An investigation of comorbid psychological disorders, sleep problems, gastrointestinal symptoms and epilepsy in children and adolescents with autism spectrum disorder: A two year follow-up

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Abstract

Research has recently focused on studying comorbidity in the autism spectrum but little research has been conducted in follow-up studies or conducting longitudinal research into these conditions. Mannion, Leader, and Healy (2013) examined the frequency of comorbid disorders in children and adolescents with autism spectrum disorder and the predictors of sleep problems. The current study is a follow-up study conducted two years later with 56 participants. Age, gender, level of intellectual disability, presence of epilepsy, attention deficit/hyperactivity disorder (AD/HD) and an anxiety disorder were assessed, along with administering the Autism Spectrum Disorder- Comorbid for Children (ASD-CC) , the Children's Sleep Habits Questionnaire (CSHQ) and Gastrointestinal Symptom Inventory. The aim of the study was to determine if comorbid symptoms changed over time. An additional aim was to explore if there is a relationship between family medical history and history of autoimmune diseases, and child comorbid conditions. Sleep problems persisted in 91.5% of participants. Gastrointestinal symptoms persisted in 84.4% of participants. There was a significant difference between over-eating at baseline and at two-year follow-up, where over-eating became more severe over time. It was found that 92.9% of participants presented with a family history of autoimmune disease. The most common autoimmune diseases were osteoarthritis, psoriasis and hypothyroidism. The associations between familial autoimmune diseases and child comorbid conditions are discussed in the study.

Keywords: Comorbidity, Autism spectrum disorder, Follow-up, Comorbid Psychopathology, Sleep problems, Gastrointestinal symptoms, Autoimmune diseases, Epilepsy

An investigation of comorbid psychological disorders, sleep problems, gastrointestinal symptoms and epilepsy in children and adolescents with autism spectrum disorder: A two year follow-up.

1.1. Comorbidity in Autism Spectrum Disorder (ASD)

Comorbidity is defined as the co-occurrence of two or more disorders in the same person (Matson & Nebel-Schwalm, 2007). Recent research has identified the importance of comorbidity research in autism spectrum disorder (ASD) in relation to diagnosis and treatment priorities (Mannion & Leader, 2013b; Matson & Goldin, 2013; Matson & Williams, 2014). Research has identified the range and types of comorbidities from babies and infants (Fodstad, Rojahn, & Matson, 2010; Kozlowski, Matson, Belva, & Rieske, 2012), childhood (Matson, Fodstad, & Dempsey, 2009; Mannion, Leader, & Healy, 2013), adolescents (Simonoff et al., 2008) and adults (Davis et al., 2011; LoVullo & Matson, 2009). Research has also investigated the frequency and predictors of comorbidity (Mannion et al., 2013; Mannion & Leader, 2013a). Much more research is needed into many areas of comorbidity in ASD including longitudinal research. Longitudinal research is needed to determine if and how comorbid symptoms change over time in individuals with ASD. Comorbid conditions include comorbid psychopathology, epilepsy, sleep problems and gastrointestinal symptoms. Research is needed to better understand the change in these symptoms as individuals with ASD age.

1.2. Preliminary Studies

Mannion et al. (2013) examined the frequency of current comorbid diagnosis, comorbid psychopathology, sleep problems and gastrointestinal symptoms in children and adolescents with ASD. The authors found that 46.1% of children and adolescents with ASD had a comorbid psychological or medical diagnosis. When intellectual disability was included as a potential comorbid diagnosis, 78.7% had a comorbid diagnosis. The prevalence of attention-deficit hyperactivity disorder was 18% and 15.7% of individuals had

an anxiety disorder. Mannion et al. (2013) found that the majority (80.9%) of participants presented with sleep problems, while 70.3% of participants presented with gastrointestinal symptoms. As well as investigating the frequency of comorbid conditions, the predictors of sleep problems were examined. Under-eating, avoidant behavior, and total gastrointestinal symptoms predicted sleep problems. Abdominal pain was found to predict sleep anxiety.

Mannion and Leader (2013a) expanded on Mannion et al. (2013) by investigating predictors of comorbid psychopathology and gastrointestinal symptoms. A high prevalence of repetitive behaviors, tantrum behaviors, avoidant behaviors, worry/depressed behaviors, conduct behaviors, and eating problems were found. It was found that sleep disordered breathing and daytime sleepiness predicted abdominal pain and bloating. Sleep anxiety predicted abdominal pain. It was also found that total GI symptoms predicted comorbid psychopathology. Nausea predicted worry/depressed behavior, avoidant behavior and conduct behavior. Abdominal pain and constipation also predicted conduct behavior. Diarrhea predicted tantrum behavior.

1.3. Comorbid Psychopathology

Longitudinal research has been conducted investigating children with autism and comorbid psychiatric disorders (Kim, Freeman, Paparella, & Forness, 2012; Mannion, Brahm, & Leader, 2014) and attention-deficit/hyperactivity disorder (AD/HD; Fein, Dixon, Paul, & Levin, 2005). Comorbid psychiatric disorders have been found to be relatively stable over time (Kim et al., 2012). While little research has been conducted with children with ASD, even less is known about comorbid conditions in adolescence and adulthood. Magiati, Tay, and Howlin (2014) conducted a systematic review of longitudinal follow-up studies in adulthood. The review found that 16 out of 25 studies provided some information on comorbid conditions in adulthood. It was found that only one study (Gray et al., 2012)

examined change in comorbid symptoms over time. With regards to specific comorbid psychopathology symptoms, research has found anxiety and depression to increase with age (Mayes, Calhoun, Murray, & Zahid, 2011; Vasa et al., 2013). In contrast, research found comorbid psychopathology to not increase with age (Davis et al., 2011; Strang et al., 2012). While Davis et al. (2011) found that anxiety rises from toddlerhood to childhood, it was found that anxiety decreases from childhood to young adulthood and again increases from young adulthood into older adulthood. Research is needed on the age related variations of comorbid psychopathology in the same participants over time.

1.4. Epilepsy

Nordin and Gillberg (1998) recommended that follow-up studies should include clear descriptions of comorbid conditions, and that the long-term effects of the conditions and their possible interactions with each other should be evaluated. Follow-up studies have been conducted in individuals with ASD investigating whether they developed epilepsy (Bolton et al., 2007; Billstedt, Gillberg, & Gillberg, 2005; Hara, 2007). Billstedt et al. (2005) found that new cases of epilepsy appeared in the post-adolescent period, but no individual developed epilepsy after the age of 20 years. Bolton et al. (2007) found that 22% of individuals developed epilepsy. This highlights the importance of following up on the diagnosis of epilepsy in our current study. Mannion et al. (2013) found that 10.1% of children and adolescents with ASD had epilepsy. The current study will allow us to determine if participants had developed an epilepsy diagnosis within the previous two years.

1.5. Sleep Problems

Mannion and Leader (2014b) discussed age related variations in sleep problems in ASD in their review, and commented on the need for research to better understand what happens to sleep problems as children age. Goldman, Richdale, Clemons, and Malow (2012) examined

younger children, older children and adolescents with ASD. The research found that sleep problems persist throughout the age span from early childhood through adolescence in children with ASD. The study also found that types of sleep problems tend to change with age. Parents of younger children with ASD reported more difficulties with sleep anxiety, bedtime resistance, night wakings, and parasomnias. Parents of adolescents with ASD reported more difficulties with falling asleep, getting enough sleep on a regular basis, and daytime sleepiness. Mannion et al. (2013) found that 80.9% of participants presented with sleep problems. Mannion and Leader (2013a) found that 67.8% of participants presented with both sleep problems and gastrointestinal symptoms, while 12.6% presented with sleep problems only. This would suggest that sleep problems and gastrointestinal symptoms seem to commonly occur together in children and adolescents with ASD.

1.6. Gastrointestinal Symptoms

Research has found gastrointestinal symptoms, such as constipation and feeding issues, to be more common in children with ASD when compared to matched controls (Ibrahim, Voigt, Katusic, Weaver, & Barbaresi, 2009). Kral, Eriksen, Souders, and Pinto-Martin (2013) commented on the need for longitudinal studies conducted over an extended period of time to assess children's dietary intake and GI health. Mazurek, Keefer, Shui, and Vasa (2014) examined the gastrointestinal symptom of abdominal pain at baseline and at follow-up one year later in children with ASD. A fourth of participants (25.8%) presented with chronic abdominal pain at baseline, while 30.7% presented with chronic abdominal pain one year later. It was found that abdominal pain persisted for 86.7% of those who presented with pain at baseline. For those without abdominal pain at baseline, 23.8% presented with new abdominal pain at follow-up one year later. Mannion et al. (2013) found that 79.3% of children and adolescents with ASD presented with at least one gastrointestinal (GI) symptom within the previous 3 months. The most common GI symptom was abdominal pain with

51.7% of participants experiencing it. The current study aims to further explore gastrointestinal symptoms, and aims to examine whether there is a relationship between gastrointestinal symptoms and family medical history, especially history of autoimmune diseases.

1.7. Family Medical History

Research has investigated the relationship between family medical history and ASD (Williams, Oliver, Allard, and Sears, 2003). Brimacombe, Ming, and Parikh (2007) found that 89% of families of children with autism reported some type of familial disorder. The most common were depression, thyroid disorders, diabetes, AD/HD, speech and language disorders, anxiety and rheumatoid arthritis. Vasa et al. (2012) investigated the relationship between maternal mood disorders and child diagnosis of autism spectrum disorder versus Asperger's Syndrome. Maternal history of bipolar disorder or depression was more strongly associated with having a child with Asperger's Syndrome than having a child with ASD. Having a child with Asperger's Syndrome was also more likely if mothers had the first onset of mood disorders prior to having children.

Research has focused on the relationship between autoimmune diseases and ASD (Ashwood & Van de Water, 2004; Atladóttir et al., 2009; Chen et al., 2013; Comi, Zimmerman, Frye, Law, & Peeden, 1999; Kuo et al., 2014). Sweeten, Bowyer, Posey, Halberstadt, and McDougle (2003) compared families with a child with a pervasive developmental disorder (PDD) to families with a child with an autoimmune disease, and to families with a healthy control child. Autoimmune diseases were more frequent in the families of a child with PDD compared to the other groups. It was found that hypothyroidism and rheumatic fever were more common in the families with a child with PDD than in the healthy control families. Croen, Grether, Yoshida, Odouli, and Van de Water (2005)

investigated the association between maternal autoimmune diseases and childhood ASD. While both psoriasis and type 1 diabetes were found to be more common in mothers of children with ASD than controls, after controlling for maternal factors, only psoriasis was found to be significantly associated with ASD.

1.8. Family History of Autoimmune Diseases and Gastrointestinal Symptoms

Research has begun to explore the relationship between gastrointestinal symptoms and the immune system in ASD (Brown & Mehl-Madrona, 2011; Stigler, Sweeten, Posey, & McDougle, 2009). It has been found that Ulcerative colitis was present in significantly more mothers of children with infantile autism (Mouridsen, Rich, Isager, & Nedergaard, 2007). It was found that 2.7% of mothers of children with infantile autism had a diagnosis of ulcerative colitis, compared to 0.3% of controls. Valicenti-McDermott et al. (2006) examined the association of gastrointestinal symptoms with a family history of autoimmune disease. Family history of autoimmune disease was reported in 38% of the ASD group and in 34% of control participants. The researchers found that there was no association between family history of autoimmune disease and GI symptoms in children with ASD.

Valicenti-McDermott, McVicar, Cohen, Wershil, and Shinnar (2008) found an association between language regression, a family history of autoimmune disease, and gastrointestinal symptoms. An abnormal stool pattern was indicative of a child's gastrointestinal symptoms. Children with language regression were more likely to exhibit an abnormal stool pattern, had an increased family history of celiac disease or inflammatory bowel disease and of rheumatoid arthritis. Of all of the children with a family history of autoimmune disease, an abnormal stool pattern was reported more frequently in those with language regression than those without language regression. An abnormal stool pattern was found in 78% of those with a family history of autoimmune disease and language regression

and, compared to 15% of those with a family history of autoimmune disease, but without language regression. Peters et al. (2014) commented that obtaining a family history of GI symptoms "could be useful in establishing a genetic or familial component to bowel symptoms" (p.1431).

1.9. Family History of Autoimmune Disorders and Epilepsy

Ong, Kohane, Tianxi, Gorman, and Mandl (2014) examined the relationship between epilepsy and autoimmune diseases in typically developing children and adults. The risk of epilepsy was found to be significantly higher in those with autoimmune disease. This risk was found to be higher in children than in adults, where children had a five-fold increased risk of epilepsy, while adults had a four-fold increased risk of epilepsy. Adults with type 1 diabetes or myasthenia gravis had a five-fold increased risk of epilepsy.

1.10. Current Study

Mannion et al. (2013) investigated the frequency of comorbid symptoms and the predictors of sleep problems. The purpose of the current study is to determine if there is a change in comorbid symptoms over a two-year time period. These comorbid symptoms include comorbid psychopathology, epilepsy, sleep problems, and gastrointestinal symptoms. The study also aims to explore if there is a relationship between child comorbid symptoms and family medical history, including autoimmune diseases.

2. Method

2.1. Participants

Participants were 56 children and adolescents with a diagnosis of autism spectrum disorder (in accordance with DSM-IV-TR criteria). Participants were recruited through schools, ASD service providers, parent support groups and online forums. The 89 participants who

participated in the original study (Mannion et al., 2013), were contacted and were invited to participate in a two year follow-up. Of the 89 original participants, 56 participated in the follow-up study. The mean age of the sample was 11 years (*S.D* = 42.91 months), ranging from 5 to 19 years. It was found that 87.5 % (*n*=49) were males and 12.5% (*n*=7) were female. It was found that 62% (*n* = 35) of participants had an intellectual disability. A mild intellectual disability was reported for 29% of males (*n* =14) and for 29% of females (*n*= 2). A moderate intellectual disability was reported for 30% of males (*n* = 15). A severe intellectual disability was reported for 6% of males (*n* = 3) and for 29% of females (*n*=2).

2.2. Measures

2.2.1. Demographic information. A self-constructed questionnaire provided information on the participant's' age, gender, whether they had an intellectual disability and what level of intellectual disability. Presence or absence of epilepsy, AD/HD and an anxiety disorder were reported, as well as any other current comorbid diagnosis.

2.2.2. Gastrointestinal Symptom Inventory. The Gastrointestinal Symptom Inventory (Autism Treatment Network, 2005) is a 35-item questionnaire that was developed in the early days of the Autism Treatment Network (ATN). There are also additional items should a participant exhibit certain symptomatology, and therefore includes 77 items in total. The ATN is the first network of hospitals and physicians dedicated to developing a model of comprehensive medical care for children and adolescents with autism through seventeen participating institutions in the U.S. and Canada. This tool has not been validated. It was based on previous questionnaires and on clinical symptom assessment for children with autism and identified gastrointestinal disorders. The inventory is scored initially dichotomously i.e. whether or not the child has any gastrointestinal symptoms. The inventory also allows branching into specific areas of symptomatology: abdominal pain, abnormal

bowel movements, reflux, and food insensitivity. These branches will allow determination of rates of these categories as well. It has been used in published research (Mannion et al., 2013; Mannion & Leader, 2013a; Mazefsky, Schreiber, Olino, & Minschew, 2014; Mazurek et al., 2013).

2.2.3. Autism Spectrum Disorder – Comorbid for Children (ASD-CC). The ASD-CC (Matson & Gonzalez, 2007) is a 39-item informant-based rating scale designed to assess symptoms of psychopathology and emotional difficulties which commonly occur with ASD. Items are included to address conditions such as AD/HD, depression, conduct disorder, eating disorders/difficulties, OCD, specific phobias, and tic disorders. Caregivers rate each item to the extent it has been a recent problem as either 0= "not a problem or impairment; not at all", 1= "mild problem or impairment", 2= "severe problem or impairment", or X= "does not apply or don't know". Inter-rater and test–retest reliability for the ASD-CC has been found to be moderately good (k = .46 and k = .51, respectively) with very good internal consistency (α= .91) reported (Matson & Dempsey, 2008). Factor analysis yielded seven subscales for the ASD-CC: 1) Tantrum Behavior, 2) Repetitive Behavior, 3) Worry/Depressed, 4) Avoidant Behavior, 5) Under-Eating, 6) Conduct and 7) Over-Eating. Construct validity was established for Tantrum Behavior, Worry/Depressed, Repetitive Behavior, Conduct, and Over-Eating factors.

2.2.4. Children's Sleep Habits Questionnaire (CSHQ). The CSHQ (Owens, Nobile, McGuinn, & Spirito, 2000) is a 52-item parental-report, sleep-screening instrument designed for typically developing children ages 4 to 10 years. However, it has been used with younger children with autism spectrum disorders (Goodlin-Jones, Sitnick, Tang, Liu, & Anders, 2008), as well as with an older population of children with ASD (Goldman et al., 2011). Forty-two of the items are rated on a three-point Likert scale, with the responses being 'Rarely' (never or one time a week), 'Sometimes' (2 to 4 times a week), and 'Usually'

(5 or more times a week). Each question was asked in relation to the previous week. The second column of questions is to determine if the item is considered a problem for caregivers. Beside each item, parents can choose 'Yes', 'No', or 'N/A' under the 'Problem?' column. Thirty-three of the items are used in deriving the total sleep disturbance score and the subscales of the questionnaire. There are 8 subscales of the CSHQ, including bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, day-time sleepiness, and sleep disordered breathing. The CSHQ is not intended to be used to diagnose specific sleep disorders, but rather to identify sleep problems and the possible need for further evaluation. While there are no established "norms" for the total subscale scores, a total CSHQ score of 41 has been reported to be a sensitive clinical cut-off for identification of probable sleep problems (Owens, Spirito, & McGuinn, 2000).

2.2.5. Autoimmune Disease in Family Members Questionnaire. The Autoimmune Disease in Family Members Questionnaire is a 45-item questionnaire that investigates which first- or second-degree relatives had received a diagnosis of specific autoimmune diseases. Examples of disorders inquired about in the questionnaire include arthritis, lupus, psoriasis, multiple sclerosis, ulcerative colitis, Crohn's disease, hyperthyroidism/ Graves' disease, hypothyroidism/ Hashimoto's thyroiditis, and type 1 diabetes. The questionnaire was used in previous research (Sweeten et al., 2003).

2.2.6. Family history of medical, developmental, and psychological disorders. A self-constructed questionnaire was used to obtain information on family history of medical, developmental, and psychiatric disorders that were not used in the Autoimmune Disease in Family Members Questionnaire. Information on family history of medical conditions (including epilepsy and Celiac Disease), intellectual disability, and anxiety disorders were obtained.

2.3. Informants

Informants were parents of children and adolescents diagnosed with autism spectrum disorder. Rating scales were completed by parents independently according to the instructions printed on top of the questionnaires.

3. Results

3.1. Analyses

Chi-Square tests were run for comorbid diagnosis, epilepsy, AD/HD, and anxiety disorders at baseline and at follow-up, two years later. A repeated measure MANOVA was run for sleep problems. Bonferroni adjustment for multiple comparisons was applied. A repeated measure ANOVA was run for GI total score. Chi-Square tests were used for the individual GI symptoms. A repeated measure MANOVA was run for the Autism Spectrum Disorder-Comorbid for Children (ASD-CC).

3.2. Current comorbid diagnoses

As can be seen from Table 1, comorbid diagnoses were relatively stable.

Insert Table 1 about here

No difference was found between any of the comorbid diagnoses at baseline and at two-year follow-up. Chi-Squares found that the comorbid diagnoses were highly related to each other at pre- and post-tests. Therefore there was no difference in comorbid diagnosis (p=.00), epilepsy (p=.00), AD/HD (p=.00), and anxiety disorder (p=.00). Obsessive compulsive disorder (OCD) was the most common anxiety disorder with 37.5% (n=5) of those who were diagnosed with an anxiety disorder having the diagnosis. The next most common disorder was Generalized Anxiety Disorder (GAD) with 25% (n=2) of individuals presenting with it.

3.3. Sleep Problems

The prevalence of sleep problems were 78.6% (*n*=44), whereby a sleep problem is classified as a score of 41 or more on the CSHQ. The mean score on the CSHQ was 47.55 (*SD*=9.40). A summary of the subscale means and standard deviations are included in Table 2.

Insert Table 2 about here

Sleep problems persisted in 91.5% (*n*=43) of participants from baseline to follow-up. Sleep problems developed in 22.2% (*n*=2) of participants who had not experienced sleep problems at baseline.

3.4. Gastrointestinal symptoms

It was found that 73.2% (*n*=41) of participants presented with at least one gastrointestinal symptom within the last 3 months. 21.4% (*n*=12) presented with one symptom only, while 14.3% (*n*=8) presented with two symptoms. 10.7% (*n*=6) presented with three gastrointestinal symptoms, while 19.6 % (*n*=11) presented with four symptoms. A small percentage of participants (7.1%) (*n*=4) presented with all five gastrointestinal symptoms within the last three months. As detailed in Table 3, there was a trend for the persistence of GI symptoms over time.

Insert Table 3 about here

It was found that at least one GI symptoms persisted in 84.4% (*n*=38) of participants between baseline and follow-up, two years later. In those that did not present with GI symptoms at baseline, it was found that 20% (*n*=2) of these participants presented with GI symptoms two years later. Specifically, of these GI symptoms it was found that abdominal pain persisted in 72.4% (*n*=21) of participants from baseline to follow-up. Diarrhea persisted from baseline to follow-up in 77.8% (*n*=21) of participants. Constipation persisted in 67.9%

(*n*=19) of participants from baseline to follow-up. Bloating persisted from baseline to follow-up in 66.7% (*n*=8) of participants. It was found that nausea persisted from baseline to follow-up in 43.8% (*n*=7) of participants. No significant difference was found between the total number of GI symptoms at baseline and at follow-up (*p*=.46). No difference was found between any of the GI symptoms at baseline and at follow-up. Chi-Squares found that all GI symptoms were highly related to each other at pre- and post-tests. Therefore there was no difference in abdominal pain (*p*=.00), diarrhea (*p*=.00), constipation (*p*=.00), bloating (*p*=.005), and nausea (*p*=.085) from baseline to two-year follow-up.

3.5. Gastrointestinal Symptoms and Sleep Problems

It was found that 64.3% (*n*=36) of participants presented with both sleep problems and gastrointestinal symptoms. It was found that 14.3% (*n*=8) presented with sleep problems only, and 8.9% (*n*=5) presented with gastrointestinal symptoms only. Only 12.5% (*n*=7) presented with neither sleep problems nor gastrointestinal symptoms. Sleep problems occurred in 94.4% (*n*=17) of those with bloating. Sleep problems occurred in 93.3% (*n*=14) of those with nausea. Sleep problems occurred in 92.6% (*n*=25) of those with abdominal pain. Sleep problems occur in 88.5% (*n*=23) of those with diarrhea, and in 87.5% (*n*=21) of those with constipation.

3.6. Autism Spectrum Disorder-Comorbid for Children (ASD-CC)

The mean score of the ASD-CC was 26.02 (*SD*=11.32). A summary of the ASD-CC and subscale means are provided in Table 4.

Insert Table 4 about here

All of the mean subscale scores in the study were determined to have no or minimal impairment when compared to establish cut-offs in Thorson and Matson (2012). The

frequency, percentage, and level of impairment of ASD-CC subscale endorsements are included in Table 5.

Insert Table 5 about here

3.7. Family Medical History and Autoimmune Diseases

It was found that 98.2% (*n*=55) of participants had some type of familial disorder. It was found that 92.9% (*n*=52) of participants presented with a family history of autoimmune disease, while 89.3% (*n*=50) of participants presented with another psychological, developmental or medical disorder. The most common autoimmune diseases were osteoarthritis (old age arthritis) with 55.4% (*n*=31) of the sample having a family member with the diagnosis. This was followed by psoriasis at 39.3% (*n*=22), and hypothyroidism, also known as Hashimoto's thyroiditis with 32.1% (*n*=18) of the sample with a family member with the diagnosis. A summary of the most common autoimmune disorders, where autoimmune diseases are listed if over 5% of the sample had a family member with the diagnosis is given in Table 6.

Insert Table 6 about here

The number and type of relatives with an autoimmune disease is given in Table 7.

Insert Table 7 about here

The most common other disorder was Autism, Asperger's disorder or another Pervasive Developmental Disorder (PDD) with 46.4% (*n*=26) of the sample having a family member (excluding the participant with ASD) with a diagnosis. Attention-deficit/hyperactivity disorder (AD/HD) was the next most common disorder with 44.6% (*n*=25) of the sample having a family member with the diagnosis. This was followed by major depression with

39.3% (*n*=22) of the sample having a family member with a diagnosis. A summary of the most common other disorders are included in Table 8.

Insert Table 8 about here

The number and type of relatives with other disorders is given in Table 9.

Insert Table 9 about here

3.8. Relationship between Comorbid Conditions and Family Medical History of Autoimmune Diseases

Pearson correlations were conducted to determine if there is a relationship with the most common familial autoimmune diseases and other disorders, and child's current gastrointestinal symptoms, sleep problems, and comorbid psychopathology. A small positive correlation was found between family history of hypothyroidism (Hashimoto's thyroiditis) and total number of gastrointestinal symptoms, r (54) =.27, p=.048. A moderate positive correlation was found between family history of hypothyroidism and bloating, r (54) =.35, p=.009, and sleep disordered breathing, r (54) =.32, p=.018.

A moderate positive correlation was found between family history of hyperthyroidism (Graves' disease) and total number of gastrointestinal symptoms, r (54) =.40, p=.002. Moderate positive correlations were found between family history of hyperthyroidism and diarrhea, r (54) =.41, p=.002, constipation, r (54) =.35, p=.008, and an anxiety disorder diagnosis, r (54) =.34, p=.010. A small positive correlation was found between family history of Hyperthyroidism and abdominal pain, r (54) =.30, p=.030.

A summary of the remaining associations between family autoimmune disease and other disorders, and child current comorbid disorder are given in Table 10.

Insert Table 10 about here

Ulcerative colitis was found to be negatively associated with repetitive behavior, positively associated with worry/depressed, sleep duration, and daytime sleepiness. Crohn's disease was associated negatively with repetitive behavior and positively associated with worry/depressed and sleep duration. AD/HD was associated with an anxiety disorder diagnosis, total number of GI symptoms, nausea, constipation, sleep duration, and daytime sleepiness.

Major depression was negatively associated with bedtime resistance and positively associated with worry/depressed and an anxiety disorder diagnosis. Bipolar disorder was also found to be negatively associated with intellectual disability and positively associated with worry/depressed and daytime sleepiness. OCD was associated with an anxiety disorder diagnosis, worry/depressed, sleep disordered breathing, and nausea. Anxiety disorder was associated with abdominal pain. Schizophrenia was also associated with abdominal pain and bedtime resistance.

A family history of autism was associated with daytime sleepiness. Rheumatic fever was associated with sleep duration. Arthritis, where informants were unsure of the specific type was found to be associated with epilepsy. Rheumatoid arthritis was negatively associated with intellectual disability. Multiple miscarriages were also found to be associated with intellectual disability. Multiple blood clots were associated with conduct behavior.

4. Discussion

Sleep problems continue to be a common comorbid condition for children in this two-year follow-up study. It was found that 78.6% of children and adolescents presented with sleep problems, defined as a score of 41 or more on the CSHQ. Sleep problems persisted in

91.5% of participants from baseline to follow-up. However, there were significant differences found between a number of subscales from baseline to follow-up with all being higher at baseline than at two-year follow-up. Therefore, it appears that sleep problems did decrease as children got older, though for a large majority, sleep problems did still reach clinical cut-off levels. Types of sleep problems that decreased included bedtime resistance, sleep onset delay, sleep anxiety, night waking, parasomnias, and daytime sleepiness. This is supported by Goldman et al. (2012), who found that younger children had more bedtime resistance, sleep anxiety night waking, and parasomnias than older children or adolescents. Mannion and Leader (2014b) discussed the need for longitudinal sleep research. Research is needed to better understand whether sleep problems do get better or even disappear into adulthood. Future research needs to examine sleep problems in adults with ASD, as well as conducting more longitudinal research on sleep patterns and sleep problems in ASD.

Gastrointestinal symptoms persisted from baseline to two-year follow-up in 84.4% of individuals. As well as gastrointestinal symptoms persisting, new gastrointestinal symptoms developed in some individuals. It was found that in those who did not present with GI symptoms at baseline, 20% of these developed new symptoms. GI symptoms persisted across the variety of symptoms including abdominal pain, diarrhea, constipation, bloating, and nausea. Abdominal pain persisted from baseline to follow-up in 72.4% of participants. This is supported by Mazurek et al. (2014) who found that chronic abdominal pain that lasted for 3 months or more persisted in 86.7% of individuals over the course of one year. In the current study, new cases of abdominal pain developed in 15.4% of individuals. Again, this finding is supported by Mazurek et al. (2014) who found that abdominal pain developed in 23.8% % of participants without baseline abdominal pain. Diarrhea persisted in 77.8% of individuals, while 14.3% of individuals developed new symptoms of diarrhea. Constipation persisted in 67.9% of individuals, while developing in 14.8% of individuals. Bloating

persisted in 66.7% of individuals and new cases of bloating developed in one fifth (20.9%) of participants. Nausea persisted in 43.8% of individuals, while new cases developed in 17.9% of individuals. In this sample, GI symptoms persisted for the majority of participants while new cases of these symptoms developed in the time from baseline to two-year follow-up. Future research needs to consider gastrointestinal issues and how they respond to treatment over time.

It was found that there was no significant difference between participants having a comorbid diagnosis at baseline and at follow-up. This tells us that comorbid diagnoses are relatively stable. While there was no significant difference between AD/HD diagnosis at baseline and at follow-up, it must be noted that 10.9% of individuals who did not present with AD/HD at baseline presented with it at follow-up. AD/HD symptoms may be a lot more common in ASD than previously thought. The DSM-5 has been introduced recently, which now allows for a diagnosis of both ASD and AD/HD. It is possible that we may see more children and adolescents being diagnosed with AD/HD in the future (Mannion & Leader, 2014a). No significant difference was found between anxiety disorder diagnosis at baseline and at follow-up. It was reported that 5% (n=3) of those who did not present with an anxiety disorder at baseline now presented with anxiety at follow-up. It is important that anxiety is recognised and diagnosed in all individuals with ASD, especially in individuals who are non-verbal and may be unable to communicate their feelings.

There was a significant difference in over-eating subscale scores from baseline to follow-up. Over-eating was higher at follow-up. Previous research has found obesity to be a common issue in children and adolescents with ASD (Broder-Fingert, Brazauskas, Lindgren, Iannuzzi, & Van Cleave, 2014; Curtin, Jojic, & Bandini, 2014; Egan, Dreyer, Odar, Beckwith, & Garrison, 2013). Ho and Spiegel (2008) commented on the possible association between obesity and functional gastrointestinal disorders in the general population. It is

possible that there may be a similar relationship between over-eating, obesity, and GI symptoms in individuals with ASD. This needs to be further explored in future research.

The majority (98.2%) of participants presented with a familial history of a disorder of some type, where 92.9% presented with a family history of an autoimmune disease and 89.3% presented with another psychological, developmental or medical disorder. This finding is supported by Brimacombe et al. (2007) who found that 89% of families with ASD reported some type of familial disorder. The most common autoimmune disease was osteoarthritis where 55.4% of participants had a family member with the diagnosis. The next most common autoimmune disease was psoriasis with 39.3% of the sample having a familial history of the disorder. This finding of psoriasis being a common autoimmune disease in ASD is supported by Croen et al. (2005). Hypothyroidism was the next most common autoimmune disease with 32.1% of the sample with a family member with the disease. Previous research has supported this finding of a family history of hypothyroidism being common in ASD (Brimacombe et al., 2007; Comi et al., 1999; Sweeten et al., 2003). Autism, Asperger's Syndrome or another Pervasive Developmental Disorder (PDD) were the most common other disorder, with 46.4% of the sample having a family member (excluding the participant with ASD) having a diagnosis. It was found that 44.6% of the sample presented with a family history of AD/HD. A family history of major depression was reported in 39.3% of the sample. This finding of family history of AD/HD and depression being common in ASD is supported by Brimacombe et al. (2007).

A number of interesting findings were reported based on the associations between family history of disorders and the current comorbid symptoms of the child. Family history of major depression and bipolar disorder were associated with child worry/depressed score on the ASD-CC. An association was reported between family history of major depression and the child having an anxiety disorder. These finding suggest that there is a genetic or familial

role in the development of depression in individuals with ASD. A family history of OCD was associated with child worry/depressed score on the ASD-CC. Family history of OCD was associated with the child having a diagnosis of an anxiety disorder. This finding also suggests how there is a relationship between family history of an anxiety disorder and child anxiety symptoms.

Family history of the thyroid disorders of hypothyroidism and hyperthyroidism were both found to be associated with total number of GI symptoms. Hypothyroidism was associated with the child GI symptom of bloating. Hyperthyroidism was associated with the child GI symptoms of diarrhea, constipation, and abdominal pain. This is a very interesting finding and suggests a relationship between autoimmune disease, in particular thyroid disorders, and GI symptoms. Future research needs to be conducted to examine this relationship further.

While one may expect a relationship to be found between family history of ulcerative colitis and Crohn's disease, and child GI symptoms; no relationship was found. However, both family history of ulcerative colitis and Crohn's disease were found to be associated with child worry/depressed behavior, repetitive behavior, and sleep duration. It may be possible that children are presenting with non-gastrointestinal manifestations of GI symptoms. This finding is supported by Buie et al. (2010) who discussed how problem behavior and sleep problems may actually be presentation of GI disorders. Mannion and Leader (2013a) found a relationship between GI symptoms and sleep problems. They also found a relationship between GI symptoms and worry/depressed behavior. Research is needed to explore the relationship between depression and GI symptoms in ASD.

A family history of AD/HD was found to be associated with total number of GI symptoms, nausea, and constipation. This finding is supported by McKeown, Hisle-Gorman,

Eide, Gorman, and Nylund (2013) who found that children with AD/HD had an increased prevalence of constipation and fecal incontinence compared to typically developing children. Research needs to explore the relationship between AD/HD and GI symptoms in individuals with ASD. A family history of an anxiety disorder was found to be associated with abdominal pain. Family history of OCD was associated with nausea. Mannion and Leader (2013a) found that gastrointestinal symptoms predicted worry/depressed and avoidant behavior on the ASD-CC, which together form a measure of anxiety. More research needs to be conducted on the relationship between anxiety and GI symptoms. Family history of schizophrenia was found to be associated with abdominal pain. This was a surprising finding and one where more research needs to be conducted upon.

A family history of arthritis, specifically where informants were unsure of the exact type of arthritis was found to be associated with the child comorbid symptom of epilepsy. This finding is supported by Ong et al. (2014) who found a 3.6% increase in epilepsy in children who had rheumatoid arthritis compared to children who did not have an autoimmune disease. The relationship between family history of arthritis and child epilepsy needs to be explored further in future research.

Sleep problems were associated with family history of a number of disorders including hypothyroidism, ulcerative colitis, Crohn's disease, AD/HD, major depression, bipolar disorder, OCD, Schizophrenia, ASD, and rheumatic fever. Sleep problems are a very common issue in children and adolescents with ASD. We need to better understand the relationship between family history of autoimmune disease and other disorders, and child sleep problems.

Anxiety is a comorbid condition that affects many individuals with ASD. Anxiety is an issue that may be difficult to diagnose especially in individuals who are non-verbal and

express anxiety in alternative manners such as challenging behavior. The current study found that family history of hyperthyroidism was associated with child diagnosis of an anxiety disorder. Family history of AD/HD was also associated with child anxiety disorder. More research is needed to explore the relationship between family medical history and child anxiety. Anxiety is an area of comorbidity research where much more research needs to be conducted.

There were also some interesting findings of the current study in relation to intellectual disability. The majority of participants presented with an intellectual disability. Familial history of multiple miscarriages was found to be associated with a child having an intellectual disability. It is important to note that it is not just the mothers of children with ASD that are experiencing multiple miscarriages. Family history of multiple miscarriages accounted for first and second degree relatives of the child with ASD. Rheumatoid arthritis was also found to be associated with intellectual disability. The relationship between family history of autoimmune diseases and child intellectual disability needs to be investigated in future research. Since many children present with both ASD and intellectual disability, the role that intellectual disability plays needs to be considered in research. Familial history of multiple blood clots was associated with child conduct behavior. This relationship needs to be investigated in future research.

However, the current study has a number of limitations. Firstly, the data obtained was by parental report. None of the participants were evaluated directly by the authors of the current study. Where level of intellectual disability was reported, it was by parental report and was not evaluated by the authors of the study. Ideally, objective measures should be used to measure comorbid conditions. While parental report was used to assess comorbidity, previous research has indicated that there is a large percentage of agreement between parental report and clinical evaluation. Gorrindo, Williams, Lee, Walker, McGrew, and Levitt (2012)

used the Questionnaire on Pediatric Gastrointestinal Symptoms-Rome III Version (QPGS) which is a 71 item parent report instrument that assesses GI symptoms and classifies functional GI disorders (FGID) according to Rome III criteria. Gorrindo et al. (2012) also included clinical evaluation in their study. Gorrindo et al. (2012) found that parent report of any gastrointestinal dysfunction in those with ASD was highly concurrent (92.1%) with a clinical diagnosis of any gastrointestinal dysfunction. Some GI symptoms are easier for parents to observe such as bloating, constipation, or diarrhea. However, GI symptoms such as nausea, abdominal pain, and gastroesophageal reflux are much more difficult for parents to observe, especially in children with ASD who are non-verbal. The observations found through parental reports merit replication through more direct examinations of comorbidities in individuals with ASD.

Secondly, treatment was not assessed in the current study. No information was available about whether participants had received treatment, and if so, what treatment they had received over the two-year period. It is possible that some participants had received treatment for their comorbid symptoms in the two-year period since the preliminary study. Future research needs to consider how GI symptoms and other comorbid symptoms respond to treatment over time. Thirdly, the correlations found between familial history of autoimmune diseases and child comorbid symptoms must be considered preliminary. Multiple comparisons were made in our analysis of the data, and this must be considered a limitation of the current study. Future research is needed to replicate and to further investigate these possible relationships. Finally, there is no age and sex-matched control group in the current study. It is possible that similar patterns may be seen in typically developing children and adolescents. Future research needs to investigate the presence of comorbid symptoms, as well as their persistence over time in a typically developing control group.

In conclusion, this study was the first to investigate longitudinal course of a number of different comorbid disorders, including GI symptoms, sleep problems, epilepsy, AD/HD, anxiety disorders, and comorbid psychopathology. Additionally, this study investigated the association between family history of autoimmune disorders and other psychological, developmental and medical disorders, and child comorbid symptoms. A number of interesting findings were reported such as the relationship between familial history of depression and child depressive symptoms, as well as the relationship between thyroid disorders (hyperthyroidism and hyperthyroidism) and GI symptoms. Future research needs to further explore the longitudinal course of comorbid disorders as individuals with ASD age over time. Research needs to be conducted on adults with ASD to examine whether comorbid symptoms are an issue for these individuals also. In just a few years, the children and adolescents in the current study will be reaching adolescence and adulthood. We need to better understand comorbidity as individuals with ASD age.

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Table 1.

Current comorbid diagnoses.

Comorbid Diagnosis	Time 1 (*n*) (%)	Time 2 (*n*) (%)	Number participants gained/ lost symptoms	% Change
Intellectual disability	35(62%)	35 (62%)	Same	
Comorbid disorder (including intellectual disability)	44 (78.6%)	46 (82.1%)	+2	16.67%
			-0	
Comorbid disorder (excluding intellectual disability)	24 (42.9%)	29 (51.8%)	+5	15.63%
			-0	
Epilepsy	5(8.9%)	6 (10.7%)	+1	1.96%
			-0	
AD/HD	10(17.9%)	15 (26.8%)	+5	10.9%
			-1	10%
Anxiety disorder	5(8.9%)	8(14.3%)	+3	5.88%
			-0	

Table 2.

Children's Sleep Habits Questionnaire (CSHQ) subscales, mean scores and standard deviations.

CSHQ Subscale	Time 1 *M* (*SD*)	Time 2 *M* (*SD*)	Increase (+)/ Decrease (-) from baseline.	*F*	*p*
Bedtime resistance	9.09 (4.25)	7.66 (2.88)	-	6.23	.016*
Sleep onset delay	2.64 (1.17)	2.16 (0.85)	-	8.95	.004**
Sleep duration	5.50 (2.66)	5.20 (2.03)	-	.81	.37
Sleep anxiety	6.73 (3.04)	5.84 (2.07)	-	5.72	.02*
Night wakings	4.75 (2.12)	4.23 (1.55)	-	4.98	.03*
Parasomnias	10.11 (3.02)	9.02 (2.04)	-	10.19	.002**
Sleep disordered breathing	3.45 (1.43)	3.70 (1.03)	+	3.08	.085
Daytime sleepiness	13.34 (4.34)	12.30 (3.47)	-	5.10	.028*

*$p<.05$ **$p<.01$

Table 3.

Gastrointestinal symptoms.

Gastrointestinal symptoms	Time 1 (*n*) (%)	Time 2 (*n*) (%)	Number participants gained/ lost symptoms	% Change
Abdominal Pain	45 (51.7%)	27 (48.3%)	+4	15.4%
			-8	27.6%
Diarrhea	40 (45.9%)	26 (46.4%)	+4	14.3%
			-6	22.2%
Constipation	43 (49.4%)	24 (42.9%)	+4	14.8%
			-9	32.1%
Bloating	22 (25.3%)	18 (32.1%)	+9	20.9%
			-4	33.3%
Nausea	26 (29.9%)	15 (26.8%)	+7	17.9%
			-9	56.3%

Table 4.

ASD-CC subscale means and standard deviations.

Subscale	Time 1 *M* (*SD*)	Time 2 *M* (*SD*)	Increase (+)/ Decrease (-) from baseline.	*F*	*p*
Tantrum behaviors	8.45 (4.24)	7.57 (3.83)	-	3.23	.078
Repetitive behaviors	6.96 (3.71)	6.04 (3.84)	-	3.16	.081
Worry/depressed	3.04 (2.72)	2.79 (2.58)	-	.83	.367
Avoidant behaviors	6.05 (2.92)	5.68 (2.96)	-	1.25	.269
Under-eating	.93 (1.52)	0.84 (1.59)	-	.25	.620
Conduct behaviors	1.68 (1.84)	1.32 (1.67)	-	2.71	.105
Over-eating	1.11 (1.64)	1.35(1.99)	+	9.08	.004**

**$p<.01$

Table 5.

Frequency, percentage and level of impairment of ASD-CC factor endorsements.

Factor	Level of impairment	Frequency	Percentage
Tantrum behaviors	No/Minimal	49	87.5%
	Moderate	3	5.4%
	Severe	4	7.1%
Repetitive behaviors	No/Minimal	40	71.4%
	Moderate	14	25%
	Severe	2	3.6%
Worry/depressed	No/Minimal	48	85.7%
	Moderate	7	12.5%
	Severe	1	1.8%
Avoidant behaviors	No/Minimal	32	57.1%
	Moderate	21	37.5%
	Severe	3	5.4%
Under-eating	No/Minimal	45	80.4%
	Moderate	6	10.7%
	Severe	5	8.9%
Conduct behaviors	No/Minimal	45	8.4%
	Moderate	8	4.3%
	Severe	3	5.4%
Over-eating	No/Minimal	38	67.9%
	Moderate	9	16.1%
	Severe	9	16.1%

Table 6.

Number of families with an autoimmune disease.

Autoimmune Disease	Number of families	Percentage
Osteoarthritis (Old Age Arthritis)	31	55.4%
Psoriasis	22	39.3%
Hypothyroidism (Hashimoto's thyroiditis)	18	32.1%
Rheumatoid arthritis (Onset after age 16)	15	26.8%
Hyperthyroidism (Graves' disease)	10	17.9%
Multiple miscarriages (3 or more)	10	17.9%
Ulcerative colitis	9	16.1%
Crohn's disease	9	16.1%
Rheumatic fever	8	14.3%
Multiple sclerosis	7	12.5%
Arthritis (Unsure of type)	6	10.7%
Vitiligo	5	8.9%
Childhood onset (Type 1) diabetes	4	7.1%
Psoriatic arthritis	3	5.4%
Multiple blood clots	3	5.4%

Table 7.

Number of families with at least one member with an autoimmune disease.

Relative	Number of families
Mother	19
Father	11
Brother	5
Sister	3
Grandmother	35
Grandfather	17
Uncle	8
Aunt	17
First Cousin	6
Other	23

Table 8.

Number of families with other disorders.

Disorder	Number of families	Percentage
Autism, Asperger's disorder or another Pervasive Developmental Disorder (PDD)	26	46.4%
AD/HD	25	44.6%
Major depression	22	39.3%
Intellectual disability	17	30.4%
OCD	10	17.9%
Anxiety disorder	10	17.9%
Bipolar disorder (Manic depression)	7	12.5%
Seizure disorder/Epilepsy	7	12.5%
Schizophrenia	4	7.1%
Celiac disease	4	7.1%

Table 9.

Number of families with at least one member with other types of disorders.

Relative	Number of families
Mother	13
Father	5
Brother	17
Sister	7
Grandmother	8
Grandfather	6
Uncle	11
Aunt	16
First Cousin	16
Other	20

Table 10.
Associations between family autoimmune disease and child comorbid condition.

Family Autoimmune Disease	Child Comorbid Condition	*r*	*p*
Hypothyroidism	Total GI symptoms	.27	.048*
	Bloating	.35	.009**
	Sleep Disordered Breathing (CSHQ)	.32	.018*
Hyperthyroidism	Total GI symptoms	.40	.002**
	Diarrhea	.41	.002**
	Constipation	.35	.008**
	Abdominal Pain	.30	.030*
	Anxiety Disorder	.34	.010*
Ulcerative colitis	Repetitive behavior (ASD-CC)	-.27	.040*
	Worry/depressed (ASD-CC)	.44	.001**
	Sleep Duration (CSHQ)	.39	.003**
	Daytime Sleepiness (CSHQ)	.33	.013*
Crohn's disease	Sleep Duration (CSHQ)	.30	.027*
	Worry/depressed (ASD-CC)	.26	.049*
	Repetitive Behavior (ASD-CC)	-.31	.020*
AD/HD	Anxiety Disorder	.35	.008**
	Total GI	.34	.010*
	Nausea	.27	. 046*
	Constipation	.31	.020*
	Sleep duration (CSHQ)	.31	.022*
	Daytime Sleepiness (CSHQ)	.40	.002**
Major Depression	Worry/depressed (ASD-CC)	.28	.036*
	Anxiety Disorder	.30	.025*
	Bedtime Resistance (CSHQ)	-.29	.031*
Bipolar Disorder	Worry/depressed (ASD-CC)	.37	.005**
	Daytime Sleepiness (CSHQ)	.34	.010*
	Intellectual Disability	-.27	.049*
OCD	Worry/depressed (ASD-CC)	.35	.008**
	Anxiety Disorder	.34	.010*
	Nausea	.35	.008**
	Sleep disordered breathing (CSHQ)	.37	.005**
Anxiety Disorder	Abdominal Pain	.39	.003**
Schizophrenia	Abdominal Pain	.29	.032*
	Bedtime Resistance (CSHQ)	.32	.015*
Autism, Asperger's or PDD	Daytime Sleepiness (CSHQ)	.29	.029*
Multiple blood clots	Conduct (ASD-CC)	.29	.031*
Multiple miscarriages	Intellectual Disability	.27	.049*
Rheumatoid arthritis	Intellectual Disability	-.36	.006**
Unsure of type of arthritis	Epilepsy	.44	.001**
Rheumatic fever	Sleep Duration (CSHQ)	.26	.049*

*$p<.05$
**$p<.01$