

Observational Study

Epidemiological Profile of Children with Neurodevelopmental Disorders in a Diagnostic Center in Southern Puerto Rico, 2006-2017

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ABSTRACT

Objective

This study has the purpose of developing an epidemiological profile of children with neurodevelopmental disorders in southern Puerto Rico.

Methods

This is an exploratory study with a mixed design that was carried out in a diagnostic center located in Ponce, Puerto Rico. The population under study were children within 0-18-years-old of both sexes diagnosed with a neurodevelopmental disorder using the diagnostic and statistical manual of mental disorders (DSM-4) and DSM-5 criteria. The sample under investigation were all the children in the secondary database of children who received health services in the diagnostic center during 2016-2017. Additionally, to the data from the secondary database, a hand-writing record review was performed to obtain data related to comorbidities and family history. The bivariate and multivariate analysis evaluated the association between each neurodevelopmental disorder, and each disease reported in the family history of diseases. Also bivariate, and multivariate analysis assessed the association between each neurodevelopmental disorder, and each comorbidity reported.

Results and Conclusion

The mean age and standard deviation of the sample were 5.2 ± 3.20 , and 80.5% were males. Most of the children lived in Ponce, Puerto Rico. The sample size did not have normal distribution because the sample size was too small and selected by non-probabilistic methods. Furthermore, 88.2% of the children received a previous evaluation related to the problem, and 70.5% received treatment for the symptoms. The results revealed that neurodevelopmental disorders frequently co-occurred. Also, other comorbidities commonly co-occurred with these disorders. Mental disorders were commonly reported with autism, attention deficit and hyperactivity disorder (ADHD) and communication disorders. Autism was also linked to a family history of mental disorders.

Keywords

Childhood; Neurodevelopmental disorder; Disabilities; Developmental delays.

INTRODUCTION

Neurodevelopmental disorders (NDDs) are a group of conditions that a child may be born with or develop during childhood¹ are characterized by impairments in cognition, communication, behavior, and/or skills resulting from abnormal brain development.² This group of conditions may cause disability dur-

ing the life of the child.³ Social, academic, and occupational functions are some of the aspects that may be affected in their lives.¹ Also, children affected by NDD may experience delays or deficits in achieving developmental milestones.¹ According to international classification of diseases-11 (ICD-11), NDD are disorders of intellectual development, developmental speech or language disorders, attention deficit, and hyperactive disorder, stereotyped movement

disorders, motor coordination disorders, developmental learning disorders, autism and other NDDs.⁴

NDDs can have similar symptoms⁵ or overlap in common symptoms of most co-occurrence which are related to cerebral dysfunction and cognitive problems. Also, poor motor abilities can be present in children with NDD affecting academic achievement.⁶ Furthermore, many of these children can present aggressive behaviors and sensory processing problems.^{7,8} Prevalence of NDDs' in males twice the prevalence in females.⁹ The two most prevalent NDDs' in the United States are autism spectrum disorder (ASD) and attention deficit and hyperactivity disorder (ADHD).¹⁰

The NDDs' can co-occur¹¹ as well as, these children can suffer from other comorbidities.¹² Other mental and physical diseases can be present, along with NDD. Furthermore, studies found a higher prevalence of psychiatric disorders in the family history of diseases of children with autism. A study concluded that the psychiatric disorders in parents of children with autism were higher compared to the parents of children without autism.¹³ Another study found that bipolar disorder in both parents increased the risk in the offspring.¹⁴ Also, another study in Denmark concluded that the history of any psychiatric disorder increased the risk of autism and suggested that the cause is a genetic link between schizophrenia and autism.¹⁵

Furthermore, in the United States in 1999, researchers found that children were twice more at risk of developing ASD in families where two or more family members had an auto-immune disease,¹⁶ this finding was confirmed by Hughes et al.¹⁷ The families with three or more members were 5.5 more likely, and the children whose mother suffered from an auto-immune illness were 8.8 more likely at risk of developing ASD. Asthma and allergies are two auto-immune diseases strongly associated¹⁸ with ASD. However, a meta-analysis was conducted to evaluate the association between suffering from asthma and autism. The study assessed the odds ratio (OR) from ten studies. However, although asthma may have a high prevalence in children with autism, no association was found.¹⁹

This study had the purpose of developing an epidemiological profile of children with NDD in southern Puerto Rico. Also, this study sought to identify the clinical characteristics and family history of disease in close relation to the individuals. Furthermore, to evaluate the association between comorbidities reported and family history of diseases reported with the NDD.

MATERIALS AND METHODS

This study is an exploratory study with a cross-sectional design carried out in a diagnostic center located in Ponce, Puerto Rico. Univariate analysis was performed to describe the sample under study. Bivariate and multivariate analyses were performed to determine associations between comorbidities, family history of conditions, and NDDs'. The study was approved by Ponce Health Sciences University Institutional Review Board (IRB).

Sample

The population under study was obtained from a secondary data-

base created previously to the study in a diagnostic center in southern, Puerto Rico. The population sample sought was for children up to 18-years-old of both sexes with a NDD using either the diagnostic and statistical manual of mental disorders-4 (DSM-4) or DSM-5 published diagnostic criteria. All children in the database were considered for inclusion in the sample. Two hundred fifty-seven (257) children were ultimately deemed appropriate for analysis.

Data Collection

A secondary database created independently and prior to the study was explored for the analysis. This database was created using a single, unified data collection instrument based on several tools title "initial interview." In the approach designed, a social worker interviews the child's caregiver as a first approach using this questionnaire in the diagnostic center under study. The interview collects data about socio-demographic information, clinical history, and family history of diseases. Furthermore, a hand-writing record review was performed to obtain data related to the principal diagnosis of the children and comorbidities reported. The "Interdisciplinary Diagnostic Certification of the ASD" on the records was used to obtain the final diagnosis, comorbidities, and possible observations based on the DSM-4 for the cases evaluated before 2013 and DSM-5 for the cases evaluated after 2013. Also, the case report form document was used to collect and confirm sociodemographic variables of interest. Chart review provided an official principal diagnosis of any children included in the study.

Statistical Analysis

The statistical program used to perform the quantitative analysis was statistical package for the social sciences (SPSS) version 26. Forty-eight (48) cases were excluded out of two hundred fifty-seven subjects in the database. One child was excluded from the sample because it was a repeated case, and forty-seven were excluded due to missing information. Missing values were taken into consideration to perform the analysis. A Kolmogorov-Smirnoff test was performed to determine if the sample had a normal distribution because small samples in a study sometimes did not have a normal distribution.²⁰ In the database, each condition reported appeared classified into categories. The categories available were developmental problems, neurological disorders, chronic diseases, mental diseases, and mental retardation. The variables were re-categorized because all the diseases appeared as an open fill. Each condition reported in the family was created as a dichotomous variable (Yes/No) to perform the bivariate and multivariate analysis.

Fisher's exact test evaluated the associations between each NDD and each comorbidity reported, such as ASD, ADHD, mental disorder, and the association between each NDD and each disease reported in the family history of diseases. A multivariate analysis was performed through logistic regression to evaluate the odds of presenting each comorbidity among children with ASD as compared with other NDDs' adjusted by age and sex. Children with autism were used as a reference group for the bivariate and multivariate analysis.

RESULTS

The mean age and standard deviation of the sample were 5.2 ± 3.20 , and 80.5% were males. Most of the children lived in Ponce, Puerto Rico. The normality test (Kolmogorov-Smirnov) performed revealed a statistical significance of 0.000, indicating that the sample does not have a normal distribution. Furthermore, 88.2% of the children received a previous evaluation related to the problem, and 70.5% received some treatment for the symptoms before coming to the diagnostic center. The most-reported previous diagnostic evaluations were speech and language, psychological and occupational. The most-reported previous treatments were therapies, psychological treatment, and prescription drugs. The frequency of children by NDD diagnosis were calculated considering the missing values. There was no identified primary diagnosis for thirty-four children. 71.7% ($n=160$) autism spectrum disorder and 14.8% ($n=33$) were primarily diagnosed with communication disorder. These disorders represented 87% of all disorders identi-

fied. Other disorders diagnosed in the center were ADHD (5.8% ($n=13$)), global developmental delay (3.1% ($n=7$)), motor disorder (1.8% ($n=4$)), learning disorder (1.8% ($n=4$)) and intellectual disability (0.9% ($n=2$)) (Figure 1).

Regarding the comorbidities, the two more reported were sensory problems (24.9%) and mental problems (24.9%). The two less reported comorbidities were cardiovascular diseases (0.5%) and vision problems (0.5%) (Table 1).

The most-reported diseases in family history were developmental problems ($n=160$) and chronic conditions ($n=161$) (Figure 2).

The comorbidities and diseases most reported for each NDD and also reported in family history were given consideration. In children with autism, other NDD's were reported. Also, mental disorders and sleep problems were present in this sample of

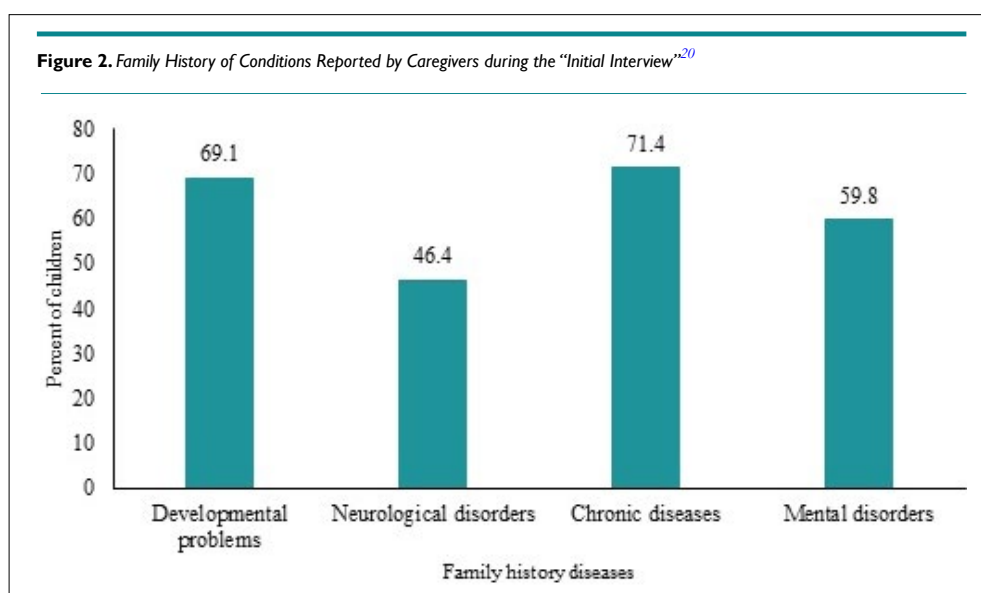
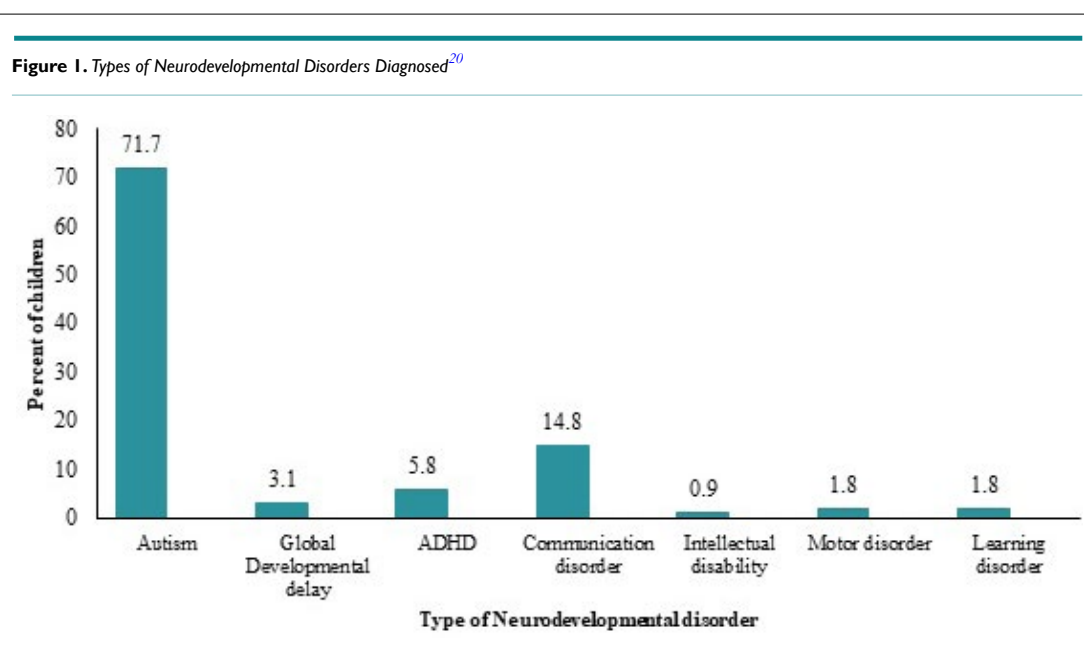


Table 1. Comorbidities Report²⁰

Comorbidity Diagnosed	n	Percentage (%)
Sensory problems	52	24.9
Mental disorders	52	24.9
Feeding problems	6	2.9
Gastrointestinal problems	6	2.9
Metabolism disorder	5	2.4
Sleeping problems	5	2.4
Asthma	5	2.4
Allergies	5	2.4
Problems in diary skills	4	1.9
Audition problems	2	1.0
Neurologic disorders	2	1.0
Dysphagia	2	1.0
Cardiovascular diseases	1	0.5
Vision problems	1	0.5

Table 2. Association between Autism Spectrum Disorder and Comorbidities Reported²⁰

Comorbidities Reported	Autism n (%)	Other NDDs' n (%)	Unadjusted OR (CI)	Adjust OR (CI)	p Value
ADHD					
Yes	36(25.2%)	10(15.2%)	1.8 [0.871-4.07]	1.0 [0.460-2.4]	0.888
No	107(74.8%)	56(84.8%)			
Communication Disorder					
Yes	103(72.0%)	16(13.4%)	8.0 [4.1-15.7]	6.9 [3.2-15]	0.000
No	40(28.0%)	50(75.8%)			
Motor Disorder					
Yes	52(36.4%)	13(19.7%)	2.3 [1.16-4.6]	2.1 [0.987-4.8]	0.05
No	91(63.6%)	53(80.3%)			
Learning Disorder					
Yes	17(11.9%)	8(12.1%)	0.97 [0.399-2.39]	0.467 [0.151-1.4]	0.185
No	126(88.1%)	58(87.9)			
Sensory Problems					
Yes	38(26.6%)	14(21.2%)	1.3 [0.669-2.6]	1.0 [0.487-2.4]	0.835
No	105(73.4%)	52(78.8%)			
Mental Disorder					
Yes	22(15.4 %)	30(45.5%)	0.21 [112-.0424]	0.17 [0.079-0.373]	0.00
No	121(84.6%)	36(54.5%)			
NDD's: Neurodevelopmental disorders; CI: Confidence intervals; Adjusted by age and sex by each comorbidity reported					

children. A statistically significant association was found between autism and communication disorder (OR=6.9; IC 95%. 3.2, 15). Also, the analysis revealed that there exists a statistically significant association between autism and motor disorder (OR=2.18; IC 95% 987, 4.8). Furthermore, there exists an association between mental disorders and autism (OR=0.71; 0.079-0.373) (Table 2).

In children with ADHD, a communication disorder were reported. Another comorbidity reported was mental disorders. Furthermore, a statistically significant (p -value=0.002) association between ADHD and mental problems (OR=0.028; IC 95% 0.003, 0.27) was found (Table 3).

In children with a communication disorder (CD), motor disorders were reported (21.2%). Other comorbidities, mostly reported in children with CD were sensory problems and mental disorders. Besides, communication disorders and mental disorders (OR=0.35; IC 95% 12, 0.98) are associated (Table 4).

Regarding the family history of diseases, in children with Autism, a family history of NDD's was reported. The NDD's reported in family history was autism, speech and language disorders (LDs'), learning disorder (LDs'), and ADHD. Also, other chronic diseases were present in the family history.

Table 3. Association between Children with Attention Deficit Disorder and Other²⁰

Comorbidities Reported	Autism n (%)	Other NDDs' n (%)	Unadjusted OR (CI)	Adjust OR (CI)	p Value
Communication Disorder					
Yes	103(72.0%)	6(46.2%)	3.0 [0.95-9.4]	0.61 [0.09-3.9]	0.609
No	40(28.0%)	7(53.8%)			
Mental Disorder					
Yes	22(15.4%)	11(84.6%)	0.03 [0.007-0.15]	0.03 [0.03-0.27]	0.002
No	121(84.6%)	2(15.4%)			
DHD, Attention Deficit and Hyperactivity Disorder; CI, Confidence Intervals; Adjusted by age and sex by each comorbidity reported					

Table 4. Association between Children with a Communication Disorder and Other²⁰

Comorbidities Reported	Autism n (%)	Other NDDs' n (%)	Unadjusted OR (CI)	Adjust OR (CI)	p Value
Motor Disorder					
Yes	52(36.4%)	7(21.2%)	2.1 [0.86-5.2]	2.7 [0.91-8.1]	0.072
No	91(63.6%)	26(78.8%)			
Sensory Problems					
Yes	38(26.6%)	8(24.2%)	1.1 [0.47-2.7]	0.80 [0.27-2.3]	0.700
No	105(73.4%)	25(75.8%)			
Mental Disorder					
Yes	22(15.4%)	12(36.4%)	0.31 [0.137-0.739]	0.35 [0.12-0.98]	0.046
No	121(84.6%)	21(63.6%)			
CD: Communication disorder; CI: Confidence Intervals, Adjusted ORs' were adjusted by age and sex by each comorbidity reported					

DISCUSSION

The results in our sample revealed that most of the children who came for diagnosis and treatment to the diagnostic center were males. That coincided with Boyle et al⁹ research, where they conclude NDD male prevalence as twice female prevalence. Most of the children lived in Ponce, but the town of residence of many children was unknown. The majority of the children were older than three-years-old, and the mean age was 5.2±3.20-years. That coincides with Arora et al²¹ study, where they conclude that the higher prevalence of children with NDD in India was between 6-9-years-old. However, APA¹ established that frequently the first symptoms onset in early development often before starting school. There were no differences between the mean ages by sex.

In the sample studied, 88.2% had already received a previous evaluation related to concerns expressed by the parents. The most-reported previous diagnostic assessments were speech and language, psychological and occupational. Also, 70.5% reported received in the past some formal treatment for the symptoms. The most-reported previous treatments were therapies, psychological treatment, and prescription drugs. This means that most children have a previous finding or concern evaluated by the parents before reaching a final diagnosis of a neurodevelopmental condition. In the United States, ASD and ADHD are the most common NDD diagnosed.¹⁰

ASD was the most diagnosed followed by CD and ADHD. NDDs can co-occur with each other.^{1,11} Our findings show the co-occurrence between them. In children with autism, communication disorders and motor disorders were reported. Our results confirmed that because CD was reported in children with ADHD.

The children with ASD have 6.9 times more possibilities of reporting CD and 2.18 times more possibilities of reporting motor disorder (MD) than children with other NDDs. Furthermore, results revealed that children with ASD have 0.112 times fewer chances of reporting ADHD than children with global developmental delay (GDD). Other comorbidities reported in the sample were sensory processing problems, sleep problems, and mental disorders.

Holland⁸ and Blackmer et al²² coincide with our findings that children with a NDD can present sleep problems. In this study, sleep disorders/problems were reported in children with autism and communication disorders. Also, in children with autism, asthma and allergies were reported. Nevertheless, no association was found. These findings coincide with the meta-analysis carried out in 2016 in which they found no association between the two conditions and ASD.¹⁸ It must be taken into consideration that were a few reports of these comorbidities in our sample.

In addition, mental disorders are associated with ASD, ADHD Communication disorder, and Learning disorder. Children with autism have 83% fewer possibilities of reporting a mental disorder than children with other NDDs. Besides, children with autism have 98% fewer chances of reporting a mental disorder than children with ADHD and 65% fewer possibilities of reporting a mental disorder than children with a communication disorder. Furthermore, children with autism have 93% fewer possibilities for reporting a mental disorder than children with a learning disorder.

Also, some diseases in family history can increase the possibility of reporting NDD. According to Comi et al¹⁶ exists an association between family history of asthma, allergies, and autism. A family history of asthma was reported in children with autism and communication disorder, but no association was found. Other studies found an association between mental disorders and autism.^{10,12-14} These studies found the mental disorders increase the risk of autism. In this study, the analysis found the opposite.

A family history of mental disorders is associated with autism but as a protective factor. Children with autism have 51% fewer possibilities of reporting a family history of mental disorders than children with other NDDs. Besides, children with autism have 3.76 more chances of reporting a family history of diabetes than children with CD. Regarding qualitative analysis, the caregivers expressed their concerns regarding the symptoms and signs presented in the children.

CONCLUSION

In this study, most of the children were in early childhood when they came for diagnosis and treatment. Furthermore, males were the most diagnosed with NDDs. The most diagnosed disorder was autism. NDDs co-occurred. Also, other comorbidities co-occurred with these disorders. Family history of developmental problems and chronic diseases were leading conditions reported by caregivers. The caregivers stated that onset symptoms were the cause of worry; some of the symptoms include developmental milestones delay, communication, and social interaction deficits, aggressive behavior, and deficits in intellectual functions.

STRENGTHS AND LIMITATIONS

This study is the first study carried out in a diagnostic center in the south of Puerto Rico to evaluate NDDs. This study is an exploratory study that can serve as a base study for other epidemiological studies. However, this study has several limitations. The first limitation is the selection of the sample was by a no-probabilistic method. For that reason, our findings and conclusions cannot be extrapolated to the general population. The second limitation identified was the incomplete information for some of the variables under study. The third limitation identified was the information obtained from the secondary database was based on self-reports. And the fourth limitation was the instrument utilized to get the information for the secondary database was not designed for research purposes (mostly qualitative).

PUBLIC HEALTH RELEVANCE

This study is critical because it helps to understand the clinical characteristics, concerns, and needs of children with NDD and their caregivers. This study is a basis for further studies related to these disorders. More studies are required to support the development of better intervention programs for these children and their families.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

All authors have read and approved the final article. All consent to the publication of this article.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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AUTHOR CONTRIBUTIONS

Accountability

Laura Deliz Bauzá and Luisa Morales had full access to all of the data in the study and assume responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and Study Design

María Pacheco, Iris Martínez and Luisa Morales.

Acquisition of Data

María Pacheco.

Analysis and Interpretation of Data

María Pacheco, Iris Martínez and Luisa Morales.

Drafting of the Manuscript

María Pacheco, Laura Deliz.

Critical Revision of the Manuscript for Important Intellectual Content

Laura Deliz, Luisa Morales.

Statistical Analysis

María Pacheco, Iris Martínez and Luisa Morales.

Acquisition of Funding

Luisa Morales.

Study Supervision

Laura Deliz and Luisa Morales.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

- American Psychiatric Association (APA). *Neurodevelopmental Disorders*. Washington DC, USA: New School Library; 2013.
- Mullin AP, Gokhale A, Moreno-De-Luca A, Sanyal S, Waddington JL, Faundez V. Neurodevelopmental disorders: Mechanisms and boundary definitions from genomes, interactomes and proteomes. *Transl Psychiatry*. 2013; 3(12): e329. doi: [10.1038/tp.2013.108](https://doi.org/10.1038/tp.2013.108)
- America's Children and the Environment (ACE). Health: Neurodevelopmental disorders. 2015. Web site. <https://www.epa.gov/americaschildrenenvironment/ace-health-neurodevelopmental-disorders>. Accessed December 9, 2021.
- Stein DJ, Szatmari P, Gaebel W, et al. Mental, behavioral and neurodevelopmental disorders in the ICD-11: And international perspective on key changes and controversies. *BMC Medicine*. 2020; 18(21). doi: [10.1186/s12916-020-1495-2](https://doi.org/10.1186/s12916-020-1495-2)
- Van Loo KMJ, Martens GJM. Genetic and environmental factors in complex neurodevelopmental disorders. *Curr Genomics*. 2007; 8(7): 429-444. doi: [10.2174/138920207783591717](https://doi.org/10.2174/138920207783591717)
- Higashionna T, Iwanaga R, Tokunaga A, et al. Relationship between motor coordination, cognitive abilities, and academic achievement in Japanese children with neurodevelopmental disorders. *Hong Kong J Occup Ther*. 2017; 30: 49-55. doi: [10.1016/j.hk-jot.2017.10.002](https://doi.org/10.1016/j.hk-jot.2017.10.002)
- Centers for Disease Control and Prevention (CDC). Disability and safety: Aggressive behavior and violence. 2018a. Web site. <https://www.cdc.gov/ncbddd/disabilityandsafety/aggression.html>. Accessed December 9, 2021.
- Holland K. Understanding sensory issues in children. Web site. <https://www.healthline.com/health/childrens-health/sensory-issues-in-children>. Accessed September 20, 2019.
- Boyle CA, Boulet S, Scheleve LA, et al. Trends in the prevalence of developmental disabilities in US children, 1997-2008. *Pediatrics*. 2011; 6: 1034-1042. doi: [10.1542/peds.2010-2989](https://doi.org/10.1542/peds.2010-2989)
- National Center on Birth Defects and Developmental (NCBDD). Increase in developmental disabilities among children in the United States. 2019. Web site. <https://www.cdc.gov/ncbddd/developmentaldisabilities/features/increase-in-developmental-disabilities.html>. Accessed September 26, 2019.
- Megan-Cleaton MA, Kirby A. Why do we find it so hard to calculate the Burden of neurodevelopmental disorders? *Journal of Childhood & Developmental Disorders*. 2018; 4(3). doi: [10.4172/2472-1786.100073](https://doi.org/10.4172/2472-1786.100073)
- Alabaf S, Gillberg C, Lundstrom S, et al. Physical health in children with neurodevelopmental disorders. *J Autism Dev Disord*. 2019; 49: 83-95. doi: [10.1007/s10803-018-3697-4](https://doi.org/10.1007/s10803-018-3697-4)
- Daniels JL, Forssen U, Hultman CM, et al. Parental psychiatric disorders associated with autism spectrum disorders in the offspring. *Pediatrics*. 2008; 121(5): e1357-1362. doi: [10.1542/peds.2007-2296](https://doi.org/10.1542/peds.2007-2296)
- Sullivan P, Magnusson C, Reichenberg A, et al. Family history of schizophrenia and bipolar disorder as risk factors for Autism. *Arch Gen Psychiatry*. 2012; 69: 1099-1103. doi: [10.1001/archgenpsychiatry.2012.730](https://doi.org/10.1001/archgenpsychiatry.2012.730)
- Larsson, H. J., Eaton, W. W., Madsen, K. M., et al. Risk factors for autism: Perinatal factors, parental psychiatric history, and socioeconomic status. *Am J Epidemiol*. 2005; 161(10): 916-925; discussion 926-918. doi: [10.1093/aje/kwi123](https://doi.org/10.1093/aje/kwi123)
- Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *J Child Neurol*. 1999; 14(6): 388-394. doi: [10.1177/088307389901400608](https://doi.org/10.1177/088307389901400608)
- Hughes H, Mills Ko E, Destanie B, Ashwood P. Immune dysfunction and autoimmunity as pathological mechanism in autism spectrum disorder. *Front Cell Neuroscience*. 2018; 12: 405. doi: [10.3389/fncel.2018.00405](https://doi.org/10.3389/fncel.2018.00405)
- Croen LA, Grether JK, Yoshida CK, Odouli R, Hendrick V. Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch Gen Psychiatry*. 2011; 68(11): 1104-1112. doi: [10.1001/archgenpsychiatry.2011.73](https://doi.org/10.1001/archgenpsychiatry.2011.73)
- Zheng Z, Zhang L, Zhu T, Huang J, Qu Y, Mu D. Association between asthma and autism spectrum disorder: A meta-

analysis. *PLoS One*. 2016; 11(6): e0156662. doi: [10.1371/journal.pone.0156662](https://doi.org/10.1371/journal.pone.0156662)

20. Pacheco M, Bauza LD, Martinez I, Morales L. Epidemiological profile of children with neurodevelopmental disorders in a diagnostic center in Southern Puerto Rico, 2006-2017. 2021; 1-22. doi: [10.21203/rs.3.rs-789641/v1](https://doi.org/10.21203/rs.3.rs-789641/v1)

21. Arora S, Ge R, Neyshabur B, Zhang Y. *Stronger Generalization Bounds for Deep Nets via a Compression Approach*. NY, USA; Cornell University; 2018.

22. Blackmer J, Biyani P, Tsioutsoulis K. "8 amazing secrets for getting more clicks": Detecting clickbaits in news streams using article informality. Paper presented at: AAAI Conference on Artificial Intelligence. California, USA: 2016.