



# Prevalence and demographic characteristics of comorbid epilepsy in children and adolescents with cerebral palsy: a nationwide population-based study

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## Abstract

**Introduction** The nationwide prevalence of cerebral palsy (CP) is unknown due to the lack of a population-based registration system for CP in Taiwan. This study was the largest nationwide, population-based, cross-sectional study to estimate the prevalence of CP, prevalence rates of comorbid epilepsy in patients with CP, and association with socioeconomic status (SES) in Taiwan. The crude prevalence rate and age- and gender-specific prevalence rates were estimated.

**Methods** A total of 8419 patients with CP were enrolled, and the estimated prevalence of CP was 1.76‰ in the pediatric population and 1.51‰ and 1.98‰ in girls and boys, respectively. The prevalence rate of epilepsy in patients with CP was 29.8%.

**Results** The result revealed a higher prevalence of CP and epileptic CP in members of families with lower insurance premiums than those with higher insurance premiums and those from East Taiwan compared with those from other areas of Taiwan. Moreover, a higher prevalence of CP is shown in rural area than urban area.

**Discussion** SES and geographic variables were significantly associated with the risk of epilepsy in children with CP. Patients with epileptic CP had a higher odds ratio of several neuropsychiatric diseases, including mental retardation, ophthalmologic problems, hearing impairment, and hydrocephalus.

**Keywords** Pediatric epilepsy · Socioeconomic status · National Health Insurance

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## Introduction

Epilepsy and cerebral palsy (CP), common neurological disorders in children, place a marked burden on children with such conditions, their families, and society. CP represents a group of permanent, nonprogressive disorders that affect the development of movement and posture, thus limiting the activity of individuals with CP. Because CP is a nonprogressive pathology in immature brains [1], and it is associated with scarring, some form of brain abnormality, seizures, or epilepsy disorders. Besides, CP in children is frequently comorbid with epilepsy and has been widely studied [2–10]. We previously reported that CP is the second most common comorbidity in pediatric epilepsy and has a higher odds ratio (OR) of 91.4 (95% confidence interval [CI] 65.8–127.0) than the general population [11]. Epilepsy has been used as a marker of severity and often worsens the quality of life of patients with CP [10, 12], and maybe more disabling than the original motor disorder. Compared with children suffering from epilepsy alone, epilepsy in children with CP is characterized by an earlier age of onset, a higher frequency of partial seizure, a

higher proportion of brain imaging with abnormal pathology, a greater need for polytherapy, and second-line anti-epileptic drugs, and with lower probability of remaining seizure-free [3, 6–8, 10]. However, most of the studies were hospital-based with the possibility of selection bias. Furthermore, the nationwide prevalence of CP is unknown because of the lack of an exclusive population-based registration system for CP in Taiwan.

Epilepsy in children with CP has a relatively poor prognosis. Some studies have reported epilepsy is associated with severe CP and mental retardation [13, 14]. As such, specific data on the proportional distribution of age and gender and the socioeconomic status (SES) of children with CP, as well as the causes of CP, are highly important for developing preventive measures and treatment programs, particularly for children with epileptic CP. Other associated somatic and neuropsychiatric comorbidities may increase the economic burden on families directly affected and, more generally, health care costs in Taiwan.

In 1995, Taiwan established the National Health Insurance (NHI) program to provide equitable and universal health care coverage to all its citizens. This program covers approximately 98–99% of the 26 million population of Taiwan [15]. Considering this almost universal coverage rate, medical information data collected from this program is ideal for epidemiological studies. The present study investigated the prevalence of CP in a large sample of Taiwanese patients, the prevalence of epilepsy in children with CP, and the relationship between prevalence of CP, comorbidity rate of epilepsy in CP patients, age, gender, and SES. Furthermore, we statistically determined the comorbidity ratio of other common CP-associated neuropsychiatric diseases and somatic problems in the epileptic CP and nonepileptic CP subgroups to understand the effect of epilepsy in patients with CP.

## Methods and materials

Data in this study were obtained from the NHI Research Database (NHIRD) for 2010 and 2011. This study was approved by and conducted in accordance with the Institutional Review Board of Kuang-Tien General Hospital, and the analyzed data covered the entire population of Taiwan aged from 1 month to 19 years ( $n = 4,793,535$ ). We analyzed the association of gender, age, and other socioeconomic characteristics (e.g., household income, residential location, and urbanization level), with epileptic and nonepileptic CP. Common associated cognition problems, neurological issues, and nutritional problems of CP were investigated and examined. We also used a control group of children without CP but undergoing rehabilitation or registered in the catastrophic registry for comparing the comorbidity rate of epilepsy (Fig. 1).

## Demographics and covariates

This study designated SES according to occupation and household income level. Household income was grouped into three categories according to insurance premiums: NTD\$0–19,999, NTD\$20,000–39,999, and NTD\$40,000 or more. Occupation could be another evaluation dimension of SES. Nonsalaried citizens, such as unemployed people, students, and elderly people, are designated as dependents by the Bureau of National Health Insurance (BNHI) and government. Others were defined as “Independents” [16, 17]. Geographic variations refer to differences among populations in terms of genetic traits across the natural geographic range of a species. Residential location was classified into four regions (northern, central, southern, and eastern Taiwan; Fig. 1), as in previous studies based on the NHIRD. Most economically and politically important cities are located in the northern region; whereas, the eastern region has the lowest number of such cities. In eastern Taiwan, the rift valley presents a unique geographic landscape not observed in the other areas. Furthermore, East Taiwan is the least economically developed and accounts for mixed racial populations [18].

To determine the degree of urbanization, we used the location from the NHI registration as a proxy parameter for SES. We used the criteria for urbanization defined by the NHIRD according to the township in which each beneficiary resided [19]. The NHRI classifies all 359 townships in Taiwan into seven clusters: urban (levels 1 and 2), suburban (levels 3 and 4), or rural (levels 5–7) [20].

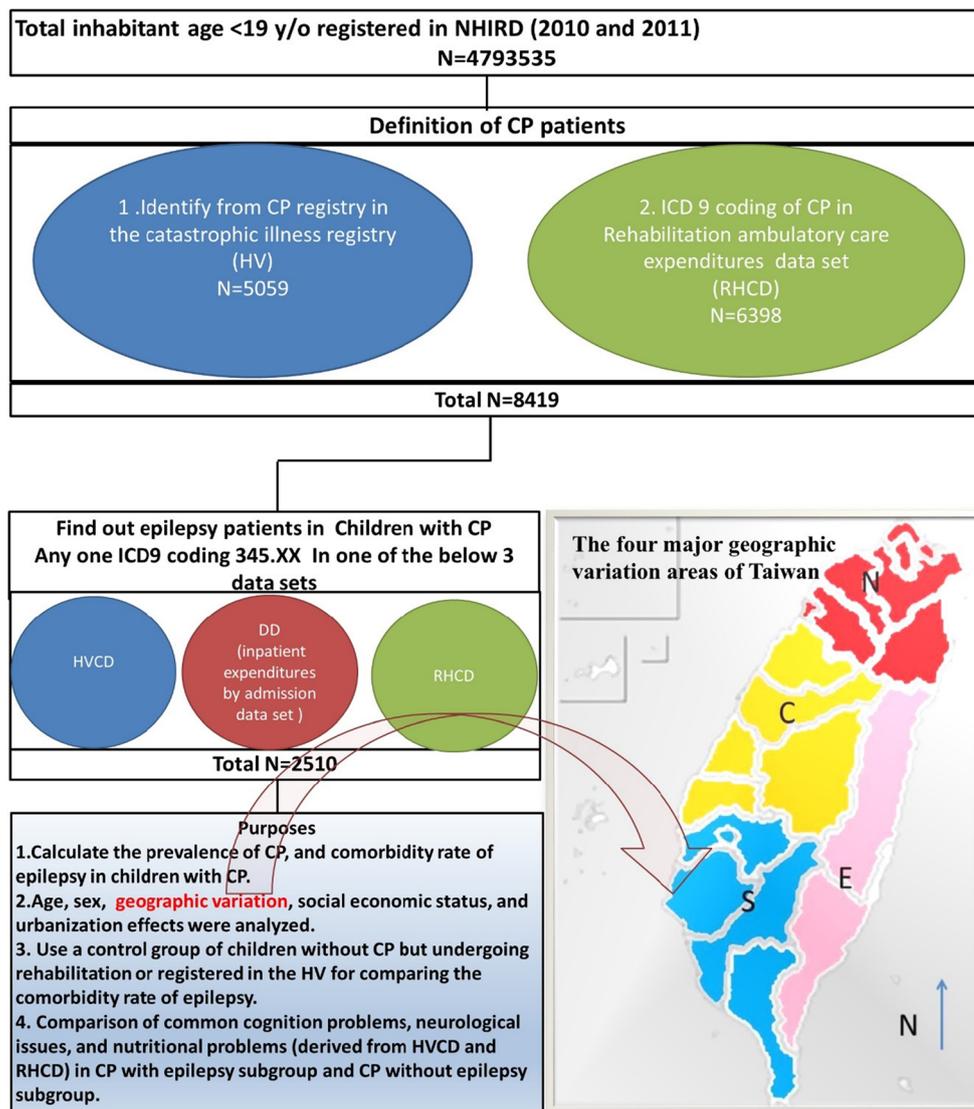
## Data analysis

We used SQL Server 2012 (Microsoft, Redmond, WA, USA) to link data from various data sets, including the registry of beneficiaries, total admission claims, and outpatient claims, to the registries of beneficiaries and patients with catastrophic illnesses. Microsoft Excel 2013 and SPSS version 19.0 (IBM, Armonk, NY, USA) were employed for data processing, namely data selection, merging, and aggregation and the performance of calculations. The logistic regression test was used for our stratified analysis of the prevalence of CP and epileptic CP based on age, gender, SES, urbanization level, and geographic location. A two-tailed  $p < .05$  was considered statistically significant, and we used chi-squared test in our analysis for the OR of comorbidities.

## Results

We analyzed 6398 and 5109 patients with CP from the HV and RHCD data sets, respectively. Among the 8419 patients with CP, 2510 also had epilepsy (Fig. 2). The crude epilepsy comorbidity rate of patients with CP was 29.8%. Table 1

**Fig. 1** Flow chart of the current study protocol



displays the logistic regression used to analyze the effect of age, sex, geographic location, degree of urbanization, and SES, on CP prevalence in general pediatric population and on epilepsy comorbid with CP by obtaining the OR.

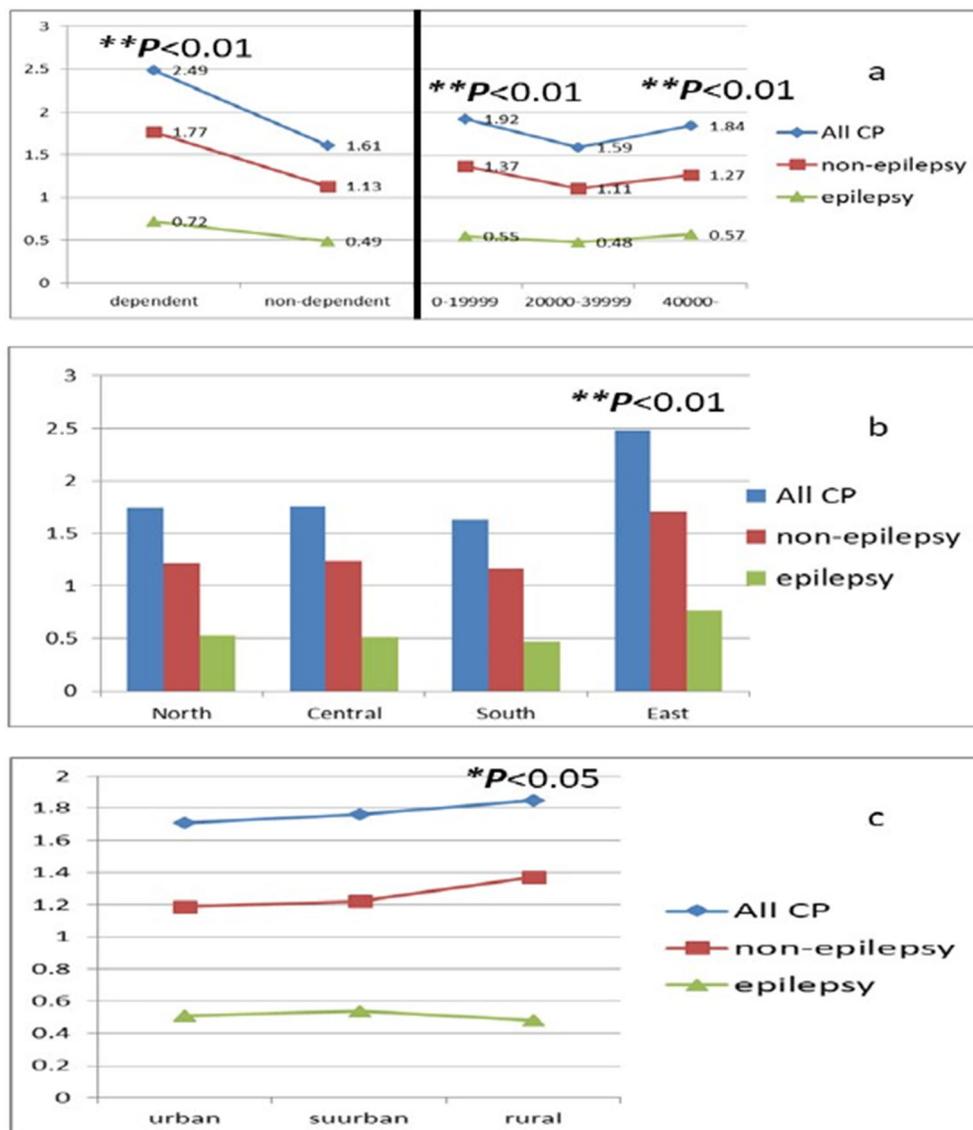
Table 2 describes the commonest comorbidities in children with CP including “other developmental or learning problems” (35.6%), “language or speech problems” (18.3%), mental retardation (11.5%), ophthalmic problems (6.4%), and nutritional problems (6.1%). Regarding to the comparison of common comorbidities in CP with epilepsy subgroup and CP without epilepsy subgroup, CP patients with epilepsy had a significantly higher OR ( $p < 0.05$ , chi-squared test) than did those without epilepsy with regard to several neuropsychiatric diseases, including mental retardation (OR = 2.26, 95% CI = 1.97–2.59), ophthalmologic problems (OR = 1.83, 95% CI = 1.53–2.19), hearing impairment (OR = 1.45, 95% CI = 1.03–2.05), and hydrocephalus (OR = 2.56, 95% CI = 1.77–3.70). No significant language or speech problems, ADHD, learning

or developmental problems, autism spectrum disorders, or nutritional problems were observed.

## Discussion

In this study, we estimated the prevalence over the study period of CP and epilepsy in the CP population. We also investigated their correlation with gender, age, and other socioeconomic characteristics, namely household income, residential location, and urbanization level. Age, gender, SES, geographic location, and degree of urbanization are independent risk factors for CP. Patients with CP had a significantly higher risk of epilepsy than their non-CP counterparts. Female patients with CP (age 15–19 years) living in urban areas had a higher risk of epilepsy. Furthermore, we observed that CP patients with epilepsy had a higher prevalence of other neurological impairments than CP patients without epilepsy.

**Fig. 2** Socioeconomic characters stratified analysis on the prevalence of epileptic CP and nonepileptic CP of current study. **a** Household income levels. **b** Geographic location of inhabitants' residence. **c** Urbanization level of households' registration



CP is a common neurological disease. In general, population-based studies worldwide have estimated the prevalence of CP to range from 1.5 to more than 4 per 1000 live births or in children of a defined age range [21–23]. In developed countries, the overall estimated prevalence rate of CP is 2–2.5 cases per 1000 live births [24], including a multicountries CP collaboration registries data in Europe, the Surveillance of CP in Europe [25]. In detail, there are approximately 1.7–2.0 per 1000 1-year survivors in the USA, 2.0 per 1000 live births in the UK. And there were 2.61 per 1000 school-age children in France [1]. According to the registry of CP in Austria, CP rates were either stabilized or decreased, particularly for children born extremely preterm, since the early 1990s [26]. Recently, some nationwide population studies focused on the prevalence of CP in Asian were reported, including 1.25 per 1000 children aged 0–17 years in China, and 1.96 per 1000 children aged 0–19 years in Japan, and 2.6 per 1000 children in South Korea

[27–29]. The prevalence of CP in Taiwan, as reported in our study, is similar to that reported in other developed countries. Interestingly, our result was very similar to the report of Japan [27]. Both studies estimated CP prevalence per 1000 population aged 5 to 9 years lay in the higher range than other age subgroup, and this gradually declined with age. The prevalence is significantly lower for patients aged 15–19. It was possible due to lower life expectancy of CP population, especially in CP with multiple impairments or with severe impaired mobility [30, 31]. In South Korea's study [28], between 2004 and 2008, the overall prevalence of CP showed an annual increase from 2.2 in 2004 to 3.2 in 2008 per 1000 children, respectively.

Regarding to socioeconomic and geographic factors, currently little and conflicting evidence has been obtained on the association of socioeconomic inequalities with the prevalence of CP. Evidence has suggested that the effect of SES on CP prevalence is stronger than those of the mediating factors of

**Table 1** Sociodemographic analysis of (1) CP in current general population and (2) epilepsy in children with CP diagnosis

Variable	Risk of CP in current pediatric general population OR (95% CI)	Risk of epilepsy in children with CP OR (95% CI)
Age		
0–4	*1.09 (1.01–1.16)	1.00 (–)
5–9	**1.54 (1.45–1.64)	1.10 (0.95–1.27)
10–14	**1.39 (1.31–1.47)	1.03 (0.89–1.19)
15–19	1.00 (–)	*1.19 (1.02–1.38)
Sex		
F	1.00 (–)	**1.33 (1.21–1.46)
M	**1.31 (1.25–1.37)	1.00 (–)
Region		
North	*1.07 (1.01–1.13)	1.09 (0.97–1.23)
Central	*1.08 (1.02–1.15)	1.04 (0.91–1.12)
South	1.00 (–)	1.00 (–)
East	**1.52 (1.34–1.73)	1.13 (0.85–1.48)
Urbanization		
Urban	1.00 (–)	*1.25 (1.04–1.49)
Suburban	1.03 (0.98–1.08)	*1.27 (1.06–1.53)
Rural	*1.08 (1.01–1.17)	1.00 (–)
Socioeconomic status		
Occupation		
Dependent	**1.54 (1.46–1.63)	1.00 (–)
Independent	1.00 (–)	1.06 (0.94–1.19)
Insurance level (NTD\$)		
0–19,999	**1.21 (1.15–1.27)	1.00 (–)
20,000–39,999	1.00 (–)	1.07 (0.96–1.20)
≥ 40,000	**1.16 (1.09–1.22)	1.13 (0.99–1.28)

\* $p < 0.05$ , \*\* $p < 0.01$  (by logistic regression model)

preterm birth, low birth weight, and postnatal trauma [32–34]. Our results revealed significantly higher prevalence of CP in members of families having lower insurance premiums than those having higher insurance premiums, as well as those

from East Taiwan compared with other areas, and significant higher in rural area than in urban with a trend of gradually higher incidence of CP from urban through suburban to rural areas. The reasons for these disparities may be uneven medical

**Table 2** Comparison of common cognition problems, neurological issues, and nutritional problems in CP with epilepsy subgroup and CP without epilepsy subgroup

	Total prevalence rate (%)	CP with epilepsy, $n = 2510$ , $n$ , (rate (%))	Without epilepsy, $n = 5909$ , $n$ , (rate (%))	Odds ratio
**Mental retardation	11.5	447 (17.8)	517 (8.8)	2.26 (1.97–2.59)
Language or speech problems	18.3	460 (18.3)	1078 (18.2)	1.00 (0.89–1.13)
Other developmental or learning problems	35.6	920 (36.7)	2075 (35.1)	1.07 (0.97–1.18)
Autistic spectrum disorder	1.9	58 (2.3)	103 (1.7)	1.33 (0.96–1.85)
ADHD	2.8	69 (2.7)	169 (2.9)	0.96 (0.72–1.28)
**Ophthalmic problems	6.4	229 (9.1)	307 (5.2)	1.83 (1.53–2.19)
*Hearing loss	1.7	54 (2.2)	88 (1.5)	1.45 (1.03–2.05)
**Hydrocephalus	1.4	60 (2.4)	56 (0.9)	2.56 (1.77–3.70)
Nutritional problems	6.1	169 (6.7)	347 (5.9)	1.16(0.96–1.40)

\* $p < 0.05$  \*\* $p < 0.01$  (by chi-squared test)

resource allocation and utilization, a shortage of health care personnel, and a lack of medical knowledge. Geographic variations that have been reported would further influence the survival, the recreation, and leisure participation of CP population [35, 36]. In the current study, epileptic CP was more prevalent in urban than in rural areas, possibly because of the tendency for families with children having CP to move to more affluent areas to seek adequate medical resources and efficient health care personnel. A study [34] based on 753 children with CP reported a significantly higher prevalence in the most deprived quintile. The study estimated that two thirds of the excess cases in the population associated with greater socioeconomic deprivation were normal-birth weight cases, and one third of cases were low-birth weight cases because of the higher prevalence of low-birth weight in more deprived populations. Therefore, we believe that public health care providers and policies should reinforce comprehensive prenatal care and early developmental delay risk intervention programs for children from families with lower insurance premiums, those in East Taiwan, and those in rural areas.

The prevalence of epilepsy is five times more common in patients with CP compared to normal children [10]. Studies have estimated that 15–60% of patients with CP also have epilepsy [2–10], in concordance with our results. Similar to our results, mental retardation, speech and language difficulties, primary sensory impairment (i.e., hearing and vision), and social interaction and behavioral problems are more common in patients with CP than in the general population. These problems increase the economic burden on the families that are directly affected and increase health care costs. A previous study [37] analyzed data on 199 patients with CP in South Taiwan who had visited an outpatient rehabilitation department, and it reported 47.2% (94/199) of patients had associated disorders, such as seizures, strabismus, visual and hearing impairment, a cleft palate, and hyperkinetic syndrome. In accordance with our results, numerous studies have reported that a large proportion of children with CP have some type of cognitive impairment [38–40]; this number increases with the prevalence of epilepsy [13, 14]. However, most prevalence rate of these comorbidities of CP in this study is obviously lower than literatures reported, especially for ophthalmic and hearing problems [41, 42]. The results may underestimate the prevalence of these comorbidities due to common limitation of most health insurance claim database. An exclusive population-based registration system for CP would provide more correct information in this issue. A recent research using the Korean Database of Cerebral Palsy that collected complete demography, birth history, onset and type of CP, and brain magnetic resonance imaging (MRI) finds that functional ability and accompanying impairments, reported speech-language disorder (43.9%), ophthalmologic impairment (32.9%), and intellectual disability (30.3%) were the three most common accompanying impairments [43]. These results are in line with

the clinical situation of children with CP. Our result at least shows the proportion of patients in CP population who needs medical service because of these comorbid conditions.

Moreover, we observed that CP with epilepsy confers a higher comorbidity rate of other neurological impairments than does CP without epilepsy. The associations of intellectual disability, ophthalmologic problems, and hearing impairment with epilepsy in children with CP are most probably related to the severity of their brain lesions. Children with CP caused by CNS malformation, CNS infection, and gray matter damage all showed a higher frequency of epilepsy than children with CP of other etiology [9]. A study at a tertiary hospital of Jaipur in Rajasthan India reported asphyxia was the most common risk factor of CP (45.5%), quadriplegia (56.6%) was the most common topographical type observed, and intellectual disability (47.7%) followed by epilepsy (41.6%) was the most common comorbidity [44]. Another example, periventricular leukomalacia (PVL) is often associated with epilepsy, visual and auditory damage, intellectual issues, and the delay of language speech. The severity of motor impairment and cognitive impairment was associated with the lateral ventricular volumes [45, 46]. However, in a study focused on children with cerebral palsy (CP) due to white matter injury in the Victorian Cerebral Palsy Registry database, they found most of the seizure disorders in these children are those of the age limited, epileptic syndromes of childhood, and with favorable outcome [47]. In another study aimed to determine the prevalence of neurodevelopmental impairments at age 10 years among children born extremely preterm, they found 25% had cognitive impairment, 11% had CP, 7% had autistic spectrum disorder, and 7% had epilepsy. Overall, nearly 70% were free of neurodevelopmental impairment, but 40% of children with impairments had multiple diagnoses. In addition, they found decreasing gestational age was associated with increasing number of impairments [48]. Those results implied the severity of motor limitation, intellectual disability, and epilepsy are consisted to the severity of their brain lesions, and it seems that different etiology of CP has a different severity of epilepsy and other neurodevelopmental outcome. However, the etiologies of CP are not discussed in this study due to data limitation.

Our study had certain limitations. First, because the diagnoses were based on administrative claims, some may represent a tentative, rather than final, diagnosis. However, because our definition of CP was in accordance with that of the HV registry and patients in rehabilitation, the prevalence of CP, as measured herein, is likely to be accurate. Second, we did not differentiate between the etiologies and subtypes of CP nor stratify our analysis based on the severity of CP or epilepsy because of the general secondary data limitation. Third, the reliability and validity of the secondary data in the NHIRD could not be verified. However, the BNHI uses a medical review system to avoid incorrect or tentative diagnoses.

Finally, most prevalence rate of the common comorbidities of CP in current study is obviously lower than literatures reported. A nationwide population-based registration system that collected complete sociodemographic, maternal and birth history, gestational age, onset and type of CP, brain MRI, electroclinical features of seizure disorders, associated neuropsychiatric and somatic comorbidities, and possible etiologies, exclusively for CP would provide more correct information in this issue.

## Conclusion

This was the largest nationwide, population-based, cross-sectional study on the prevalence of CP and comorbidity of epilepsy in Taiwan. The findings could be substantial relevance in both medical and health care policy. Regarding to the comprehensive treatment, a multidisciplinary team focusing on social and emotional development, communication, education, nutrition, and mobility for improving motor functions and reducing disability may facilitate the treatment of the complex neurological disorders of patients with CP. SES, urbanization stratification, and geographic variables are significantly associated with the risk of CP in children. These disparities should be addressed by the agencies responsible for ensuring equitable public health care for all citizens of Taiwan. The pattern of socioeconomic inequalities should be further investigated in other regions and should be considered in etiological research and the effective delivery and evaluation of services. In the future, a national with well-designed registration system exclusively for CP should provide more complete information in this issue.

## Compliance with ethical standards

This study was approved by and conducted in accordance with the Institutional Review Board of Kuang-Tien General Hospital.

**Conflict of interest** The authors declare that they have no conflict of interest.

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