


# Association of cerebral palsy with autism spectrum disorder 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 autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (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** 177 899 children aged 3–17 years among NHIS participants from 1997 to 2003 and 2008 to 2018.

**Results** Among the 177 899 children included in this analysis, 602 (0.33%) had cerebral palsy, 1997 (1.16%) had ASD, and 13 697 (7.91%) had ADHD. Compared with children without cerebral palsy, children with cerebral palsy had a higher prevalence of ASD (6.09% vs 1.15%;  $p<0.001$ ) and ADHD (15.91% vs 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 to 7.91) for ASD ( $p<0.001$ ) and 1.95 (95% CI 1.43 to 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.

**Conclusion** 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.

## INTRODUCTION

Cerebral palsy is a neurological disorder of motor impairment that results from non-progressive disturbances during brain development in fetuses or infants.<sup>1 2</sup> It is a major cause of childhood disability. Worldwide prevalence estimates for cerebral palsy ranged from about 1.6 per 1000 live births in high-income countries to more than 4 per 1000 live births in low- and middle-income countries or children of a defined age range.<sup>3</sup> Cerebral palsy varies in the timing of the lesion, the clinical presentation and the site and severity of the impairments.<sup>4</sup> The multifactorial aetiology

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cerebral palsy is caused by non-progressive disturbances that occur in the developing fetal or infant brain. Neurodevelopmental disorders, such as intellectual disability and learning disability, are well-documented comorbid conditions among children with cerebral palsy.

## WHAT THIS STUDY ADDS

⇒ This study quantified the ORs 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.

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, intra-uterine infection, birth asphyxia, untreated maternal hypothyroidism, congenital malformations and perinatal stroke.<sup>5 6</sup> Most children with cerebral palsy have an abnormal brain MRI scan, including white matter damage, basal ganglia or deep grey matter damage, congenital malformation and focal infarcts.<sup>7</sup> Motor disorders in cerebral palsy are often associated with disturbances of sensation, perception, cognition, communication, behaviour and epilepsy.<sup>8</sup> Individuals with cerebral palsy have an increased risk for



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emotional lability, irritability, impulsiveness and behavioural problems.<sup>9</sup> Some neurodevelopmental disorders, such as intellectual disability and learning disability, are well-documented comorbid conditions among children with cerebral palsy.<sup>10</sup>

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are childhood-onset neurodevelopmental disorders with a worldwide prevalence of 1% and 5%, respectively.<sup>11</sup> ASD is characterised by repetitive behaviours and restricted interests, social impairments and communication difficulties,<sup>12</sup> and ADHD is characterised by persistent and impairing inattention, hyperactivity and impulsivity.<sup>13</sup> Comorbidity and overlapping traits between ASD and ADHD are common.<sup>11 14 15</sup> Moreover, previous clinical and epidemiological studies reported that the prevalence of ASD and ADHD was higher in children with cerebral palsy, compared with children without cerebral palsy.<sup>8</sup> For example, the US Autism and Developmental Disabilities Monitoring Network 2008 reported that co-occurring ASD frequency was 6.9% among 8-year-old children with cerebral palsy,<sup>16</sup> which was higher than the overall estimated ASD population prevalence of 1.1% in the same survey year.<sup>17</sup> 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.<sup>7</sup> ASD and ADHD are inter-related neurodevelopmental disorders and they may share pathological mechanisms and clinical features with cerebral palsy.<sup>18</sup> While previous studies have noted a higher co-occurrence of ASD and ADHD in children with cerebral palsy,<sup>8 19 20</sup> very few studies have quantified the association (ie, OR or risk ratio) of cerebral palsy with ASD and ADHD.<sup>21 22</sup> In this study, we analysed large population-based data to quantify the association of cerebral palsy with ASD and ADHD, in a nationally representative sample of US children.

## METHODS

### 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 USA.<sup>23</sup> It has become the principal source of information on the health of the civilian non-institutionalised population of the USA. 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. Annual sample size of the NHIS is about 35 000 households containing approximately 87 500 persons. In NHIS 1997–2018, the total household response rate ranged from 64.2% to 91.8% and the conditional response rate for the sample child component ranged from 85.6% to 93.5%. In the current

analysis, we included 177 899 children aged 3–17 years among participants in the NHIS from 1997 to 2003 and 2008 to 2018. We did not include data during survey years from 2004 to 2007 because a previous report from the National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention indicated that there was a high likelihood of interviewer error for cerebral palsy in 2004–2007 arising from a questionnaire change during those years.<sup>24</sup> All the NHIS datasets can be found on the U.S. CDC website (<https://www.cdc.gov/nchs/nhis/data-questionnaires-documentation.htm>).

### Ascertainment of cerebral palsy, ASD and ADHD

For each interviewed family in the household, one sample child (if any children aged  $\leq 17$  years are present) is randomly selected through the field representative's computer program, and no differential sampling probabilities are applied to the children.<sup>25</sup> 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 (ie, yes) to the question: "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 sample child received a diagnosis of ASD from a physician or other health professional. From 1997 to 2013, this question was asked as part of a 10-condition checklist. From 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 (ie, yes) to the question: "Has a doctor or health professional ever told you that [the sample child] had attention-deficit/hyperactivity disorder (ADHD) or attention-deficit disorder (ADD)?" Among NHIS participants, more than 99% responded to the questions regarding a diagnosis of cerebral palsy and neurodevelopmental disorders.

### Covariate assessment

Information on age, sex, race/ethnicity, family highest education level, family income and geographic region was collected using a standardised 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 non-response 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  $\chi^2$  test for categorical variables. We estimated the OR and 95% CI of ASD, ADHD and other neurodevelopmental disabilities according to the history 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 V.9.4 (SAS Institute, Cary, North Carolina, USA). Two-sided  $p < 0.05$  was considered statistically significant.

## RESULTS

Among the 177 899 children aged 3–17 years included in this analysis, 602 (0.33%) had cerebral palsy, 1997 (1.16%) had ASD, and 13 697 (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 to 8.62) vs 1.15% (95% CI 1.07 to 1.22);  $p < 0.001$ ) and ADHD (15.91% (95% CI 12.07 to 19.75) vs 7.89% (95% CI 7.72 to 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 to 7.91) for ASD ( $p < 0.001$ ) and 1.95 (95% CI 1.43 to 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 to 4.59)) than whites (1.51 (1.00 to 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 an even larger number of participants.

In a sensitivity analysis among children ( $n=152\,043$ ) whose information was reported by their parents rather than other members in the household, the results were similar to our main results (online supplemental table 1).

## 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 a fivefold risk for ASD and a doubled risk for ADHD. The associations persisted after adjustment for

**Table 1** Characteristics of the study population among US children aged 3–17 years, by cerebral palsy diagnosis

Variables	Children without cerebral palsy (n, weighted %)	Children with cerebral palsy (n, weighted %)
No. of participants	177 297	602
Age, year	9.99 (0.01)	10.19 (0.23)
Sex, n (%)		
Male	91 280 (51.1)	350 (57.6)
Female	86 017 (48.9)	252 (42.4)
Race/ethnicity, n (%)		
Hispanic	48 209 (20.6)	140 (16.7)
Non-Hispanic white	87 497 (57.3)	325 (60.6)
Non-Hispanic black	26 412 (14.1)	102 (15.6)
Other	15 179 (8.0)	35 (7.1)
Family highest education level, n (%)		
Less than high school	39 159 (19.5)	132 (18.9)
High school	20 476 (11.5)	61 (9.9)
College or higher	116 741 (68.5)	405 (70.8)
Missing	921 (0.5)	4 (0.4)
Ratio of family income to the federal poverty level, n (%)		
<1.0	28 697 (16.5)	105 (19.4)
1.0–1.9	34 978 (19.7)	155 (24.3)
2.0–3.9	47 234 (26.8)	149 (26.2)
>4.0	42 562 (24.3)	121 (19.6)
Missing	23 826 (12.6)	72 (10.5)
Geographic region, n (%)		
Northeast	29 462 (17.3)	109 (17.4)
Midwest	36 451 (23.4)	128 (24.3)
South	64 159 (36.3)	237 (38.3)
West	47 225 (23.0)	128 (20.0)
ASD, n (%)		
No	175 336 (98.9)	566 (93.9)
Yes	1961 (1.1)	36 (6.1)
ADHD, n (%)		
No	163 705 (92.1)	497 (84.1)
Yes	13 592 (7.9)	105 (15.9)

Data are presented as weighted means and SEs in parentheses for continuous variables and frequencies and weighted percentages in parentheses for categorical variables.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

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,<sup>8 19 20</sup> very few studies have quantified the

**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	1961/177 297	36/602	
Model 1*	1.00 (reference)	5.29 (3.39 to 8.26)	<0.001
Model 2†	1.00 (reference)	5.07 (3.25 to 7.91)	<0.001
ADHD			
No. of cases/total participants	13592/177297	105/602	
Model 1*	1.00 (reference)	2.10 (1.57 to 2.82)	<0.001
Model 2†	1.00 (reference)	1.95 (1.43 to 2.66)	<0.001

\*Model 1: adjusted for age and sex.

†Model 2: model 1 plus race/ethnicity, family highest education level, family income to poverty ratio and geographic region. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

association (ie, OR or risk ratio) of cerebral palsy with ASD and ADHD in children, using a multivariable model adjusting for potential covariates. For example, Pålman *et al* screened for ASD and ADHD in a cohort of 200 children aged 7–18 years from the cerebral palsy register of western Sweden and found that ASD and ADHD were common comorbidities in children with cerebral palsy.<sup>20</sup> However, the sample size of this Swedish study<sup>20</sup> was limited and ORs of ASD and ADHD were not examined using a multivariable model. Similar to our findings, Rackauskaite *et al* reported that after adjustment for the social variables, the ORs for ASD (OR=2.5; 95% CI 1.5 to 4.4) and ADHD (OR=2.0; 95% CI 1.2 to 3.2) were statistically significantly increased for children and adolescents with cerebral palsy compared with those without cerebral palsy in a cohort of 10–16 years children and adolescents in the Danish National Cerebral Palsy Registry.<sup>21</sup> Another study, using data from the Norwegian Patient Registry,

reported a significant risk difference of ASD and ADHD between individuals with and without cerebral palsy.<sup>22</sup>

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. Premature birth is the most prevalent risk factor for cerebral palsy.<sup>26</sup> In a previous study of 213 children diagnosed with cerebral palsy in Australia, 78% had a history of premature birth.<sup>27</sup> Premature birth has been also associated with an increased risk of ASD<sup>28</sup> and ADHD.<sup>29</sup> Maternal infection, another common risk factor for cerebral palsy,<sup>30</sup> has been associated with the risk of ASD.<sup>31</sup> Maternal obesity was significantly associated with not only an increased risk of cerebral palsy<sup>32</sup> but also an increased risk of ASD and ADHD.<sup>33</sup> Perinatal hypoxic-ischaemic conditions (including middle cerebral artery

**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 (years)							
3–11	343/102 227	4.23 (2.41 to 7.43)	<0.001	0.38	2.36 (1.57 to 3.55)	<0.001	0.43
12–17	259/75 672	5.74 (3.03 to 10.88)	<0.001		1.74 (1.08 to 2.80)	0.02	
Sex							
Boys	350/91 630	4.18 (2.44 to 7.16)	<0.001	0.13	1.86 (1.28 to 2.72)	0.001	0.61
Girls	252/86 269	8.91 (4.04 to 19.66)	<0.001		2.18 (1.32 to 3.60)	0.002	
Race/ethnicity							
White	325/87 822	4.99 (2.81 to 8.85)	<0.001	0.95	1.51 (1.00 to 2.26)	0.05	0.03
Non-white	277/90 077	4.90 (2.52 to 9.53)	<0.001		2.92 (1.85 to 4.59)	<0.001	

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

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

infarction), an important cause of cerebral palsy,<sup>34</sup> was also related to an increased risk of ASD and ADHD.<sup>35 36</sup> In addition, low Apgar score at birth was also associated with a higher risk for cerebral palsy<sup>37</sup> and ASD.<sup>38</sup>

This study has several strengths. First, it was based on a large, multiracial/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 responding to the questions regarding a diagnosis of cerebral palsy and neurodevelopmental disorders. Third, the use of a nationally representative sample of US population facilitates better generalisability 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 be subject to misreporting and recall bias. Second, routine methods for diagnosing ASD or ADHD may not be suitable for children with motor problems.<sup>8</sup> There could be underidentification of ASD and ADHD due to overshadowing of the motor disorder. This could vary with different gross motor function levels as more severe motor problems, indicated by a higher Gross Motor Function Classification System (GMFCS) level, may present more challenges for ASD and ADHD diagnostic processes. Third, compared with the general population, children with cerebral palsy could also be overidentified with ASD and ADHD because of the need for more frequent contact with healthcare services. Fourth, over the past two decades, there have been changes in the diagnostic criteria for ASD and cerebral palsy, which could also affect the associations. Fifth, we could not assess the association of different subtypes and different GMFCS levels of cerebral palsy<sup>39</sup> with different subtypes of ASD and ADHD (ie, primarily hyperactive-impulsive, primarily inattentive and combined type ADHD). Whether the observed association between cerebral palsy and ASD/ADHD differs across subtypes and severity levels of cerebral palsy or ASD/ADHD warrants further investigation.

In conclusion, in a nationwide population-based study of US children, we found that cerebral palsy was associated with a fivefold increased risk of ASD and a doubled risk of ADHD. These findings indicate cerebral palsy as an early-life sign for children who are at risk of developing ASD or ADHD because cerebral palsy is generally diagnosed during the first or second year after birth. Further investigation is warranted to replicate our findings and determine the underlying mechanisms.

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