome.

Findings confirm that there is a strong link between GI symptoms and behavior problems. GI symptoms predicted the frequency and severity of SIB in this sample. Buie et al. (2010) has suggested that individuals with ASD and GI symptoms are at risk for problem behaviors, whereby GI symptoms, particularly pain, is a setting event for behavior problems such as SIB or aggression. In this study, 91 % of the sample presented with symptoms of ASD. This finding may imply that the high frequency of behavior problems in this sample was as a result of the high rate of comorbid GI and ASD symptoms. This finding highlights the need for clinical screening for ASD and GI symptoms in children and adolescents with 22q deletion syndrome.

A significant moderate relationship was found between GI symptoms and sleep problems, suggesting that high levels of GI symptoms were associated with high levels of sleep problems. GI symptoms and sleep problems were predictors of one another, suggesting that the relationship between these two comorbidities are bi-directional in children and adolescents with 22q deletion syndrome. These findings indicate the need for further investigation into the relationship between GI symptoms and sleep problems in individuals with 22q. A better understanding of GI symptoms and sleep problems and their relationship to 22q deletion syndrome is imperative in order to improve the management and treatment of children and adolescents with 22q deletion syndrome experiencing these comorbidities.

This study also highlighted the frequency of sleep problems in children and adolescents with 22q. In total, 91 % of children and adolescents with 22q experienced sleep problems. This is much higher than Moulding et al. (2019), who found 60 % of young people with 22q deletion syndrome experienced sleep problems. The most common reported sleep problems across all age groups in the sample were daytime sleepiness, parasomnias, and bedtime resistance. Previous research reported sleep-related breathing disorders as the most common in 22q deletion syndrome (Crockett et al., 2014; Heike et al., 2007; Kennedy et al., 2014). Clinicians should be aware of the high rates of sleep problems in children and adolescents with 22q, paying special attention to daytime sleepiness, parasomnias and bedtime resistance. Treatment of these sleep problems should be the main focus for future research in 22q deletion syndrome.

Sleep problems were found to be predictors of behavior problems, specifically the frequency of SIB, aggressive/destructive behavior and stereotyped behavior. Given that common sleep problems were daytime sleepiness, parasomnias, and bedtime resistance,

a number of hypotheses can be made. It may be hypothesised that behavior problems occur as a result of the tiredness associated with daytime sleepiness in children and adolescents with 22q deletion syndrome. Behavior problems may arise as a result of experiencing parasomnias at night time. The high incidence of bedtime resistance in this sample may indicate that children may act out, exhibiting maladaptive behavior by resisting going to bed.

This study had some limitations. Firstly, the authors of this study did not directly assess the participant's comorbid symptoms. Instead, parental reports were used. Ideally, objective measures should be used to measure comorbid conditions. Despite this limitation, previous research has indicated that there is a strong agreement between clinical evaluations and parental-report. Giardino et al. (2014) combined both parental-report using the Pediatric Gastrointestinal Symptoms-Rome III Version and clinical evaluation to assess GI symptoms in ASD. Giardino et al. (2014) found that parental-report of any GI symptoms in those with ASD was highly concurrent (92.1 %) with a clinical diagnosis of any GI symptoms. Some GI symptoms are easier to observe such as constipation and diarrhea. However, other symptoms such as bloating, nausea and abdominal pain are much more difficult for parents to observe. Future research may incorporate clinical examinations to give a more accurate account of specific comorbidities.

There is a potential for response bias in this research. Parents of children and adolescents with a diagnosis of 22q deletion syndrome were recruited to participate in this study regardless of whether their child experienced GI symptoms, sleep problems, behavior problems, or ASD symptoms. It may be the case that only those parents who felt their child presented with these comorbidities decided to participate as they may have more interest in participating in research that resonates with a current concern for them and their families. This could be a considered a potential bias in the interrelationships found within the study. This is important to note when making comparisons between the current study and other studies that used other methodologies, such as medical records.

A further limitation was that this study did not include a typically developing control group. Future research may include a control sample of typically developing children and adolescents in order to get a more accurate account of the differences in comorbid conditions between children and adolescents with 22q deletion syndrome, and typically developing children and adolescents.

This study successfully demonstrated that GI symptoms, sleep problems, behavior problems and ASD symptoms are highly comorbid in children and adolescents with 22q. Results found a moderate association between GI symptoms and sleep problems in the 22q deletion syndrome. Higher rates of GI symptoms and sleep problems significantly predicted each other. A small relationship was found between GI symptoms and behavior problems, in particular the frequency and severity of SIB. Significant small to moderate relationships were also found between sleep problems and behavior problems indicating that higher rates of sleep problems in the sample were related to more behavior problems such as the frequency and severity of SIB, the frequency and severity of aggressive/destructive behavior as well as the frequency of stereotyped behavior. Sleep problems also predicted the frequency of SIB, aggressive/destructive behavior and stereotyped behavior. These findings highlight the importance of screening for these specific comorbidities when a child is first diagnosed with 22q deletion syndrome. Consideration of the relationship between parent-reported comorbid disorders in individuals with 22q deletion syndrome allows for a more accurate diagnosis and more effective treatment plans to be designed in order to treat these symptoms, resulting in optimal long-term outcomes for children and adolescents with 22q deletion syndrome.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of National University of Ireland Galway and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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CRediT authorship contribution statement

Geraldine Leader: Conceptualization, Methodology, Supervision, Writing - review & editing, Visualization. **Maeve Murray:** Investigation, Formal analysis, Writing - original draft. **Páraic S. O'Súilleabháin:** Formal analysis, Writing - review & editing. **Leanne Maher:** Formal analysis, Writing - review & editing. **Katie Naughton:** Formal analysis, Writing - review & editing. **Sophia Arndt:** Formal analysis, Writing - review & editing. **Keeley White:** Writing - original draft, Supervision. **Ivan Traina:** Resources. **Arlene Mannion:** Conceptualization, Methodology, Supervision, Writing - original draft, Writing - review & editing, Visualization.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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