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Association of Cerebral Palsy with Autism and Attention Deficit Hyperactivity Disorder in Children: A Large-Scale Nationwide Population-Based Study

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Supplementary Table. Sensitivity analysis for the association of cerebral palsy with ASD and ADHD in US children, whose information was reported by their parents (n=152043).

	OR (95% CI)		P-value
	Without cerebral	**With cerebral palsy**	
ASD			
No. of cases/total	1797/151548	28/495	
Model 1[a]	1.00 (reference)	5.02 (3.05-8.27)	<0.001
Model 2[b]	1.00 (reference)	4.77 (2.89-7.86)	<0.001
ADHD			
No. of cases/total	11570/151548	87/495	
Model 1[a]	1.00 (reference)	2.01 (1.43-2.81)	<0.001
Model 2[b]	1.00 (reference)	1.84 (1.28-2.65)	<0.001

[a] Model 1: adjusted for age and sex.

[b] Model 2: model 1 plus race/ethnicity, family highest education level, family income to poverty ratio, and geographic region.

Association of Cerebral Palsy with Autism and Attention Deficit Hyperactivity Disorder in Children: A Large-Scale Nationwide Population-Based Study

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ABSTRACT

Objective To examine the association of cerebral palsy with ASD and ADHD, providing

evidence for interdisciplinary medical service for children with cerebral palsy.

Design A large-scale nationwide population-based study.

Setting the National Health Interview Survey (NHIS).

Patients 177899 children aged 3-17 years old among NHIS participants from 1997 to 2003

and 2008 to 2018.

Results Among the 177899 children included in this analysis, 602 (0.33%) had cerebral

palsy, 1997 (1.16%) had ASD, and 13697 (7.91%) had ADHD. Compared to children

without cerebral palsy, children with cerebral palsy had a higher prevalence of ASD (6.09%

versus 1.15%; $P < 0.001$) and ADHD (15.91% versus 7.89%; $P < 0.001$). After adjustment

for age, sex, race/ethnicity, family highest education level, family income level, and

geographical region, the OR among children with cerebral palsy, compared with children

without cerebral palsy, was 5.07 (95% CI 3.25-7.91) for ASD ($P < 0.001$) and 1.95 (95% CI

1.43-2.66) for ADHD ($P < 0.001$). Furthermore, the association of cerebral palsy with ASD

and ADHD remained significant in all subgroups stratified by age, sex and race.

Conclusions In a large, nationally representative sample of US children, this study shows

that children with cerebral palsy are at an increased risk of ASD and ADHD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Children with cerebral palsy are more likely to have cognitive impairment. Besides, neurodevelopmental disorders, including intellectual disability and learning disability, are well documented comorbid conditions among children with cerebral palsy.

WHAT THIS STUDY ADDS

This study quantified the odds ratios of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) among children with cerebral palsy, compared with children without cerebral palsy. Furthermore, the association of cerebral palsy with ASD and ADHD remained significant in all subgroups stratified by age, sex and race.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

Cerebral Palsy, ASD and ADHD are usually diagnosed in different clinical specialties, with different intervention approaches. Therefore, This study provides evidence of their co-occurrence risk, and informs better interdisciplinary clinic care.

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INTRODUCTION

Cerebral palsy is a neurological disorder of motor impairment that results from non-progressive disturbances during brain development in fetuses or infants [1, 2]. It is a major cause of childhood disability. Worldwide, prevalence estimates for cerebral palsy ranged from 1.5 to more than 4 per 1000 live births or children of a defined age range [3]. Cerebral palsy varies in the timing of the lesion, the clinical presentation, and the site and severity of the impairments [1]. The multifactorial etiology of cerebral palsy may involve any insults with a negative impact on the developing fetal or neonatal brain, such as preterm birth, fetal growth restriction, multiple gestation, intrauterine infection, birth asphyxia, untreated maternal hypothyroidism, congenital malformations, and perinatal stroke [3, 4]. Most children with cerebral palsy have an abnormal brain magnetic resonance imaging (MRI) scan, including white matter damage, basal ganglia or deep grey matter damage, congenital malformation, and focal infarcts [5]. Motor disorders in cerebral palsy are often associated with disturbances of sensation, perception, cognition, communication, behavior, and epilepsy [6]. Individuals with cerebral palsy have increased risk for emotional lability, irritability, impulsiveness, and behavioral problems [7]. Neurodevelopmental disorders, including intellectual disability and learning disability, are well documented comorbid conditions among children with cerebral palsy.

Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) are childhood-onset neurodevelopmental disorders with a worldwide prevalence of 1% and 5%, respectively [8]. ASD is characterized by repetitive behaviors and restricted interests, social impairments, and communication difficulties [9, 10], and ADHD is characterized by persistent and impairing inattention, hyperactivity, and impulsivity.[11] Comorbidity and

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overlapping traits between ASD and ADHD are common [8, 12, 13]. Moreover, previous clinical and epidemiological studies reported that the prevalence of ASD and ADHD was higher in children with cerebral palsy, compared to children without cerebral palsy [6]. Recently, the UK National Institute for Health and Care Excellence Clinical Guideline on cerebral palsy underlined the importance of investigating the prevalence of ASD and ADHD in children and young people with cerebral palsy.[5] ASD and ADHD are interrelated neurodevelopmental disorders and they may share pathological mechanisms and clinical features with cerebral palsy [14]. However, there has been no quantitative assessment about the association (i.e., odds ratio or risk ratio) of cerebral palsy with ASD and ADHD. This may be due to the limited sample size (up to 2000) in previous studies [6], which precludes a robust estimation of the association between relatively rare conditions such as cerebral palsy and most neurodevelopmental disorders.

In this study, we analyzed large population-based data to quantify the association of cerebral palsy with ASD and ADHD, in a nationally representative sample of US children.

METHODS

Research Ethics Approval Statement

The NHIS was approved by the Research Ethics Review Board of the NCHS and the U.S. Office of Management and Budget. All respondents provided oral consent prior to participation. The University of Science and Technology of China Institutional Review Board determined that the present study was exempt based on the use of deidentified data and approved the manuscript submission (ID: 202112241025000533025).

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Study Population

The National Health Interview Survey (NHIS), conducted annually by the Centers for

Disease Control and Prevention, is a leading health survey in the United States [15]. It has

become the principal source of information on health of the civilian noninstitutionalized

population of the United States. Annual sample size of the NHIS is about 35,000 households

containing about 87,500 persons. The NHIS collects data on a broad range of health topics

for all household members, including children, through in-person household interviews. The

NHIS has a large sample size and a relatively high response rate.

In the current analysis, we included 177899 children aged 3-17 years old among

participants in the NHIS from 1997 to 2003 and 2008 to 2018. A previous study indicated

that there was high likelihood of interviewer error for cerebral palsy in 2004-2007 arising

from a questionnaire change during those years [16], therefore, we excluded survey years from

2004 to 2007 in the current analysis.

Ascertainment of Cerebral Palsy and Neurodevelopmental Outcomes

For each interviewed family in the household, one sample child (if any children aged

≤ 17 years are present) is randomly selected through the field representative's computer

program, and no differential sampling probabilities are applied to the children [17]. Detailed

health-related information, including information on physical and mental health, is collected

for the sample child. This information is provided by an adult (usually a parent) who is

knowledgeable about the child's health.

Cerebral palsy was defined based on an affirmative response (i.e., yes) to the question

[18]: "Has a doctor or health professional ever told you that [the sample child] had cerebral

palsy?" ASD was defined based on an affirmative response to a question asking whether the

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sample child received a diagnosis of ASD from a physician or other health professional.[19]

From 1997 to 2013, this question was asked as part of a 10-condition checklist. In 2014

onward, the question became a stand-alone item and the wording was revised to name

specific conditions, including autism, Asperger disorder, pervasive developmental disorder,

and ASD. ADHD was defined based on an affirmative response (i.e., yes) to the question:[20]

"Has a doctor or health professional ever told you that [the sample child] had attention-

deficit/hyperactivity disorder (ADHD) or attention-deficit disorder (ADD)?"

Covariates Assessment

Information on age, sex, race/ethnicity, family highest education level, family income,

and geographic region was collected using standardized questionnaire during the interview.

Race and Hispanic ethnicity were self-reported and classified based on the 1997 Office of

Management and Budget Standards. Family highest education level was classified into less

than high school, high school, and college or higher. Family income levels were classified

according to the ratio of family income to federal poverty level (<1.0, 1.0-1.9, 2.0-3.9, and $\geq$

4.0).

Statistical Analysis

We included survey sampling weights, strata, and primary sampling units in all the

analyses to account for the unequal probabilities of selection, oversampling, and nonresponse

in the complex survey design. Therefore, the results in this study are nationally representative

of the US children. Comparisons of baseline characteristics among children with and without

cerebral palsy were performed using linear regression for continuous variables and the chi-

square test for categorical variables. We estimated the odds ratio (OR) and 95% confidence

interval (CI) of ASD, ADHD, and other neurodevelopmental disabilities according to history

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of cerebral palsy diagnosis using multivariable logistic regression, adjusting for age, sex, race/ethnicity, family highest education level, family income to poverty ratio, and geographic region. All data analyses were conducted using survey procedures of SAS 9.4 (SAS Institute Inc., Cary, NC). Two-sided P<0.05 was considered statistically significant.

RESULTS

Among the 177899 children of 3-17 years included in this analysis, 602 (0.33%) had cerebral palsy, 1997 (1.16%) had ASD, and 13697 (7.91%) had ADHD. Children with cerebral palsy were more likely to be male and more likely to have lower family income than those without cerebral palsy (**Table 1**).

Compared with children without cerebral palsy, children with cerebral palsy had a higher prevalence of ASD (6.09% [95% CI 3.56-8.62] versus 1.15% [95% CI 1.07-1.22]; P < 0.001) and ADHD (15.91% [95% CI 12.07-19.75] versus 7.89% [95% CI 7.72-8.06]; P < 0.001). After adjustment for age, sex, race/ethnicity, family highest education level, family income level, and geographical region, compared with children without cerebral palsy, the OR among children with cerebral palsy was 5.07 (95% CI 3.25-7.91) for ASD (P < 0.001) and 1.95 (95% CI 1.43-2.66) for ADHD (P < 0.001) (**Table 2**). These associations remained significant in stratified analyses by age, sex, and race/ethnicity. The association between cerebral palsy and ADHD appeared to be stronger among non-whites (2.92 [1.85-4.59]) than whites (1.51 [1.00-2.26]) (P for interaction = 0.03) (**Table 3**). There was suggesting evidence that the association between cerebral palsy and ASD may differ according to age and sex, which warrants further investigation in future studies with even larger number of participants.

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In a sensitivity analysis among children (n=152043) whose information was reported by their parents rather than other members in the household, the results were similar to our main results (**Supplementary Table**).

DISCUSSION

Using data from a large nationwide population-based study, we found a significant and positive association of cerebral palsy with ASD and ADHD. Compared with children without cerebral palsy, children with cerebral palsy were at five-fold and doubled risk for ASD and ADHD, respectively. The associations persisted after adjustment for age, sex, race/ethnicity, family highest education level, family income level, and geographical region.

To our knowledge, although previous studies have reported a higher prevalence of ASD and ADHD in children with cerebral palsy than in children without cerebral palsy [6], no previous study has quantified the association (i.e., odds ratio or risk ratio) of cerebral palsy with ASD and ADHD in children. The significant association of cerebral palsy with ASD and ADHD is not surprising, because all these conditions result from impairment of certain functions in the brain. Cerebral palsy, ASD and ADHD may share early-life risk factors that may affect brain development during pregnancy and in infancy. Prematurity birth is the most prevalent risk factor for cerebral palsy [21]. In a previous study of 213 children diagnosed with cerebral palsy in Australia, 78% had a history of prematurity birth [22]. Prematurity birth has been associated with increased risk of ASD [23, 24] and ADHD [25]. Maternal infection, another common risk factor for cerebral palsy [26-29], has been associated with risk of ASD [30]. Maternal obesity was significantly associated with not only increased risk of cerebral palsy [31], but also increased risk of ASD and ADHD [32-34]. Perinatal hypoxic-ischemic conditions, an important

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cause of cerebral palsy [35], was also related to increase risk of ASD [36] and ADHD [37]. In addition, low Apgar score at birth was also associated with higher risk for cerebral palsy[38] and ASD [39].

This study has some strengths. First, it was based on a large, multi-racial/ethnic population. The large sample size improves the statistical power and robustness of the estimates, which is critical for assessing the association of rare exposure and outcomes such as cerebral palsy and most neurodevelopmental disorders. Second, the NHIS uses in-person household interviews for data collection. As a result, the questionnaire completeness in the NHIS is extraordinarily high, with more than 99% of participants responded to the questions regarding diagnosis of cerebral palsy and neurodevelopmental disorders. Third, the use of a nationally representative sample of US population facilitates better generalizability of the findings to a broader population. There are several limitations of this study. First, information on physician's diagnosis of cerebral palsy and neurodevelopmental disorders was self-reported, which may subject to misreporting and recall bias. Second, the gold standard methods for diagnosing ASD or ADHD are not suitable for children with motor problems [6]. Third, we could not assess the association of different subtypes of cerebral palsy [40] with different subtypes of ASD and ADHD (i.e., primarily hyperactive-impulsive, primarily inattentive, and combined type ADHD). Whether the observed association between cerebral palsy and ASD differs across subtypes of cerebral palsy or ASD warrants further investigation.

In conclusion, in a nationwide population-based study of US children, we found that cerebral palsy was associated with five-fold increased risk of ASD and doubled risk of

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ADHD. Further investigation is warranted to replicate our findings and determine the

underlying mechanisms.

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References

1.   Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. *Lancet*. 2014;**383**:1240-9. doi: 10.1016/S0140-6736(13)61835-8.
2.   Aisen ML, Kerkovich D, Mast J*, et al.* Cerebral palsy: clinical care and neurological rehabilitation. *Lancet Neurol*. 2011;**10**:844-52. doi: 10.1016/S1474-4422(11)70176-4.
3.   Stavsky M, Mor O, Mastrolia SA, Greenbaum S, Than NG, Erez O. Cerebral Palsy-Trends in Epidemiology and Recent Development in Prenatal Mechanisms of Disease, Treatment, and Prevention. *Front Pediatr*. 2017;**5**:21. doi: 10.3389/fped.2017.00021.
4.   MacLennan AH, Thompson SC, Gecz J. Cerebral palsy: causes, pathways, and the role of genetic variants. *Am J Obstet Gynecol*. 2015;**213**:779-88. doi: 10.1016/j.ajog.2015.05.034.
5.   National Institute for Health and Care Excellence. Cerebral palsy in under 25s: assessment and management (NICE Guideline, No. 62). London: National Institute for Health and Care Excellence (UK); 2017.
6.   Craig F, Savino R, Trabacca A. A systematic review of comorbidity between cerebral palsy, autism spectrum disorders and Attention Deficit Hyperactivity Disorder. *Eur J Paediatr Neurol*. 2019;**23**:31-42. doi: 10.1016/j.ejpn.2018.10.005.
7.   Downs J, Blackmore AM, Epstein A*, et al.* The prevalence of mental health disorders and symptoms in children and adolescents with cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol*. 2018;**60**:30-8. doi: 10.1111/dmcn.13555.
8.   American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Washington, DC: American Psychiatric Association; 2013.
9.   Lai MC, Lombardo MV, Baron-Cohen S. Autism. *Lancet*. 2014;**383**:896-910. doi: 10.1016/S0140-6736(13)61539-1.
10.   Lord C, Charman T, Havdahl A*, et al.* The Lancet Commission on the future of care and clinical research in autism. *Lancet*. 2021. doi: 10.1016/S0140-6736(21)01541-5.
11.   Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet*. 2016;**387**:1240-50. doi: 10.1016/S0140-6736(15)00238-X.
12.   Craig F, Lamanna AL, Margari F, Matera E, Simone M, Margari L. Overlap Between Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder: Searching for Distinctive/Common Clinical Features. *Autism Res*. 2015;**8**:328-37. doi: 10.1002/aur.1449.
13.   Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry*. 2008;**47**:921-9. doi: 10.1097/CHI.0b013e318179964f.
14.   Schiariti V, Mahdi S, Bolte S. International Classification of Functioning, Disability and Health Core Sets for cerebral palsy, autism spectrum disorder, and attention-deficit-hyperactivity disorder. *Dev Med Child Neurol*. 2018;**60**:933-41. doi: 10.1111/dmcn.13922.
15.   Adams PF, Kirzinger WK, Martinez M. Summary health statistics for the U.S. population: National Health Interview Survey, 2012. *Vital Health Stat 10*. 2013:1-95.

16.   Boyle CA, Boulet S, Schieve LA, *et al.* Trends in the prevalence of developmental disabilities in US children, 1997-2008. *Pediatrics*. 2011;**127**:1034-42. doi: 10.1542/peds.2010-2989.

17.   Parsons VL, Moriarity C, Jonas K, Moore TF, Davis KE, Tompkins L. Design and estimation for the national health interview survey, 2006-2015. *Vital Health Stat 2*. 2014:1-53.

18.   Zablotsky B, Black LI, Maenner MJ, *et al.* Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009-2017. *Pediatrics*. 2019;**144**. doi: 10.1542/peds.2019-0811.

19.   Xu G, Strathearn L, Liu B, Bao W. Prevalence of Autism Spectrum Disorder Among US Children and Adolescents, 2014-2016. *JAMA*. 2018;**319**:81-2. doi: 10.1001/jama.2017.17812.

20.   Xu G, Strathearn L, Liu B, Yang B, Bao W. Twenty-Year Trends in Diagnosed Attention-Deficit/Hyperactivity Disorder Among US Children and Adolescents, 1997-2016. *JAMA Netw Open*. 2018;**1**:e181471. doi: 10.1001/jamanetworkopen.2018.1471.

21.   Hirvonen M, Ojala R, Korhonen P, *et al.* Cerebral palsy among children born moderately and late preterm. *Pediatrics*. 2014;**134**:e1584-93. doi: 10.1542/peds.2014-0945.

22.   Strijbis EM, Oudman I, van Essen P, MacLennan AH. Cerebral palsy and the application of the international criteria for acute intrapartum hypoxia. *Obstet Gynecol*. 2006;**107**:1357-65. doi: 10.1097/01.AOG.0000220544.21316.80.

23.   Joseph RM, O'Shea TM, Allred EN, *et al.* Prevalence and associated features of autism spectrum disorder in extremely low gestational age newborns at age 10 years. *Autism Res*. 2017;**10**:224-32. doi: 10.1002/aur.1644.

24.   Harel-Gadassi A, Friedlander E, Yaari M, *et al.* Risk for ASD in Preterm Infants: A Three-Year Follow-Up Study. *Autism Res Treat*. 2018;**2018**:8316212. doi: 10.1155/2018/8316212.

25.   Lindstrom K, Lindblad F, Hjern A. Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. *Pediatrics*. 2011;**127**:858-65. doi: 10.1542/peds.2010-1279.

26.   Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. *JAMA*. 1997;**278**:207-11.

27.   Neufeld MD, Frigon C, Graham AS, Mueller BA. Maternal infection and risk of cerebral palsy in term and preterm infants. *J Perinatol*. 2005;**25**:108-13. doi: 10.1038/sj.jp.7211219.

28.   Ahlin K, Himmelmann K, Hagberg G, *et al.* Cerebral palsy and perinatal infection in children born at term. *Obstet Gynecol*. 2013;**122**:41-9. doi: 10.1097/AOG.0b013e318297f37f.

29.   Ayubi E, Sarhadi S, Mansori K. Maternal Infection During Pregnancy and Risk of Cerebral Palsy in Children: A Systematic Review and Meta-analysis. *J Child Neurol*. 2021;**36**:385-402. doi: 10.1177/0883073820972507.

30.   Jiang HY, Xu LL, Shao L, *et al.* Maternal infection during pregnancy and risk of autism spectrum disorders: A systematic review and meta-analysis. *Brain Behav Immun*. 2016;**58**:165-72. doi: 10.1016/j.bbi.2016.06.005.

31.   Villamor E, Tedroff K, Peterson M, *et al.* Association Between Maternal Body Mass Index in Early Pregnancy and Incidence of Cerebral Palsy. *JAMA*. 2017;**317**:925-36. doi: 10.1001/jama.2017.0945.

32.   Rivera HM, Christiansen KJ, Sullivan EL. The role of maternal obesity in the risk of neuropsychiatric disorders. *Front Neurosci*. 2015;**9**:194. doi: 10.3389/fnins.2015.00194.

33.   Andersen CH, Thomsen PH, Nohr EA, Lemcke S. Maternal body mass index before pregnancy as a risk factor for ADHD and autism in children. *Eur Child Adolesc Psychiatry*. 2018;**27**:139-48. doi: 10.1007/s00787-017-1027-6.

34.   Godfrey KM, Reynolds RM, Prescott SL, *et al.* Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinol*. 2017;**5**:53-64. doi: 10.1016/S2213-8587(16)30107-3.

13

35.   Hankins GD, Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. *Obstet Gynecol*. 2003;**102**:628-36. doi: 10.1016/s0029-7844(03)00574-x.

36.   Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. *Mol Autism*. 2017;**8**:13. doi: 10.1186/s13229-017-0121-4.

37.   Zhu T, Gan J, Huang J, Li Y, Qu Y, Mu D. Association Between Perinatal Hypoxic-Ischemic Conditions and Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis. *J Child Neurol*. 2016;**31**:1235-44. doi: 10.1177/0883073816650039.

38.   Persson M, Razaz N, Tedroff K, Joseph KS, Cnattingius S. Five and 10 minute Apgar scores and risks of cerebral palsy and epilepsy: population based cohort study in Sweden. *BMJ*. 2018;**360**:k207. doi: 10.1136/bmj.k207.

39.   Modabbernia A, Sandin S, Gross R*, et al.* Apgar score and risk of autism. *Eur J Epidemiol*. 2019;**34**:105-14. doi: 10.1007/s10654-018-0445-1.

40.   Rosenbaum P, Paneth N, Leviton A*, et al.* A report: the definition and classification of cerebral palsy April 2006. *Dev Med Child Neurol Suppl*. 2007;**109**:8-14.

Table 1. Characteristics of the study population (n= 177899), by cerebral palsy diagnosis.

Variables	Children without cerebral palsy	Children with cerebral palsy
No. of participants	177297	602
Age, year	9.99 (0.01)	10.19 (0.23)
Sex		
Male	91280 (51.05%)	350 (57.56%)
Female	86017 (48.95%)	252 (42.44%)
Race/ethnicity		
Hispanic	48209 (20.61%)	140 (16.72%)
Non-Hispanic White	87497 (57.32%)	325 (60.60%)
Non-Hispanic Black	26412 (14.11%)	102 (15.64%)
Other	15179 (7.96%)	35 (7.05%)
Family highest education		
Less than high school	39159 (19.53%)	132 (18.90%)
High school	20476 (11.51%)	61 (9.88%)
College or higher	116741 (68.51%)	405 (70.80%)
Missing	921 (0.45%)	4 (0.42%)
Family income to		
< 1.0	28697 (16.49%)	105 (19.43%)
1.0-1.9	34978 (19.72%)	155 (24.28%)
2.0-3.9	47234 (26.84%)	149 (26.20%)
>4.0	42562 (24.34%)	121 (19.61%)
Missing	23826 (12.62%)	72 (10.48%)
Geographic region		
Northeast	29462 (17.25%)	109 (17.43%)
Midwest	36451 (23.39%)	128 (24.30%)
South	64159 (36.31%)	237 (38.26%)
West	47225 (23.04%)	128 (20.00%)

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Data are presented as weighted means and standard errors in parentheses for continuous

variables, and frequencies and weighted percentages in parentheses for categorical variables.

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Table 2. Association of cerebral palsy with ASD and ADHD in US children (n=177899).

	OR (95% CI)		P-value
	Without CP	**With CP**	
ASD			
No. of	1961/177297	36/602	
Model 1[a]	1.00 (reference)	5.29 (3.39-8.26)	<0.001
Model 2[b]	1.00 (reference)	5.07 (3.25-7.91)	<0.001
ADHD			
No. of	13592/177297	105/602	
Model 1[a]	1.00 (reference)	2.10 (1.57-2.82)	<0.001
Model 2[b]	1.00 (reference)	1.95 (1.43-2.66)	<0.001

[a] Model 1: adjusted for age and sex.

[b] Model 2: model 1 plus race/ethnicity, family highest education level, family income to poverty ratio, and geographic region.

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Table 3. Stratified analysis for the association of cerebral palsy with ASD and ADHD in US children.

	No. of CP cases/participants	ASD		P for interaction	ADHD		P for interaction
		OR (95% CI)*	P-		OR (95% CI)*	P-value	
Age							
3-11 years	343/102227	4.23 (2.41-7.43)	<0.001	0.38	2.36 (1.57-3.55)	<0.001	0.43
12-17 years	259/75672	5.74 (3.03-10.88)	<0.001		1.74 (1.08-2.80)	0.02	
Sex							
Boys	350/91630	4.18 (2.44-7.16)	<0.001	0.13	1.86 (1.28-2.72)	0.001	0.61
Girls	252/86269	8.91 (4.04-19.66)	<0.001		2.18 (1.32-3.60)	0.002	
Race/ethnicity							
White	325/87822	4.99 (2.81-8.85)	<0.001	0.95	1.51 (1.00-2.26)	0.05	0.03
Non-white	277/90077	4.90 (2.52-9.53)	<0.001		2.92 (1.85-4.59)	<0.001	

Abbreviations: ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; CI, confidence intervals; OR, odds ratio.

*Multivariable model adjusted for age, sex, race/ethnicity, family highest education level, family income to poverty ratio, geographic region, except the stratifying factor.

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1   **Association of Cerebral Palsy with Autism Spectrum Disorder and Attention Deficit**

2   **Hyperactivity Disorder in Children: A Large-Scale Nationwide Population-Based Study**

3

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21   **Keywords:** cerebral palsy, autism spectrum disorder, attention-deficit/hyperactivity disorder

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1

1   **ABSTRACT**

2   **Objective** To examine the association of cerebral palsy with autism spectrum disorder (ASD

3   and attention-deficit/hyperactivity disorder (ADHD), providing evidence for interdisciplinary

4   medical service for children with cerebral palsy.

5   **Design** A large-scale nationwide population-based study.

6   **Setting** The National Health Interview Survey (NHIS).

7   **Patients** 177899 children aged 3-17 years old among NHIS participants from 1997 to 2003

8   and 2008 to 2018.

9   **Results** Among the 177899 children included in this analysis, 602 (0.33%) had cerebral

10   palsy, 1997 (1.16%) had ASD, and 13697 (7.91%) had ADHD. Compared to children

11   without cerebral palsy, children with cerebral palsy had a higher prevalence of ASD (6.09%

12   versus 1.15%; P < 0.001) and ADHD (15.91% versus 7.89%; P < 0.001). After adjustment

13   for age, sex, race/ethnicity, family highest education level, family income level, and

14   geographical region, the OR among children with cerebral palsy, compared with children

15   without cerebral palsy, was 5.07 (95% CI 3.25-7.91) for ASD (P < 0.001) and 1.95 (95% CI

16   1.43-2.66) for ADHD (P < 0.001). Furthermore, the association of cerebral palsy with ASD

17   and ADHD remained significant in all subgroups stratified by age, sex and race.

18   **Conclusions** In a large, nationally representative sample of US children, this study shows

19   that children with cerebral palsy are at an increased risk of ASD and ADHD.

20

21

22

2

1 **WHAT IS ALREADY KNOWN ON THIS TOPIC**

2 Cerebral palsy is caused by non-progressive disturbances that occurred in the developing

3 fetal or infant brain. Neurodevelopmental disorders, such as intellectual disability and

4 learning disability, are well documented comorbid conditions among children with cerebral

5 palsy.

6

7 **WHAT THIS STUDY ADDS**

8 This study quantified the odds ratios of autism spectrum disorder (ASD) and attention

9 deficit hyperactivity disorder (ADHD) among children with cerebral palsy, compared with

10 children without cerebral palsy. Furthermore, the association of cerebral palsy with ASD and

11 ADHD remained significant in all subgroups stratified by age, sex and race.

12

13 **HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

14 Cerebral palsy, ASD and ADHD are usually diagnosed in different clinical specialties,

15 with different intervention approaches. Therefore, this study provides evidence of their co-

16 occurrence risk, and informs better interdisciplinary clinic care.

17

3

1 **INTRODUCTION**

2   Cerebral palsy is a neurological disorder of motor impairment that results from non-

3 progressive disturbances during brain development in fetuses or infants [1, 2]. It is a major

4 cause of childhood disability. Worldwide prevalence estimates for cerebral palsy ranged from

5 about 1.6 per 1000 live births in high-income countries to more than 4 per 1000 live births in

6 low-and middle-income countries or children of a defined age range [3, 4]. Cerebral palsy

7 varies in the timing of the lesion, the clinical presentation, and the site and severity of the

8 impairments [5]. The multifactorial etiology of cerebral palsy may involve any insults with a

9 negative impact on the developing fetal or neonatal brain, such as preterm birth, fetal growth

10 restriction, multiple gestation, intrauterine infection, birth asphyxia, untreated maternal

11 hypothyroidism, congenital malformations, and perinatal stroke [6, 7]. Most children with

12 cerebral palsy have an abnormal brain magnetic resonance imaging (MRI) scan, including

13 white matter damage, basal ganglia or deep grey matter damage, congenital malformation,

14 and focal infarcts [8]. Motor disorders in cerebral palsy are often associated with

15 disturbances of sensation, perception, cognition, communication, behavior, and epilepsy [9].

16 Individuals with cerebral palsy have increased risk for emotional lability, irritability,

17 impulsiveness, and behavioral problems [10]. Some neurodevelopmental disorders, such as

18 intellectual disability and learning disability, are well documented comorbid conditions

19 among children with cerebral palsy [11].

20   Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD)

21 are childhood-onset neurodevelopmental disorders with a worldwide prevalence of 1% and

22 5%, respectively [12]. ASD is characterized by repetitive behaviors and restricted interests,

23 social impairments, and communication difficulties [13], and ADHD is characterized by

4

1   persistent and impairing inattention, hyperactivity, and impulsivity [14]. Comorbidity and

2   overlapping traits between ASD and ADHD are common [12, 15, 16]. Moreover, previous

3   clinical and epidemiological studies reported that the prevalence of ASD and ADHD was

4   higher in children with cerebral palsy, compared to children without cerebral palsy [9]. For

5   example, the US Autism and Developmental Disabilities Monitoring Network 2008 reported

6   that co-occurring ASD frequency was 6.9% among 8-year-old children with cerebral palsy

7   [17], which was higher than the overall estimated ASD population prevalence of 1.1% in the

8   same survey year [18]. The UK National Institute for Health and Care Excellence Clinical

9   Guideline on cerebral palsy underlined the importance of investigating the prevalence of

10   ASD and ADHD in children and young people with cerebral palsy [8]. ASD and ADHD are

11   interrelated neurodevelopmental disorders and they may share pathological mechanisms and

12   clinical features with cerebral palsy [19]. While previous studies have noted a higher co-

13   occurrence of ASD and ADHD in children with cerebral palsy [9, 20, 21], very few studies

14   have quantified the association (i.e., odds ratio or risk ratio) of cerebral palsy with ASD and

15   ADHD [22, 23].In this study, we analyzed large population-based data to quantify the

16   association of cerebral palsy with ASD and ADHD, in a nationally representative sample of

17   US children.

18

19   **METHODS**

20   **Study Population**

21   The National Health Interview Survey (NHIS), conducted annually by the Centers for

22   Disease Control and Prevention, is a leading health survey in the United States [24]. It has

23   become the principal source of information on health of the civilian non-institutionalized

5

1   population of the United States. Annual sample size of the NHIS is about 35,000 households

2   containing about 87,500 persons. The NHIS collects data on a broad range of health topics

3   for all household members, including children, through in-person household interviews. The

4   NHIS has a large sample size and a relatively high response rate. Annual sample size of the

5   NHIS is about 35 000 households containing approximately 87 500 persons. In NHIS 1997-

6   2018, the total household response rate ranged from 64.2% to 91.8% and conditional

7   response rate for the sample child component ranged from 85.6% to 93.5%. In the current

8   analysis, we included 177899 children aged 3-17 years old among participants in the NHIS

9   from 1997 to 2003 and 2008 to 2018. We did not include data during survey years from 2004

10 to 2007 because a previous report from the National Center on Birth Defects and

11 Developmental Disabilities, Centers for Disease Control and Prevention indicated that there

12 was high likelihood of interviewer error for cerebral palsy in 2004-2007 arising from a

13 questionnaire change during those years [25]. All the NHIS datasets could be found in the

14 U.S. CDC website: https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm.

15 **Ascertainment of Cerebral Palsy, ASD, and ADHD**

16   For each interviewed family in the household, one sample child (if any children aged

17 $\leq$ 17 years are present) is randomly selected through the field representative's computer

18 program, and no differential sampling probabilities are applied to the children [26]. Detailed

19 health-related information, including information on physical and mental health, is collected

20 for the sample child. This information is provided by an adult (usually a parent) who is

21 knowledgeable about the child's health.

22   Cerebral palsy was defined based on an affirmative response (i.e., yes) to the

23 question : "Has a doctor or health professional ever told you that [the sample child] had

6

1 cerebral palsy?" ASD was defined based on an affirmative response to a question asking

2 whether the sample child received a diagnosis of ASD from a physician or other health

3 professional. From 1997 to 2013, this question was asked as part of a 10-condition checklist.

4 In 2014 onward, the question became a stand-alone item and the wording was revised to

5 name specific conditions, including autism, Asperger disorder, pervasive developmental

6 disorder, and ASD. ADHD was defined based on an affirmative response (i.e., yes) to the

7 question: "Has a doctor or health professional ever told you that [the sample child] had

8 attention-deficit/hyperactivity disorder (ADHD) or attention-deficit disorder (ADD)?"

9 Among NHIS participants, more than 99% responded to the questions regarding diagnosis of

10 cerebral palsy and neurodevelopmental disorders.

11 **Covariates Assessment**

12 Information on age, sex, race/ethnicity, family highest education level, family income,

13 and geographic region was collected using standardized questionnaire during the interview.

14 Race and Hispanic ethnicity were self-reported and classified based on the 1997 Office of

15 Management and Budget Standards. Family highest education level was classified into less

16 than high school, high school, and college or higher. Family income levels were classified

17 according to the ratio of family income to federal poverty level (<1.0, 1.0-1.9, 2.0-3.9, and $\geq$

18 4.0).

19 **Statistical Analysis**

20 We included survey sampling weights, strata, and primary sampling units in all the

21 analyses to account for the unequal probabilities of selection, oversampling, and nonresponse

22 in the complex survey design. Therefore, the results in this study are nationally representative

23 of the US children. Comparisons of baseline characteristics among children with and without

7

1 cerebral palsy were performed using linear regression for continuous variables and the chi-

2 square test for categorical variables. We estimated the odds ratio (OR) and 95% confidence

3 interval (CI) of ASD, ADHD, and other neurodevelopmental disabilities according to history

4 of cerebral palsy diagnosis using multivariable logistic regression, adjusting for age, sex,

5 race/ethnicity, family highest education level, family income to poverty ratio, and geographic

6 region. All data analyses were conducted using survey procedures of SAS 9.4 (SAS Institute

7 Inc., Cary, NC). Two-sided P<0.05 was considered statistically significant.

8 **Ethics Approval Statement**

9   The NHIS was approved by the Research Ethics Review Board of the NCHS and the

10 U.S. Office of Management and Budget. All respondents provided oral consent prior to

11 participation. The University of Science and Technology of China Institutional Review

12 Board determined that the present study was exempt based on the use of de-identified data.

13

14 **RESULTS**

15   Among the 177899 children of 3-17 years included in this analysis, 602 (0.33%) had

16 cerebral palsy, 1997 (1.16%) had ASD, and 13697 (7.91%) had ADHD. Children with

17 cerebral palsy were more likely to be male and more likely to have lower family income than

18 those without cerebral palsy (**Table 1**).

19   Compared with children without cerebral palsy, children with cerebral palsy had a

20 higher prevalence of ASD (6.09% [95% CI 3.56-8.62] versus 1.15% [95% CI 1.07-1.22]; P <

21 0.001) and ADHD (15.91% [95% CI 12.07-19.75] versus 7.89% [95% CI 7.72-8.06]; P <

22 0.001). After adjustment for age, sex, race/ethnicity, family highest education level, family

23 income level, and geographical region, compared with children without cerebral palsy, the

8

1   OR among children with cerebral palsy was 5.07 (95% CI 3.25-7.91) for ASD (P < 0.001)

2   and 1.95 (95% CI 1.43-2.66) for ADHD (P < 0.001) (**Table 2**). These associations remained

3   significant in stratified analyses by age, sex, and race/ethnicity. The association between

4   cerebral palsy and ADHD appeared to be stronger among non-whites (2.92 [1.85-4.59]) than

5   whites (1.51 [1.00-2.26]) (P for interaction = 0.03) (**Table 3**). There was suggesting evidence

6   that the association between cerebral palsy and ASD may differ according to age and sex,

7   which warrants further investigation in future studies with even larger number of

8   participants.

9   In a sensitivity analysis among children (n=152043) whose information was reported

10   by their parents rather than other members in the household, the results were similar to our

11   main results (**Supplementary Table**).

12

13   **DISCUSSION**

14   Using data from a large nationwide population-based study, we found a significant

15   and positive association of cerebral palsy with ASD and ADHD. Compared with children

16   without cerebral palsy, children with cerebral palsy were at five-fold risk for ASD and

17   doubled risk for ADHD. The associations persisted after adjustment for age, sex,

18   race/ethnicity, family highest education level, family income level, and geographical region.

19   To our knowledge, although previous studies have reported a higher prevalence of

20   ASD and ADHD in children with cerebral palsy than in children without cerebral palsy [9,

21   20, 21], very few studies have quantified the association (i.e., odds ratio or risk ratio) of

22   cerebral palsy with ASD and ADHD in children, using a multivariable model adjusting for

23   potential covariates. For example, Påhlman et al. screened for ASD and ADHD in a cohort of

9

1   200 children aged 7-18 years from the cerebral palsy register of western Sweden, and found

2   that ASD and ADHD were common comorbidities in children with cerebral palsy [21].

3   However, the sample size of this Swedish study [21] was limited and odds ratios of ASD and

4   ADHD were not examined using a multivariable model. Similar to our findings,

5   Rackauskaite et al. reported that after adjustment for the social variables, the odds ratios for

6   ASD (OR=2.5; 95% CI 1.5-4.4) and ADHD (OR=2.0; 95% CI 1.2-3.2) were statistically

7   significantly increased for children and adolescents with cerebral palsy compared to those

8   without cerebral palsy in a cohort of 10-16 years children and adolescents in the Danish

9   National Cerebral Palsy Registry [22]. Another study, using data from the Norwegian Patient

10   Registry, reported significant risk difference of ASD and ADHD between individuals with

11   and without cerebral palsy [23].

12   The significant association of cerebral palsy with ASD and ADHD is not surprising,

13   because all these conditions result from impairment of certain functions in the brain. Cerebral

14   palsy, ASD and ADHD may share early-life risk factors that may affect brain development

15   during pregnancy and in infancy. Premature birth is the most prevalent risk factor for

16   cerebral palsy [27]. In a previous study of 213 children diagnosed with cerebral palsy in

17   Australia, 78% had a history of premature birth [28]. Premature birth has been also

18   associated with increased risk of ASD [29] and ADHD [30]. Maternal infection, another

19   common risk factor for cerebral palsy [31], has been associated with risk of ASD [32].

20   Maternal obesity was significantly associated with not only increased risk of cerebral palsy

21   [33], but also increased risk of ASD and ADHD [34]. Perinatal hypoxic-ischemic conditions

22   (including middle cerebral artery infarction), an important cause of cerebral palsy [35], was

10

1   also related to increase risk of ASD and ADHD[36, 37]. In addition, low Apgar score at birth

2   was also associated with higher risk for cerebral palsy[38] and ASD [39].

3   This study has several strengths. First, it was based on a large, multi-racial/ethnic

4   population. The large sample size improves the statistical power and robustness of the

5   estimates, which is critical for assessing the association of rare exposure and outcomes such

6   as cerebral palsy and most neurodevelopmental disorders. Second, the NHIS uses in-person

7   household interviews for data collection. As a result, the questionnaire completeness in the

8   NHIS is extraordinarily high, with more than 99% of participants responded to the questions

9   regarding diagnosis of cerebral palsy and neurodevelopmental disorders. Third, the use of a

10   nationally representative sample of US population facilitates better generalizability of the

11   findings to a broader population. There are several limitations of this study. First, information

12   on physician's diagnosis of cerebral palsy and neurodevelopmental disorders was self-

13   reported, which may subject to misreporting and recall bias. Second, routine methods for

14   diagnosing ASD or ADHD may not be suitable for children with motor problems [9]. There

15   could be under-identification of ASD and ADHD due to overshadowing of the motor

16   disorder. This could vary with different gross motor function levels as more severe motor

17   problems, indicated by a higher Gross Motor Function Classification System (GMFCS) level,

18   may present more challenges for ASD and ADHD diagnostic processes. Third, compared to

19   the general population, children with cerebral palsy could also be over-identified with ASD

20   and ADHD because of the need of more frequent contacts with health care services. Fourth,

21   over the past two decades, there have been changes in the diagnostic criteria for ASD and

22   cerebral palsy, which could also affect the associations. Fifth, we could not assess the

23   association of different sub-types and different GMFCS levels of cerebral palsy [40] with

11

1   different subtypes of ASD and ADHD (i.e., primarily hyperactive-impulsive, primarily

2   inattentive, and combined type ADHD). Whether the observed association between cerebral

3   palsy and ASD/ADHD differs across subtypes and severity levels of cerebral palsy or

4   ASD/ADHD warrants further investigation.

5   In conclusion, in a nationwide population-based study of US children, we found that

6   cerebral palsy was associated with five-fold increased risk of ASD and doubled risk of

7   ADHD. These findings indicate cerebral palsy as an early life sign for children who are at

8   risk of developing ASD or ADHD, because cerebral palsy is generally diagnosed during the

9   first or second year after birth. Further investigation is warranted to replicate our findings and

10   determine the underlying mechanisms.

11

12   **Contributors: QC**: writing—original draft, quantitative analysis and guarantor. **MC:**

13   writing—review and editing. **WB:** investigation, project administration, writing—review and

14   editing. **AC**: writing—review and editing. **LS:** conceptualisation, writing—review and

15   editing. **XZ:** quantitative analysis, writing—review and editing. **LM**: writing—review and

16   editing. **GF:** conceptualisation, writing—review and editing, supervision. All authors have

17   approved the final version of this manuscript.

20   **Competing interest**：No competing interest.

1   **References**

2   1.   Friedman, J.M., P. van Essen, and C.D.M. van Karnebeek, *Cerebral palsy and related*
3   *neuromotor disorders: Overview of genetic and genomic studies.* Mol Genet Metab, 2022.
4   **137**(4): p. 399-419.
5   2.   Michael-Asalu, A., et al., *Cerebral Palsy: Diagnosis, Epidemiology, Genetics, and Clinical*
6   *Update.* Adv Pediatr, 2019. **66**: p. 189-208.
7   3.   McIntyre, S., et al., *Global prevalence of cerebral palsy: A systematic analysis.* Dev Med Child
8   Neurol, 2022. **64**(12): p. 1494-1506.
9   4.   McIntyre, S., et al., *Global prevalence of cerebral palsy: A systematic analysis.* Dev Med Child
10   Neurol, 2022. **64**(12): p. 1494-1506.
11   5.   Colver, A., C. Fairhurst, and P.O. Pharoah, *Cerebral palsy.* Lancet, 2014. **383**(9924): p. 1240-
12   9.
13   6.   Stavsky, M., et al., *Cerebral Palsy-Trends in Epidemiology and Recent Development in*
14   *Prenatal Mechanisms of Disease, Treatment, and Prevention.* Front Pediatr, 2017. **5**: p. 21.
15   7.   MacLennan, A.H., S.C. Thompson, and J. Gecz, *Cerebral palsy: causes, pathways, and the role*
16   *of genetic variants.* Am J Obstet Gynecol, 2015. **213**(6): p. 779-88.
17   8.   National Institute for Health and Care Excellence, *Cerebral palsy in under 25s: assessment*
18   *and management (NICE Guideline, No. 62)*. 2017, London: National Institute for Health and
19   Care Excellence (UK).
20   9.   Craig, F., R. Savino, and A. Trabacca, *A systematic review of comorbidity between cerebral*
21   *palsy, autism spectrum disorders and Attention Deficit Hyperactivity Disorder.* Eur J Paediatr
22   Neurol, 2019. **23**(1): p. 31-42.
23   10.   Downs, J., et al., *The prevalence of mental health disorders and symptoms in children and*
24   *adolescents with cerebral palsy: a systematic review and meta-analysis.* Dev Med Child
25   Neurol, 2018. **60**(1): p. 30-38.
26   11.   Reid, S.M., et al., *Intellectual disability in cerebral palsy: a population-based retrospective*
27   *study.* Dev Med Child Neurol, 2018. **60**(7): p. 687-694.
28   12.   American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*
29   *(DSM-5)*. 2013, Washington, DC: American Psychiatric Association.
30   13.   Lai, M.C., M.V. Lombardo, and S. Baron-Cohen, *Autism.* Lancet, 2014. **383**(9920): p. 896-910.
31   14.   Thapar, A. and M. Cooper, *Attention deficit hyperactivity disorder.* Lancet, 2016. **387**(10024):
32   p. 1240-50.
33   15.   Craig, F., et al., *Overlap Between Autism Spectrum Disorders and Attention Deficit*
34   *Hyperactivity Disorder: Searching for Distinctive/Common Clinical Features.* Autism Res,
35   2015. **8**(3): p. 328-37.
36   16.   Simonoff, E., et al., *Psychiatric disorders in children with autism spectrum disorders:*
37   *prevalence, comorbidity, and associated factors in a population-derived sample.* J Am Acad
38   Child Adolesc Psychiatry, 2008. **47**(8): p. 921-9.
39   17.   Christensen, D., et al., *Prevalence of cerebral palsy, co-occurring autism spectrum disorders,*
40   *and motor functioning - Autism and Developmental Disabilities Monitoring Network, USA,*
41   *2008.* Dev Med Child Neurol, 2014. **56**(1): p. 59-65.
42   18.   Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal
43   Investigators, *Prevalence of autism spectrum disorders--Autism and Developmental*
44   *Disabilities Monitoring Network, 14 sites, United States, 2008.* MMWR Surveill Summ, 2012.
45   **61**(3): p. 1-19.

13

19. Schiariti, V., S. Mahdi, and S. Bolte, *International Classification of Functioning, Disability and Health Core Sets for cerebral palsy, autism spectrum disorder, and attention-deficit-hyperactivity disorder.* Dev Med Child Neurol, 2018. **60**(9): p. 933-941.

20. Pahlman, M., C. Gillberg, and K. Himmelmann, *Autism and attention-deficit/hyperactivity disorder in children with cerebral palsy: high prevalence rates in a population-based study.* Dev Med Child Neurol, 2021. **63**(3): p. 320-327.

21. Pahlman, M., et al., *Autism spectrum disorder and attention-deficit/hyperactivity disorder in children with cerebral palsy: results from screening in a population-based group.* Eur Child Adolesc Psychiatry, 2020. **29**(11): p. 1569-1579.

22. Rackauskaite, G., et al., *Prevalence of mental disorders in children and adolescents with cerebral palsy: Danish nationwide follow-up study.* Eur J Paediatr Neurol, 2020. **27**: p. 98-103.

23. Hollung, S.J., et al., *Comorbidities in cerebral palsy: a patient registry study.* Dev Med Child Neurol, 2020. **62**(1): p. 97-103.

24. Adams, P.F., W.K. Kirzinger, and M. Martinez, *Summary health statistics for the U.S. population: National Health Interview Survey, 2012.* Vital Health Stat 10, 2013(259): p. 1-95.

25. Boyle, C.A., et al., *Trends in the prevalence of developmental disabilities in US children, 1997-2008.* Pediatrics, 2011. **127**(6): p. 1034-42.

26. Parsons, V.L., et al., *Design and estimation for the national health interview survey, 2006-2015.* Vital Health Stat 2, 2014(165): p. 1-53.

27. Hirvonen, M., et al., *Cerebral palsy among children born moderately and late preterm.* Pediatrics, 2014. **134**(6): p. e1584-93.

28. Strijbis, E.M., et al., *Cerebral palsy and the application of the international criteria for acute intrapartum hypoxia.* Obstet Gynecol, 2006. **107**(6): p. 1357-65.

29. Harel-Gadassi, A., et al., *Risk for ASD in Preterm Infants: A Three-Year Follow-Up Study.* Autism Res Treat, 2018. **2018**: p. 8316212.

30. Lindstrom, K., F. Lindblad, and A. Hjern, *Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren.* Pediatrics, 2011. **127**(5): p. 858-65.

31. Ayubi, E., S. Sarhadi, and K. Mansori, *Maternal Infection During Pregnancy and Risk of Cerebral Palsy in Children: A Systematic Review and Meta-analysis.* J Child Neurol, 2021. **36**(5): p. 385-402.

32. Jiang, H.Y., et al., *Maternal infection during pregnancy and risk of autism spectrum disorders: A systematic review and meta-analysis.* Brain Behav Immun, 2016. **58**: p. 165-172.

33. Villamor, E., et al., *Association Between Maternal Body Mass Index in Early Pregnancy and Incidence of Cerebral Palsy.* JAMA, 2017. **317**(9): p. 925-936.

34. Andersen, C.H., et al., *Maternal body mass index before pregnancy as a risk factor for ADHD and autism in children.* Eur Child Adolesc Psychiatry, 2018. **27**(2): p. 139-148.

35. Hankins, G.D. and M. Speer, *Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy.* Obstet Gynecol, 2003. **102**(3): p. 628-36.

36. M, P.A., C. Gillberg, and K. Himmelmann, *Neuroimaging findings in children with cerebral palsy with autism and/or attention-deficit/hyperactivity disorder: a population-based study.* Dev Med Child Neurol, 2022. **64**(1): p. 63-69.

37. Zhu, T., et al., *Association Between Perinatal Hypoxic-Ischemic Conditions and Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis.* J Child Neurol, 2016. **31**(10): p. 1235-44.

38. Persson, M., et al., *Five and 10 minute Apgar scores and risks of cerebral palsy and epilepsy: population based cohort study in Sweden.* BMJ, 2018. **360**: p. k207.

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39. Modabbernia, A., et al., *Apgar score and risk of autism.* Eur J Epidemiol, 2019. **34**(2): p. 105-114.

40. Rosenbaum, P., et al., *A report: the definition and classification of cerebral palsy April 2006.* Dev Med Child Neurol Suppl, 2007. **109**: p. 8-14.

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1 **Table 1. Characteristics of the study population among U.S. Children aged 3-17 years,**

2 **by cerebral palsy diagnosis.**

Variables	Children without cerebral palsy (N, weighted %)	Children with cerebral palsy (N, weighted %)
No. of participants	177297	602
Age, year	9.99 (0.01)	10.19 (0.23)
Sex, N (%)		
Male	91280 (51.1)	350 (57.6)
Female	86017 (48.9)	252 (42.4)
Race/ethnicity, N (%)		
Hispanic	48209 (20.6)	140 (16.7)
Non-Hispanic White	87497 (57.3)	325 (60.6)
Non-Hispanic Black	26412 (14.1)	102 (15.6)
Other	15179 (8.0)	35 (7.1)
Family highest education level, N (%)		
Less than high school	39159 (19.5)	132 (18.9)
High school	20476 (11.5)	61 (9.9)
College or higher	116741 (68.5)	405 (70.8)
Missing	921 (0.5)	4 (0.4)
Ratio of family income to the federal poverty level, N (%)		
< 1.0	28697 (16.5)	105 (19.4)
1.0-1.9	34978 (19.7)	155 (24.3)
2.0-3.9	47234 (26.8)	149 (26.2)
>4.0	42562 (24.3)	121 (19.6)
Missing	23826 (12.6)	72 (10.5)
Geographic region, N (%)		
Northeast	29462 (17.3)	109 (17.4)
Midwest	36451 (23.4)	128 (24.3)
South	64159 (36.3)	237 (38.3)
West	47225 (23.0)	128 (20.0)

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ASD, N (%)		
No	175336 (98.9)	566 (93.9)
Yes	1961 (1.1)	36 (6.1)
ADHD, N (%)		
No	163705 (92.1)	497 (84.1)
Yes	13592 (7.9)	105 (15.9)

1   Data are presented as weighted means and standard errors in parentheses for continuous

2   variables, and frequencies and weighted percentages in parentheses for categorical variables.

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1 **Table 2. Association of cerebral palsy with ASD and ADHD in US children.**

	OR (95% CI)		P-value
	Without cerebral palsy	**With cerebral palsy**	
ASD			
No. of cases/total participants	1961/177297	36/602	
Model 1[a]	1.00 (reference)	5.29 (3.39-8.26)	<0.001
Model 2[b]	1.00 (reference)	5.07 (3.25-7.91)	<0.001
ADHD			
No. of cases/total participants	13592/177297	105/602	
Model 1[a]	1.00 (reference)	2.10 (1.57-2.82)	<0.001
Model 2[b]	1.00 (reference)	1.95 (1.43-2.66)	<0.001

2 [a] Model 1: adjusted for age and sex.

3 [b] Model 2: model 1 plus race/ethnicity, family highest education level, family income to

4 poverty ratio, and geographic region.

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Table 3. Stratified analysis for the association of cerebral palsy with ASD and ADHD in US children.

	No. of cerebral palsy cases/participants	ASD		P for interaction	ADHD		P for interaction
		OR (95% CI)*	P-value		OR (95% CI)*	P-value	
Age							
3-11 years	343/102227	4.23 (2.41-7.43)	<0.001	0.38	2.36 (1.57-3.55)	<0.001	0.43
12-17 years	259/75672	5.74 (3.03-10.88)	<0.001		1.74 (1.08-2.80)	0.02	
Sex							
Boys	350/91630	4.18 (2.44-7.16)	<0.001	0.13	1.86 (1.28-2.72)	0.001	0.61
Girls	252/86269	8.91 (4.04-19.66)	<0.001		2.18 (1.32-3.60)	0.002	
Race/ethnicity							
White	325/87822	4.99 (2.81-8.85)	<0.001	0.95	1.51 (1.00-2.26)	0.05	0.03
Non-white	277/90077	4.90 (2.52-9.53)	<0.001		2.92 (1.85-4.59)	<0.001	

Abbreviations: ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; CI, confidence intervals; OR, odds ratio.

*Multivariable model adjusted for age, sex, race/ethnicity, family highest education level, family income to poverty ratio, geographic region, except the stratifying factor.

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Supplementary Table. Sensitivity analysis for the association of cerebral palsy with ASD and ADHD in US children, whose information was reported by their parents (n=152043).

	OR (95% CI)		P-value
	Without cerebral	**With cerebral palsy**	
ASD			
No. of cases/total	1797/151548	28/495	
Model 1[a]	1.00 (reference)	5.02 (3.05-8.27)	<0.001
Model 2[b]	1.00 (reference)	4.77 (2.89-7.86)	<0.001
ADHD			
No. of cases/total	11570/151548	87/495	
Model 1[a]	1.00 (reference)	2.01 (1.43-2.81)	<0.001
Model 2[b]	1.00 (reference)	1.84 (1.28-2.65)	<0.001

[a] Model 1: adjusted for age and sex.

[b] Model 2: model 1 plus race/ethnicity, family highest education level, family income to poverty ratio, and geographic region.