BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020994
Article Type:	Research
Date Submitted by the Author:	05-Dec-2017
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	EPIDEMIOLOGY, PAEDIATRICS, Developmental neurology & neurodisability < PAEDIATRICS, PUBLIC HEALTH

Characteristics of young children with developmental delays and their trends over 14 years in Taiwan: A population-based nationwide study

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ABSTRACT

Objectives: To describe the epidemiologic characteristics of developmental delays (DD) at the national level and assess the changes in over time, we conducted a study in Taiwan.

Design: We calculated the incidence rates of DD from 2003 to 2016 and assessed the trends over time.

Setting: As dictated by law, local governments in Taiwan are required to register children with DD and provide services. The central government has constructed a national registry with the data from local centers. We analysed the national registry data.

Participants: We included children who were under 6 years old, and this population ranged from 1164150 to 1577443 during the study period. All registered cases were certified through a process set forth by law.

Primary and secondary outcome measures: We calculated annual incidence rates by age, sex, and geographic area and assessed trends over the study period.

Results: The incidence of DD in children under 6 years old displayed an increasing trend over the study period, ranging from 7.0 to 16.3 per 1000 person-year. Boys had higher incidence throughout all 14 years, and the boy-to-girl rate ratios had an increasing trend over time with some fluctuations, ranging from 1.84 to 1.99. In addition, rural areas had higher incidence rates, and the rural-to-urban rate ratios ranged from 0.98 to 2.00 without apparent time trends. Girls had a higher proportion of early reporting (< 3 year) throughout all years, but the difference in the proportion of early reporting between rural and urban areas were not consistent.

Conclusions: Male sex appeared to be a risk factor for development delays, which is unlikely to be due to more attention received by boys because girls had a higher proportion of early reporting. We also found that children lived in rural areas appeared to have a higher risk of having DD.

Keywords: Developmental delays; Geographic distribution; Incidence; Registry; Sex; Taiwan

Strengths and limitations of this study

- The Taiwanese registry of children with developmental delays in included only new cases , which provides incidence data that are rarely available at the national level.
- The law in Taiwan mandates the reporting of cases, which minimizes under-reporting.
- Using nationwide registry data, this study has a large sample size, with a population of more than 1 million each year.
- The duration of data collection in this study was 14 years, and the assessment of time trends over such a long period of time at the national level has rarely been achieved in previous studies.
- The major limitation of our study is that the government does not release data on individual cases, which make it impossible to conduct the analysis in further detail.

INTRODUCTION

Developmental delays (DD) are generally defined as a child does not reach expected developmental milestones at the age.[1] Although DD are prevalent among children, data on its incidence at the national level are limited. For the identification of risk factors, incidence data are generally more useful than prevalence data. However, the majority of previous studies on DD used prevalence data, most likely because incidence data were more difficult to obtain.[2] As a result, changes in epidemiologic characteristics over time are seldom assessed, because such studies would require incidence data.

A child's development is affected by many biological and environmental factors.[1] Among biological ones, male sex is a strong risk factor.[3] Many studies found that the prevalence rate for DD was higher in boys than in girls.[3 4] Also, residents of rural areas have reported more health-related problems than those of urban areas in general,[5] and this disparity might also be true for DD. However, studies on this topic are limited and have reported inconsistent results. For example, the Multiple Indicator Cluster Survey conducted by the United Nations Children's Fund in countries with low and middle incomes did not observe consistent results in terms of differences between rural and urban areas across various countries.[6]

Under the Children Welfare Law, local governments in Taiwan have established Early Intervention Reporting and Referral Centers (EIRRCs) to register and provide services to children with DD.[7] The Children and Youth Welfare Law also mandates that institutions of welfare, education, and medicine report all children with suspected DD to the EIRRC.[8] Using data collected at the EIRRCs, the central government has constructed a national registry of children with DD. This registry provides researchers with a unique resource with which to conduct nationwide epidemiological studies. In a previous study, we analyzed the national

registry data from 2003 to 2008.[2] However, since it is difficult to precisely evaluate the trends of incidence with only 6 years' worth of data, we extended the time range from 2003 to 2008 to a 14-year period till 2016 as more data became available. This better suited our purposes of studying epidemiological characteristics of incident cases of DD and assessing time trends.

METHODS

Case definition

The Enforcement Rules of the Children and Youth Welfare Law of Taiwan[9] defined "developmental delays" as "allegedly or expected abnormal development in respect of cognitive development, physiological development, language and communication development, psycho-social development or self-governing skills that have been judged and confirmed by the accredited medical institutes under health authority." In order to receive a certificate of DD, the child requires an assessment performed by a physician at an accredited hospital, or by a trained social worker in an EIRRC,[10] who generally used the Taipei City Developmental Checklist for Preschoolers, 2nd version as the assessment tool.[11]

Data Collection

The EIRRCs collect data on newly reported cases and reports such cases to the central government, which maintains a registry of cases and publishes a yearbook each year. Before the re-organisation of the government in 2013, the registry was maintained by the Ministry of the Interior. After 2013, this responsibility fell to the Ministry of Health and Welfare. This yearbook includes the total numbers of newly reported cases by age at reporting, sex, and

area.[12] We analysed the data from 2003 to 2016.

We divided the cases into two groups, < 3 years and 3–5years, according to the age at the time of reporting and defined the group < 3 years as "early reporting".[13] Although the yearbook includes statistics on a age group "≥ 6 years," we did not include this group in our analyses because it only includes children who have not yet entered the primary school, not all children who are 6 years of age or older.

In the stratified analyses by geographic area, we divided the administrative regions in Taiwan into two groups: "urban areas" and "rural areas." An urban area is one in which more than 50% of the population live in metropolitan areas (as defined by the Directorate-General of Budget, Accounting and Statistics of Taiwan).[14] Consequently, a rural area is one in which 50% or less of the population live in metropolitan areas. In a re-organisation of administrative regions in 2011, the original Tainan City (an urban area) and Tainan County (a rural area) were merged into the new Tainan City. Data on the two original administrative regions has been unavailable since this merging, so they were both excluded from this part of the analyses.

To calculate incidence rates, we obtained data on the numbers of boys, girls, and the total population in each age group for each administrative region from the Monthly Bulletin of Interior Statistics.[15]

Data analysis

We estimated age-specific incidence rates in a given year by dividing the number of newly reported cases by the number of individuals in a specific age group. Likewise, the

sex-specific incidence rates of each year were estimated by dividing the number of newly reported cases by the number of individuals of each sex. We evaluated the differences between the two sexes by using the incidence rate ratio calculated through dividing the incidence rate in boys by the incidence rate in girls. To evaluate the geographic differences, we estimated the incidence rate in rural or urban areas in each year by first dividing the number of newly reported cases by the number of individuals in each type of area, and then obtaining the incidence rate ratio by dividing the incidence rate in rural areas by the incidence rate in urban areas. A 95% confidence interval was constructed for each rate ratio to evaluate its statistical significance.

To evaluate the difference in early reporting between boys and girls, we calculated the proportion of early reporting in boys or girls each year by dividing the number of cases under 3 years of age by the number of cases under 6 years of age in each sex. We then obtained the boy-to-girl proportion ratio of early reporting by dividing the proportion in boys by the proportion in girls. A 95% confidence interval was constructed for each proportion ratio to evaluate its statistical significance.

Likewise, to evaluate the difference of early reporting between rural and urban areas, we calculated the proportion of early reporting in rural or urban areas in each year by dividing the number of cases under 3 years of age by the number of cases under 6 years of age in each area. We then obtained the rural-to-urban proportion ratio of early reporting by dividing the proportion in rural areas by the proportion in urban areas. A 95% confidence interval was constructed for each proportion ratio to evaluate its statistical significance.

We reported descriptive statistics as numbers or percentages and used linear regressions to evaluate the trends of changes in incidence rates, incidence rate ratios, and proportion ratios over time. All the analyses were conducted using SAS 9.1, and all the statistical tests

were performed at the two-tailed significance level of 0.05.

RESULTS

During the study period of 2003 to 2016, 211661 new cases of DD under 6 years of age were registered, and the overall incidence rate was 7.0 to 16.3 per 1000 person-year. The rate was 5.7 to 15.3 per 1000 person-year in children under 3 years of age and 7.9 to 18.0 per 1000 person-year in children 3–5 years of age. We observed a general increasing trend over time in all three age groups (p <0.01 for all) (Table 1).

The overall incidence rate ranged from 9.0 to 21.3 per 1000 person-year in boys and from 4.9 to 11.0 per1000 person-year in girls. The rate was constantly higher in boys than in girls, and the boy-to-girl rate ratios had an increasing trend over time ($p < 0.01$) with some fluctuations, ranging from 1.84 to 1.99 (Table 2). All the rate ratios were statistically significant.

With the exclusion of Tainan City and County, there were 6 cities and 17 counties in Taiwan. All 6 cities and 5 of the counties were classified as urban areas, and the remaining 12 counties were classified as rural areas. The overall incidence rate ranged from 7.2 to 25.5 per 1000 person-year in rural areas and from 6.1 to 14.7 per 1000 person-year in urban areas. The incidence rates were generally higher in rural than in urban areas, except for the year 2003, in which the rural-to-urban rate ratio was not statistically significant (Table 3). In other years, the ratio fluctuated from 1.10 to 2.00 and all reached statistical significance. There was no apparent trend in the changes over time.

Table 1 The overall incidence rate of developmental delays in children under 6 years of age

Year	Reported number of cases		Population		Incidence (per 1000 person-year)		
	<3 year	3-5 year	<3 year	3-5 year	<3 year	3-5 year	<6 year
2003	4139	7557	720897	856546	5.7	8.8	7.4
2004	4058	6682	680737	846130	6.0	7.9	7.0
2005	4512	6672	641095	809663	7.0	8.2	7.7
2006	5098	6798	619354	730819	8.2	9.3	8.8
2007	6201	7273	606840	692164	10.2	10.5	10.4
2008	6655	7439	599674	654179	11.1	11.4	11.2
2009	6103	8789	587219	633676	10.4	13.9	12.2
2010	6957	9122	551334	621318	12.6	14.7	13.7
2011	5850	8816	551707	612443	10.6	14.4	12.6
2012	6270	9921	589053	600984	10.6	16.5	13.6
2013	7474	9644	622140	564244	12.0	17.1	14.4
2014	9618	9711	634646	566056	15.2	17.2	16.1
2015	9372	10319	613735	608119	15.3	17.0	16.1
2016	9160	11451	627470	636735	14.6	18.0	16.3

Table 2 The overall incidence rate and rate ratio of developmental delays in children under 6 years of age by sex

Year	Reported number of cases		Population		Incidence (per 1000 person-year)		Rate ratio [95% C.I.][a]
	Boy	Girl	Boy	Girl	Boy	Girl	
2003	7837	3859	823435	754008	9.5	5.1	1.86 [1.79, 1.93]*
2004	7183	3557	797949	728918	9.0	4.9	1.84 [1.77, 1.92]*
2005	7550	3634	758014	692744	10.0	5.2	1.90 [1.83, 1.98]*
2006	7998	3898	705549	644624	11.3	6.0	1.87 [1.80, 1.95]*
2007	9053	4421	679395	619609	13.3	7.1	1.87 [1.80, 1.94]*
2008	9463	4631	655736	598117	14.4	7.7	1.86 [1.80, 1.93]*
2009	9981	4911	637773	583122	15.6	8.4	1.86 [1.80, 1.92]*
2010	10968	5111	612072	560580	17.9	9.1	1.97 [1.90, 2.03]*
2011	9969	4697	607034	557116	16.4	8.4	1.95 [1.88, 2.02]*
2012	11069	5122	619396	570641	17.9	9.0	1.99 [1.93, 2.06]*
2013	11578	5540	616451	569933	18.8	9.7	1.93 [1.87, 1.99]*
2014	13122	6207	622626	578076	21.1	10.7	1.96 [1.90, 2.02]*
2015	13419	6272	633460	588394	21.2	10.7	1.99 [1.93, 2.05]*
2016	13939	6672	654986	609219	21.3	11.0	1.94 [1.89, 2.00]*

[a]CI: confidence interval

*$p < 0.05$.

Table 3 The overall incidence rate and rate ratio of developmental delays in children under 6 years of age by area[a]

Year	Reported number of cases[a]		Population[a]		Incidence (per 1000 person-year)		Rate ratio [95% C.I.][b]
	Rural	Urban	Rural	Urban	Rural	Urban	
2003	3016	7651	417597	1041508	7.2	7.3	0.98 [0.94, 1.03]
2004	3499	6161	401360	1010972	8.7	6.1	1.43 [1.37, 1.49]*
2005	3275	7031	379954	962324	8.6	7.3	1.18 [1.13, 1.23]*
2006	3401	7580	350937	898852	9.7	8.4	1.15 [1.10, 1.20]*
2007	3688	8794	331562	871125	11.1	10.1	1.10 [1.06, 1.14]*
2008	4843	8177	312880	847893	15.5	9.6	1.61 [1.55, 1.66]*
2009	4306	9515	298839	831537	14.4	11.4	1.26 [1.22, 1.31]*
2010	5108	9881	280108	806265	18.2	12.3	1.49 [1.44, 1.54]*
2011	5074	8779	268296	808844	18.9	10.9	1.74 [1.68, 1.80]*
2012	5829	9336	266682	833418	21.9	11.2	1.95 [1.89, 2.02]*
2013	5339	10124	261442	835199	20.4	12.1	1.68 [1.63, 1.74]*
2014	6629	10838	259828	850302	25.5	12.7	2.00 [1.94, 2.06]*
2015	5531	12576	257152	872878	21.5	14.4	1.49 [1.45, 1.54]*
2016	5591	13365	261055	908526	21.4	14.7	1.46 [1.41, 1.50]*

[a] Tainan City and Tainan County were excluded in the analyses due to a re-organization of administrative regions in 2011.

[b] CI: confidence interval

* $p < 0.05$.

The proportion of early reporting had an increased trend from 2003 to 2008 and then showed fluctuations afterwards (Table 4). Girls had a higher proportion of early reporting than boys throughout all years, with the boy-to-girl proportion ratios ranging from 0.85 to 0.94. All the proportion ratios were statistically significant, but there was no apparent trend in the changes over time. The difference in the proportion of early reporting between rural and urban areas fluctuated over time. The rural-to-urban proportion ratios ranged from 0.79 to 1.19, and there was no apparent trend in the changes over the years (Table 5).

Table 4 The proportion of early reporting of developmental delays in children under 6 years of age by sex

Year	Reported number of cases									Boy-to-girl proportion ratio of early reporting [95% C.I.] [a]
	Total			Boy			Girl			
	< 3 year	< 6 year	%	< 3 year	< 6 year	%	< 3 year	< 6 year	%	
2003	4139	11696	35.4	2660	7837	33.9	1479	3859	38.3	0.89 [0.84, 0.93]*
2004	4058	10740	37.8	2648	7183	36.9	1410	3557	39.6	0.93 [0.88, 0.98]*
2005	4512	11184	40.3	2881	7550	38.2	1631	3634	44.9	0.85 [0.81, 0.89]*
2006	5098	11896	42.9	3321	7998	41.5	1777	3898	45.6	0.91 [0.87, 0.95]*
2007	6201	13474	46.0	3953	9053	43.7	2248	4421	50.8	0.86 [0.83, 0.89]*
2008	6655	14094	47.2	4310	9463	45.5	2345	4631	50.6	0.90 [0.87, 0.93]*
2009	6103	14892	41.0	3995	9981	40.0	2108	4911	42.9	0.93 [0.90, 0.97]*
2010	6957	16079	43.3	4627	10968	42.2	2330	5111	45.6	0.93 [0.89, 0.96]*
2011	5850	14666	39.9	3896	9969	39.1	1954	4697	41.6	0.94 [0.90, 0.98]*
2012	6270	16191	38.7	4153	11069	37.5	2117	5122	41.3	0.91 [0.87, 0.95]*
2013	7474	17118	43.7	4818	11578	41.6	2656	5540	47.9	0.87 [0.84, 0.90]*
2014	9618	19329	49.8	6320	13122	48.2	3298	6207	53.1	0.91 [0.88, 0.93]*
2015	9372	19691	47.6	6066	13419	45.2	3306	6272	52.7	0.86 [0.83, 0.88]*
2016	9160	20611	44.4	5944	13939	42.6	3216	6672	48.2	0.88 [0.86, 0.91]*

[a] CI: confidence interval

* $p < 0.05$.

Table 5 The proportion of early reporting of developmental delays in children under 6 years of age by area[a]

Year	Reported number of cases						Rural-to-urban proportion ratio of early reporting [95% C.I.][b]
	Rural			Urban			
	< 3 year	< 6 year (total)	< 3 year (%)	< 3 year	< 6 year (total)	< 3 year (%)	
2003	1159	3016	38.4	2475	7651	32.3	1.19 [1.12 1.26]*
2004	1215	3499	34.7	2393	6161	38.8	0.89 [0.85 0.94]*
2005	1140	3275	34.8	2959	7031	42.1	0.83 [0.78 0.87]*
2006	1353	3401	39.8	3415	7580	45.1	0.88 [0.84 0.93]*
2007	1423	3688	38.6	4294	8794	48.8	0.79 [0.75 0.83]*
2008	2472	4843	51.0	3578	8177	43.8	1.17 [1.12 1.21]*
2009	1845	4306	42.8	3646	9515	38.3	1.12 [1.07 1.17]*
2010	2211	5108	43.3	4152	9881	42.0	1.03 [0.99 1.07]
2011	1888	5074	37.2	3555	8779	40.5	0.92 [0.88 0.96]*
2012	2054	5829	35.2	3715	9336	39.8	0.89 [0.85 0.92]*
2013	2271	5339	42.5	4366	10124	43.1	0.99 [0.95 1.02]
2014	3318	6629	50.1	5175	10838	47.7	1.05 [1.02 1.08]*
2015	2772	5531	50.1	5712	12576	45.4	1.10 [1.07 1.14]*
2016	2482	5591	44.4	5730	13365	42.9	1.04 [1.00 1.07]

[a]Tainan City and Tainan County were excluded in the analyses due to a re-organization of administrative regions in 2011.

[b]CI: confidence interval

*p< 0.05.

DISCUSSION

The overall incidence rate of DD in children under 6 years of age generally increased during the study period, which is consistent with the observation in our preliminary study.[2] We believe the increase cannot be attributed to an increase in the number of cases, because the major risk factors for DD such as genetic constructs, medical care, and socioeconomic status[1, 16] did not undergo remarkable changes over the 14-year period. Therefore, the increased incidence rate of DD is more likely to be due to the improvement in reporting of cases, which may be in turn attributable to the improvement in the awareness of the developmental abnormalities in children, lower discrimination against the patients, better service of the related agencies, more willingness demonstrated by parents and guardians to register their children, etc.[17, 18]

Since the critical period of treatment for DD is before the child reaches 3 years of age, an early diagnosis is crucial.[19] Therefore, the Taiwanese government has been promoting the reporting and intervention in cases of children with DD under 3 years of age,[2, 13] when intervention procedures are most cost effective. In fact, it is generally believed that the earlier the intervention, the better the prognosis.[20] Although we observed an increased trend in early reporting from 2003 to 2008, the trend did not persist after 2008. This might indicate that the existing measures of promotion have reached their limits of effectiveness, additional efforts and approaches are required, especially since the proportion of early reporting has never risen beyond 50%.

Previously, we used the data from the national disability registry of Taiwan, a different nationwide source of information than that used in the current study, to conduct a series of studies on major developmental disabilities, including autism spectrum disorders (ASD),

intellectual disability, and speech and language disability.[17, 18, 21] We found that the prevalence rates were consistently higher in boys than in girls. Those developmental disabilities are all major risk factors for DD. Therefore, the finding of a higher incidence of DD in boys in the current study is compatible with the findings of our previous studies. Many theories have been proposed to explain the sex difference, including both biological and sociological factors. Biologically, the higher risk in boys is often attributed to hereditary factors such as X-linked conditions.[22, 23] The central nervous system of young boys is also found to be more susceptible to damage.[22] In terms of social factors, in Asian countries, families generally display a male gender preference, and thus pay more attention to boys. [22, 23] In addition, boys are more likely to demonstrate impulsive and aggressive behaviors than girls and therefore are more likely to be referred for diagnosis. [23]

In this study, however, we found that girls had a higher proportion of early reporting than boys. This does not support the theory that the higher level of attention received by boys is a major factor contributing to the higher incidence rate of DD. In fact, a review of literature concluded that boys are more likely to have DD, but when such conditions arise in girls, a more severe form is usually manifest.[24] Our finding of a higher proportion of early reporting in girls is compatible with this conclusion. Furthermore, as the birth rate has been decreasing in Taiwan, [15] the difference in the attention received by boys and girls should be decreasing, but we found the sex difference had an increasing trend instead of a decreasing trend. Therefore, we believe biological factors contribute more than social factors to the sex difference in DD in early childhood.

In the preliminary study, we failed to identify the time trend in the sex difference (no significant trend in boy-to-girl rate ratio).[2] The current study has the advantage of a longer

follow-up period. In a separate study, which used data from the national disability registry, we found that there was a 497.30% increase in the prevalence rate of childhood ASD from 2000 to 2011in Taiwan, which is much higher than the 54.40% increase in all reported disabilities combined.[25] In addition, the boy-to-girl ratio of ASD was found to be the highest among the major conditions contributing to DD.[4, 17] Therefore, we believe the increasing trend in the boy-to-girl incidence rate ratio of DD in Taiwan can largely be attributable to the increasing trend in the number of cases of ASD.

Studies on the differences in DD between rural and urban areas are limited. There are relatively more data on childhood disabilities. The Multiple Indicator Cluster Survey conducted by the United Nations Children's Fund in developing countries did not observe a consistent result.[6] Munro reviewed several studies of intellectual disability in the U.S.A. and also found results to be inconsistent.[23] A nationwide study of childhood disability in China, however, found a higher prevalence rate in rural areas,[26] which is consistent with our finding on DD in this study. Moreover, according to the national disability registry of Taiwan, some major childhood disabilities leading to DD, including intellectual disability and speech and language disability,[18, 21] as well as all disabilities combined[27] were more prevalent in rural areas. While the lower socioeconomic status of rural residents in Taiwan should be a major factor,[28, 29] the difference might also be explained by environmental factors such as lower quality of child care, lower parental education, and limited educational and cultural opportunities.[5, 22, 30]

The registry of children with DD in Taiwan has some unique features. First of all, it included new cases only, which provides incidence data that are rarely available at the national level and are more reliable for identifying risk factors.[31] Secondly, Taiwanese law mandates that cases be reported, and therefore, instances of under-reporting are rare. The registry also has the

advantage of a large number (more than 200000) of cases. Lastly, the duration of data collection is long, which makes assessing time trends possible. The major limitation of our study is that the government does not release data on individual cases, and therefore we were unable to conduct more detailed analyses. For example, while we believe the increasing trend in the boy-to-girl incidence rate ratio of DD can largely be attributable to the increasing trend in the number of cases of ASD, we could not perform analyses to verify this.

CONCLUSIONS

The incidence rates of young children with DD have been increasing in Taiwan, which is likely to be attributable to improvements in the reporting of cases. The incidence rates are higher in boys than in girls, which is unlikely to be due to more attention received by boys because girls had a higher proportion of early reporting. In addition, the boy-to-girl rate ratio has an increasing trend of over the years, and we believe the increasing number of cases of ASD is an important factor. Rural areas had higher incidence than urban areas, which calls for further studies to identify the contributing factors.

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Acknowledgements

We would like to thank the Department of Statistics of Ministry of the Interior and the Department of Statistics of the Ministry of the Health and Welfare for providing the registry data and Miss Chao-Hui Weng for her assistance in statistical analysis.

Contributors

All the authors approved the contents of the submitted article. Y-CT and H-RG contributed

equally to this work. D-CL and Y-CT conceived and designed the experiments. D-CL and H-RG collected and analysed the data. D-CL and H-RG wrote the paper. D-CL, Y-CT, and H-RG contributed in the final approval of manuscript.

Funding

This research was supported by Ditmanson Medical Foundation Chia-Yi Christian Hospital Research Program through Grant R105-006.

Competing interests

None declared.

Ethics approval

This study has been reviewed and approved by the Institution Review Board of the Ditmanson Medical Foundation Chia-Yi Christian Hospital (CYCH-IRB No. 104016).

Data sharing statement

No additional data are available.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020994.R1
Article Type:	Research
Date Submitted by the Author:	21-Jan-2018
Complete List of Authors:	Lai, Der-Chung; Ditmanson Medical Foundation Chia-Yi Christian Hospital, Department of Physical Medicine and Rehabilitation Tseng, Yen-Cheng; Chang Jung Christian University, Language Education Center and Department of Tourism, Food, and Beverage Management Guo, How-Ran
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	EPIDEMIOLOGY, PAEDIATRICS, Developmental neurology & neurodisability < PAEDIATRICS, PUBLIC HEALTH

Characteristics of young children with developmental delays and their trends over 14 years in Taiwan: A population-based nationwide study

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ABSTRACT

Objectives: To describe the epidemiologic characteristics of developmental delays (DD) at the national level and assess the changes in over time, we conducted a study in Taiwan.

Design: We calculated the incidence rates of DD from 2003 to 2016 and assessed the trends over time.

Setting: As dictated by law, local governments in Taiwan are required to register children with DD and provide services. The central government has constructed a national registry with the data from local centers. We analysed the national registry data.

Participants: We included children who were under 6 years old, and this population ranged from 1164150 to 1577443 during the study period. All registered cases were certified through a process set forth by law.

Primary and secondary outcome measures: We calculated annual incidence rates by age, sex, and geographic area and assessed trends over the study period.

Results: The incidence of DD in children under 6 years old displayed an increasing trend over the study period, ranging from 7.0 to 16.3 per 1000 person-year. Boys had higher incidence throughout all 14 years, and the boy-to-girl rate ratios had an increasing trend over time with some fluctuations, ranging from 1.84 to 1.99. In addition, rural areas had higher incidence rates, and the rural-to-urban rate ratios ranged from 0.98 to 2.00 without apparent time trends. Girls had a higher proportion of early reporting (< 3 year) throughout all years, but the difference in the proportion of early reporting between rural and urban areas were not consistent.

Conclusions: Male sex appeared to be a risk factor for development delays, which is unlikely to be due to more attention received by boys because girls had a higher proportion of early reporting. We also found that children lived in rural areas appeared to have a higher risk of having DD.

Keywords: Developmental delays; Geographic distribution; Incidence; Registry; Sex; Taiwan

Strengths and limitations of this study

- The Taiwanese registry of children with developmental delays in included only new cases , which provides incidence data that are rarely available at the national level.
- The law in Taiwan mandates the reporting of cases, which minimizes under-reporting.
- Using nationwide registry data, this study has a large sample size, with a population of more than 1 million each year.
- The duration of data collection in this study was 14 years, and the assessment of time trends over such a long period of time at the national level has rarely been achieved in previous studies.
- The major limitation of our study is that the government does not release data on individual cases, which make it impossible to conduct the analysis in further detail.

INTRODUCTION

Developmental delays (DD) are generally defined as a child does not reach expected developmental milestones at the age.[1] Although DD are prevalent among children, data on its incidence at the national level are limited. For the identification of risk factors, incidence data are generally more useful than prevalence data. However, the majority of previous studies on DD used prevalence data, most likely because incidence data were more difficult to obtain.[2] As a result, changes in epidemiologic characteristics over time are seldom assessed, because such studies would require incidence data.

A child's development is affected by many biological and environmental factors.[1] Among biological ones, male sex is a strong risk factor.[3] Many studies found that the prevalence rate for DD was higher in boys than in girls.[3 4] Also, residents of rural areas have reported more health-related problems than those of urban areas in general,[5] and this disparity might also be true for DD. However, studies on this topic are limited and have reported inconsistent results. For example, the Multiple Indicator Cluster Survey conducted by the United Nations Children's Fund in countries with low and middle incomes did not observe consistent results in terms of differences between rural and urban areas across various countries.[6]

Under the Children Welfare Law, local governments in Taiwan have established Early Intervention Reporting and Referral Centers (EIRRCs) to register and provide services to children with DD.[7] The Children and Youth Welfare Law also mandates that institutions of welfare, education, and medicine report all children with suspected DD to the EIRRC.[8] Using data collected at the EIRRCs, the central government has constructed a national registry of children with DD. This registry provides researchers with a unique resource with which to conduct nationwide epidemiological studies. In a previous study, we analyzed the national

registry data from 2003 to 2008.[2] However, since it is difficult to precisely evaluate the trends of incidence with only 6 years' worth of data, we extended the time range from 2003 to 2008 to a 14-year period till 2016 as more data became available. This better suited our purposes of studying epidemiological characteristics of incident cases of DD and assessing time trends.

METHODS

Case definition

The Enforcement Rules of the Children and Youth Welfare Law of Taiwan[9] defined "developmental delays" as "allegedly or expected abnormal development in respect of cognitive development, physiological development, language and communication development, psycho-social development or self-governing skills that have been judged and confirmed by the accredited medical institutes under health authority." In order to be registered as a case of DD, the child requires an assessment performed by a physician at an accredited hospital, or by a trained social worker in an EIRRC,[10] who generally used the Taipei City Developmental Checklist for Preschoolers, 2nd version as the assessment tool.[11]

Data Collection

The EIRRCs collect data on newly reported cases and report such cases to the central government, which maintains a registry of cases and publishes a yearbook each year. Before the re-organisation of the government in 2013, the registry was maintained by the Ministry of the Interior. After 2013, this responsibility fell to the Ministry of Health and Welfare. This yearbook includes the total numbers of newly reported cases by age at reporting, sex, and

area.[12] We analysed the data from 2003 to 2016.

We divided the cases into two groups, < 3 years and 3–5years, according to the age at the time of reporting and defined the group < 3 years as "early reporting".[13] Although the yearbook includes statistics on a age group "≥ 6 years," we did not include this group in our analyses because it only includes children who have not yet entered the primary school, not all children who are 6 years of age or older.

In the stratified analyses by geographic area, we divided the administrative regions in Taiwan into two groups: "urban areas" and "rural areas." An urban area is one in which more than 50% of the population live in metropolitan areas (as defined by the Directorate-General of Budget, Accounting and Statistics of Taiwan).[14] Consequently, a rural area is one in which 50% or less of the population live in metropolitan areas. In a re-organisation of administrative regions in 2011, the original Tainan City (an urban area) and Tainan County (a rural area) were merged into the new Tainan City. Data on the two original administrative regions has been unavailable since this merging, so they were both excluded from this part of the analyses.

To calculate incidence rates, we obtained data on the numbers of boys, girls, and the total population in each age group for each administrative region from the Monthly Bulletin of Interior Statistics.[15]

Data analysis

We estimated age-specific incidence rates in a given year by dividing the number of newly reported cases by the number of individuals in a specific age group. Likewise, the

sex-specific incidence rates of each year were estimated by dividing the number of newly reported cases by the number of individuals of each sex. We evaluated the differences between the two sexes by using the incidence rate ratio calculated through dividing the incidence rate in boys by the incidence rate in girls. To evaluate the geographic differences, we estimated the incidence rate in rural or urban areas in each year by first dividing the number of newly reported cases by the number of individuals in each type of area, and then obtaining the incidence rate ratio by dividing the incidence rate in rural areas by the incidence rate in urban areas. A 95% confidence interval was constructed for each rate ratio to evaluate its statistical significance.

To evaluate the difference in early reporting between boys and girls, we calculated the proportion of early reporting in boys or girls each year by dividing the number of cases under 3 years of age by the number of cases under 6 years of age in each sex. We then obtained the boy-to-girl proportion ratio of early reporting by dividing the proportion in boys by the proportion in girls. A 95% confidence interval was constructed for each proportion ratio to evaluate its statistical significance.

Likewise, to evaluate the difference of early reporting between rural and urban areas, we calculated the proportion of early reporting in rural or urban areas in each year by dividing the number of cases under 3 years of age by the number of cases under 6 years of age in each area. We then obtained the rural-to-urban proportion ratio of early reporting by dividing the proportion in rural areas by the proportion in urban areas. A 95% confidence interval was constructed for each proportion ratio to evaluate its statistical significance.

We reported descriptive statistics as numbers or percentages and used linear regressions to evaluate the trends of changes in incidence rates, incidence rate ratios, and proportion ratios over time. All the analyses were conducted using SAS 9.1, and all the statistical tests

were performed at the two-tailed significance level of 0.05.

RESULTS

During the study period of 2003 to 2016, 211661 new cases of DD under 6 years of age were registered, and the overall incidence rate was 7.0 to 16.3 per 1000 person-year. The rate was 5.7 to 15.3 per 1000 person-year in children under 3 years of age and 7.9 to 18.0 per 1000 person-year in children 3–5 years of age. We observed a general increasing trend over time in all three age groups (p <0.01 for all) (Table 1).

With data on 14 years, we were able to compare the incidence among four mutually exclusive birth cohorts. Using the 2001-2003 cohort (those who were in the <3 year group in 2003) as the baseline, we observed an increasing trend in the estimated overall incidence rates in children under 6 years old. Specifically, the estimated overall incidence before 6 years of age rate was 7.5 per 1000 in the 2001-2003 birth cohort, 11.1 per 1000 in the 2004-2006 birth cohort, 13.5 per 1000 in the 2007-2009 birth cohort, and 13.9 per 1000 in the 2010-2012 birth cohort. The trend was similar to that observed in the year-by-year overall incidence rates.

The overall incidence rate ranged from 9.0 to 21.3 per 1000 person-year in boys and from 4.9 to 11.0 per1000 person-year in girls. The rate was constantly higher in boys than in girls, and the boy-to-girl rate ratios had an increasing trend over time (p < 0.01) with some fluctuations, ranging from 1.84 to 1.99 (Table 2). All the rate ratios were statistically significant.

Table 1 The overall incidence rate of developmental delays in children under 6 years of age

Year	Reported number of cases		Population		Incidence (per 1000 person-year)		
	<3 year	3-5 year	<3 year	3-5 year	<3 year	3-5 year	<6 year
2003	4139	7557	720897	856546	5.7	8.8	7.4
2004	4058	6682	680737	846130	6.0	7.9	7.0
2005	4512	6672	641095	809663	7.0	8.2	7.7
2006	5098	6798	619354	730819	8.2	9.3	8.8
2007	6201	7273	606840	692164	10.2	10.5	10.4
2008	6655	7439	599674	654179	11.1	11.4	11.2
2009	6103	8789	587219	633676	10.4	13.9	12.2
2010	6957	9122	551334	621318	12.6	14.7	13.7
2011	5850	8816	551707	612443	10.6	14.4	12.6
2012	6270	9921	589053	600984	10.6	16.5	13.6
2013	7474	9644	622140	564244	12.0	17.1	14.4
2014	9618	9711	634646	566056	15.2	17.2	16.1
2015	9372	10319	613735	608119	15.3	17.0	16.1
2016	9160	11451	627470	636735	14.6	18.0	16.3

Table 2 The overall incidence rate and rate ratio of developmental delays in children under 6 years of age by sex

Year	Reported number of cases		Population		Incidence (per 1000 person-year)		Rate ratio [95% C.I.][a]
	Boy	Girl	Boy	Girl	Boy	Girl	
2003	7837	3859	823435	754008	9.5	5.1	1.86 [1.79, 1.93]*
2004	7183	3557	797949	728918	9.0	4.9	1.84 [1.77, 1.92]*
2005	7550	3634	758014	692744	10.0	5.2	1.90 [1.83, 1.98]*
2006	7998	3898	705549	644624	11.3	6.0	1.87 [1.80, 1.95]*
2007	9053	4421	679395	619609	13.3	7.1	1.87 [1.80, 1.94]*
2008	9463	4631	655736	598117	14.4	7.7	1.86 [1.80, 1.93]*
2009	9981	4911	637773	583122	15.6	8.4	1.86 [1.80, 1.92]*
2010	10968	5111	612072	560580	17.9	9.1	1.97 [1.90, 2.03]*
2011	9969	4697	607034	557116	16.4	8.4	1.95 [1.88, 2.02]*
2012	11069	5122	619396	570641	17.9	9.0	1.99 [1.93, 2.06]*
2013	11578	5540	616451	569933	18.8	9.7	1.93 [1.87, 1.99]*
2014	13122	6207	622626	578076	21.1	10.7	1.96 [1.90, 2.02]*
2015	13419	6272	633460	588394	21.2	10.7	1.99 [1.93, 2.05]*
2016	13939	6672	654986	609219	21.3	11.0	1.94 [1.89, 2.00]*

[a]CI: confidence interval

*$p < 0.05$.

With the exclusion of Tainan City and County, there were 6 cities and 17 counties in Taiwan. All 6 cities and 5 of the counties were classified as urban areas, and the remaining 12 counties were classified as rural areas. The overall incidence rate ranged from 7.2 to 25.5 per 1000 person-year in rural areas and from 6.1 to 14.7 per 1000 person-year in urban areas. The incidence rates were generally higher in rural than in urban areas, except for the year 2003, in which the rural-to-urban rate ratio was not statistically significant (Table 3). In other years, the ratio fluctuated from 1.10 to 2.00 and all reached statistical significance. There was no apparent trend in the changes over time.

The proportion of early reporting had an increased trend from 2003 to 2008 and then showed fluctuations afterwards (Table 4). Girls had a higher proportion of early reporting than boys throughout all years, with the boy-to-girl proportion ratios ranging from 0.85 to 0.94. All the proportion ratios were statistically significant, but there was no apparent trend in the changes over time. The difference in the proportion of early reporting between rural and urban areas fluctuated over time. The rural-to-urban proportion ratios ranged from 0.79 to 1.19, and there was no apparent trend in the changes over the years (Table 5).

Table 3 The overall incidence rate and rate ratio of developmental delays in children under 6 years of age by area[a]

Year	Reported number of cases[a]		Population[a]		Incidence (per 1000 person-year)		Rate ratio [95% C.I.][b]
	Rural	Urban	Rural	Urban	Rural	Urban	
2003	3016	7651	417597	1041508	7.2	7.3	0.98 [0.94, 1.03]
2004	3499	6161	401360	1010972	8.7	6.1	1.43 [1.37, 1.49]*
2005	3275	7031	379954	962324	8.6	7.3	1.18 [1.13, 1.23]*
2006	3401	7580	350937	898852	9.7	8.4	1.15 [1.10, 1.20]*
2007	3688	8794	331562	871125	11.1	10.1	1.10 [1.06, 1.14]*
2008	4843	8177	312880	847893	15.5	9.6	1.61 [1.55, 1.66]*
2009	4306	9515	298839	831537	14.4	11.4	1.26 [1.22, 1.31]*
2010	5108	9881	280108	806265	18.2	12.3	1.49 [1.44, 1.54]*
2011	5074	8779	268296	808844	18.9	10.9	1.74 [1.68, 1.80]*
2012	5829	9336	266682	833418	21.9	11.2	1.95 [1.89, 2.02]*
2013	5339	10124	261442	835199	20.4	12.1	1.68 [1.63, 1.74]*
2014	6629	10838	259828	850302	25.5	12.7	2.00 [1.94, 2.06]*
2015	5531	12576	257152	872878	21.5	14.4	1.49 [1.45, 1.54]*
2016	5591	13365	261055	908526	21.4	14.7	1.46 [1.41, 1.50]*

[a] Tainan City and Tainan County were excluded in the analyses due to a re-organization of administrative regions in 2011.

[b] CI: confidence interval

* $p < 0.05$.

Table 4 The proportion of early reporting of developmental delays in children under 6 years of age by sex

Year	Reported number of cases									Boy-to-girl proportion ratio of early reporting [95% C.I.] [a]
	Total			Boy			Girl			
	< 3 year	< 6 year	%	< 3 year	< 6 year	%	< 3 year	< 6 year	%	
2003	4139	11696	35.4	2660	7837	33.9	1479	3859	38.3	0.89 [0.84, 0.93]*
2004	4058	10740	37.8	2648	7183	36.9	1410	3557	39.6	0.93 [0.88, 0.98]*
2005	4512	11184	40.3	2881	7550	38.2	1631	3634	44.9	0.85 [0.81, 0.89]*
2006	5098	11896	42.9	3321	7998	41.5	1777	3898	45.6	0.91 [0.87, 0.95]*
2007	6201	13474	46.0	3953	9053	43.7	2248	4421	50.8	0.86 [0.83, 0.89]*
2008	6655	14094	47.2	4310	9463	45.5	2345	4631	50.6	0.90 [0.87, 0.93]*
2009	6103	14892	41.0	3995	9981	40.0	2108	4911	42.9	0.93 [0.90, 0.97]*
2010	6957	16079	43.3	4627	10968	42.2	2330	5111	45.6	0.93 [0.89, 0.96]*
2011	5850	14666	39.9	3896	9969	39.1	1954	4697	41.6	0.94 [0.90, 0.98]*
2012	6270	16191	38.7	4153	11069	37.5	2117	5122	41.3	0.91 [0.87, 0.95]*
2013	7474	17118	43.7	4818	11578	41.6	2656	5540	47.9	0.87 [0.84, 0.90]*
2014	9618	19329	49.8	6320	13122	48.2	3298	6207	53.1	0.91 [0.88, 0.93]*
2015	9372	19691	47.6	6066	13419	45.2	3306	6272	52.7	0.86 [0.83, 0.88]*
2016	9160	20611	44.4	5944	13939	42.6	3216	6672	48.2	0.88 [0.86, 0.91]*

[a] CI: confidence interval

* $p < 0.05$.

Table 5 The proportion of early reporting of developmental delays in children under 6 years of age by area[a]

Year	Reported number of cases						Rural-to-urban proportion ratio of early reporting [95% C.I.][b]
	Rural			Urban			
	< 3 year	< 6 year (total)	< 3 year (%)	< 3 year	< 6 year (total)	< 3 year (%)	
2003	1159	3016	38.4	2475	7651	32.3	1.19 [1.12 1.26]*
2004	1215	3499	34.7	2393	6161	38.8	0.89 [0.85 0.94]*
2005	1140	3275	34.8	2959	7031	42.1	0.83 [0.78 0.87]*
2006	1353	3401	39.8	3415	7580	45.1	0.88 [0.84 0.93]*
2007	1423	3688	38.6	4294	8794	48.8	0.79 [0.75 0.83]*
2008	2472	4843	51.0	3578	8177	43.8	1.17 [1.12 1.21]*
2009	1845	4306	42.8	3646	9515	38.3	1.12 [1.07 1.17]*
2010	2211	5108	43.3	4152	9881	42.0	1.03 [0.99 1.07]
2011	1888	5074	37.2	3555	8779	40.5	0.92 [0.88 0.96]*
2012	2054	5829	35.2	3715	9336	39.8	0.89 [0.85 0.92]*
2013	2271	5339	42.5	4366	10124	43.1	0.99 [0.95 1.02]
2014	3318	6629	50.1	5175	10838	47.7	1.05 [1.02 1.08]*
2015	2772	5531	50.1	5712	12576	45.4	1.10 [1.07 1.14]*
2016	2482	5591	44.4	5730	13365	42.9	1.04 [1.00 1.07]

[a]Tainan City and Tainan County were excluded in the analyses due to a re-organization of administrative regions in 2011.

[b]CI: confidence interval

*p< 0.05.

DISCUSSION

The overall incidence rate of DD in children under 6 years of age generally increased during the study period, which is consistent with the observation in our preliminary study.[2] We believe the increase cannot be attributed to an increase in the number of cases, because the major risk factors for DD such as genetic constructs, medical care, and socioeconomic status[1, 16] did not undergo remarkable changes over the 14-year period. In fact, there were no changes in the diagnostic and reporting criteria of DD, neither. Therefore, the increased incidence rate of DD is more likely to be due to the improvement in reporting of cases, which may be in turn attributable to the improvement in the awareness of the developmental abnormalities in children, lower discrimination against the patients, better service of the related agencies, more willingness demonstrated by parents and guardians to register their children, etc.[17, 18] These were generally gradual changes, and therefore we did not observe any abrupt changes in the incidence of DD over time, indicating the lack of an obvious period effect.

In addition to cases confirmed by physicians, the registry also includes cases identified by trained social workers in the EIRRCs. This would lead to overestimation of the incidence rates. However, the registry ascertains cases through reporting rather than thorough active screenings in the communities or schools, and therefore the candidates who receive the screening generally have shown certain symptoms or signs of DD which draw the attention of care givers. Consequently, the proportion of confirmed cases in the registry is very high. Although the government never provides the statistics on the proportion of cases excluded after reporting, from our experience of running the EIRRC in the Chia-Yi City (an urban area) and Chia-Yi County (a rural are), we notice that the proportion of cases confirmed by physicians at reporting

has been increasing. Therefore, the effect of overestimating the incidence should have been decreasing and thus would not affect our conclusion of an increasing trend over time.

Since the critical period of treatment for DD is before the child reaches 3 years of age, an early diagnosis is crucial.[19] Therefore, the Taiwanese government has been promoting the reporting and intervention in cases of children with DD under 3 years of age,[2, 13] when intervention procedures are most cost effective. In fact, it is generally believed that the earlier the intervention, the better the prognosis.[20] Although we observed an increased trend in early reporting from 2003 to 2008, the trend did not persist after 2008. This might indicate that the existing measures of promotion have reached their limits of effectiveness, additional efforts and approaches are required, especially since the proportion of early reporting has never risen beyond 50%.

Previously, we used the data from the national disability registry of Taiwan, a different nationwide source of information than that used in the current study, to conduct a series of studies on major developmental disabilities, including autism spectrum disorders (ASD), intellectual disability, and speech and language disability.[17, 18, 21] We found that the prevalence rates were consistently higher in boys than in girls. Those developmental disabilities are all major risk factors for DD. Therefore, the finding of a higher incidence of DD in boys in the current study is compatible with the findings of our previous studies. Many theories have been proposed to explain the sex difference, including both biological and sociological factors. Biologically, the higher risk in boys is often attributed to hereditary factors such as X-linked conditions.[22, 23] The central nervous system of young boys is also found to be more susceptible to damage.[22] In terms of social factors, in Asian countries, families generally display a male gender preference, and thus pay more attention to boys.[22, 23] In addition, boys are more likely to

demonstrate impulsive and aggressive behaviors than girls and therefore are more likely to be referred for diagnosis. [23]

In this study, however, we found that girls had a higher proportion of early reporting than boys. This does not support the theory that the higher level of attention received by boys is a major factor contributing to the higher incidence rate of DD. In fact, a review of literature concluded that boys are more likely to have DD, but when such conditions arise in girls, a more severe form is usually manifest.[24] Our finding of a higher proportion of early reporting in girls is compatible with this conclusion. Furthermore, as the birth rate has been decreasing in Taiwan, [15] the difference in the attention received by boys and girls should be decreasing, but we found the sex difference had an increasing trend instead of a decreasing trend. Therefore, we believe biological factors contribute more than social factors to the sex difference in DD in early childhood.

In the preliminary study, we failed to identify the time trend in the sex difference (no significant trend in boy-to-girl rate ratio).[2] The current study has the advantage of a longer follow-up period. In a separate study, which used data from the national disability registry, we found that there was a 497.30% increase in the prevalence rate of childhood ASD from 2000 to 2011in Taiwan, which is much higher than the 54.40% increase in all reported disabilities combined.[25] In addition, the boy-to-girl ratio of ASD was found to be the highest among the major conditions contributing to DD.[4, 17] Therefore, we believe the increasing trend in the boy-to-girl incidence rate ratio of DD in Taiwan can largely be attributable to the increasing trend in the number of cases of ASD.

Studies on the differences in DD between rural and urban areas are limited. There are

relatively more data on childhood disabilities. The Multiple Indicator Cluster Survey conducted by the United Nations Children's Fund in developing countries did not observe a consistent result.[6] Munro reviewed several studies of intellectual disability in the U.S.A. and also found results to be inconsistent.[23] A nationwide study of childhood disability in China, however, found a higher prevalence rate in rural areas,[26] which is consistent with our finding on DD in this study. Moreover, according to the national disability registry of Taiwan, some major childhood disabilities leading to DD, including intellectual disability and speech and language disability,[18, 21] as well as all disabilities combined[27] were more prevalent in rural areas. While the lower socioeconomic status of rural residents in Taiwan should be a major factor,[28, 29] the difference might also be explained by environmental factors such as lower quality of child care, lower parental education, and limited educational and cultural opportunities.[5, 22, 30]

The registry of children with DD in Taiwan has some unique features. First of all, it included new cases only, which provides incidence data that are rarely available at the national level and are more reliable for identifying risk factors.[31] Secondly, Taiwanese law mandates that cases be reported, and therefore, instances of under-reporting are rare. The registry also has the advantage of a large number (more than 200000) of cases. Lastly, the duration of data collection is long, which makes assessing time trends possible.

The major limitation of our study is that the government does not release data on individual cases, and therefore we were unable to conduct more detailed analyses. For example, while we believe the increasing trend in the boy-to-girl incidence rate ratio of DD can largely be attributable to the increasing trend in the number of cases of ASD, we could not perform analyses to verify this. Likewise, we were unable to adjust for the geographical difference while evaluating the effects of sex or age, or study the interaction between sex and geographical

difference. In addition, the government does not provide data on the prevalence of DD, and therefore we were unable to study the prevalence of DD directly. Nonetheless, a study that used the National Health Insurance Research Database of Taiwan to estimate the prevalence of DD in children aged 0-6 years and found that the prevalence gradually increased from 0.16% to 3.25% from 1997 to 2008.[32] Even though the case definition was not exactly the same as in the current study and the source of information was different, the study also observed an increasing trend in the annual prevalence and a higher risk in boys than in girls. Geographic differences were not evaluated in that study. Our study is also limited by the range of age under observation. A likely reason of observing a significant increasing trend in the incidence without a remarkable actual increase in the number of cases is that there was a trend of cases being diagnosed (and thus reported) at an earlier age. Although this hypothesis can be tested by evaluating if there was a decreasing trend in the order population, such as 6 to 12 years old, we did not include cases diagnosed later than 6 years old because the registry only includes cases who had not yet entered the primary school, not all the cases. In the current study, we adopted the "administrative" data from a national registry which obtains the information on all persons receiving or qualifying for the services, and such an approach was found to generally result in underestimation because it does not include persons who do not receive or not qualify for the services.[33] However, the administrative data we used have the advantage of providing information on incidence. Although incidence data are preferable to prevalence for investigating risk and etiology, such data on DD are rare, and therefore epidemiology of DD has generally to be inferred from cross-sectional data.[31] It has been proposed that incidence data need to be obtained by longitudinal studies from conception or birth to death.[31] Whereas our study did not apply an active case ascertainment approach such as a house-by-house screening survey, it is a longitudinal study that followed the population from birth and thus can provide the incidence data that some researchers once

believed to be unattainable in any population.[31]

CONCLUSIONS

The incidence rates of young children with DD have been increasing in Taiwan, which is likely to be attributable to improvements in the reporting of cases. The incidence rates are higher in boys than in girls, which is unlikely to be due to more attention received by boys because girls had a higher proportion of early reporting. In addition, the boy-to-girl rate ratio has an increasing trend of over the years, and we believe the increasing number of cases of ASD is an important factor. Rural areas had higher incidence than urban areas, which calls for further studies to identify the contributing factors.

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Acknowledgements

We would like to thank the Department of Statistics of Ministry of the Interior and the Department of Statistics of the Ministry of the Health and Welfare for providing the registry data and Miss Chao-Hui Weng for her assistance in statistical analysis.

Contributors

All the authors approved the contents of the submitted article. Y-CT and H-RG contributed

equally to this work. D-CL and Y-CT conceived and designed the experiments. D-CL and H-RG collected and analysed the data. D-CL and H-RG wrote the paper. D-CL, Y-CT, and H-RG contributed in the final approval of manuscript.

Funding

This research was supported by Ditmanson Medical Foundation Chia-Yi Christian Hospital Research Program through Grant R105-006.

Competing interests

None declared.

Ethics approval

This study has been reviewed and approved by the Institution Review Board of the Ditmanson Medical Foundation Chia-Yi Christian Hospital (CYCH-IRB No. 104016).

Data sharing statement

No additional data are available.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Characteristics of young children with developmental delays and their trends over 14 years in Taiwan: A population-based nationwide study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020994.R2
Article Type:	Research
Date Submitted by the Author:	16-Feb-2018
Complete List of Authors:	Lai, Der-Chung; Ditmanson Medical Foundation Chia-Yi Christian Hospital, Department of Physical Medicine and Rehabilitation; Chia Nan University of Pharmacy & Science Tseng, Yen-Cheng; Chang Jung Christian University, Language Education Center and Department of Tourism, Food, and Beverage Management Guo, How-Ran; National Cheng Kung University Hospital, Department of Occupational and Environmental Medicine; National Cheng Kung University, Occupational Safety, Health, and Medicine Research Center and Department of Environmental and Occupational Health
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	EPIDEMIOLOGY, PAEDIATRICS, Developmental neurology & neurodisability < PAEDIATRICS, PUBLIC HEALTH

Characteristics of young children with developmental delays and their trends over 14 years in Taiwan: A population-based nationwide study

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ABSTRACT

Objectives: To describe the epidemiologic characteristics of developmental delays (DD) at the national level and assess the changes over time.

Design: We calculated the incidence rates of DD from 2003 to 2016 and assessed the trends over time.

Setting: As dictated by law, local governments in Taiwan are required to register children with DD and provide services. The central government has constructed a national registry with the data from local centers. We analysed the national registry data.

Participants: We included children who were under 6 years old, and this population ranged from 1164150 to 1577443 per year during the study period. All registered cases were certified through a process set forth by law.

Primary and secondary outcome measures: We calculated annual incidence rates by age, sex, and geographic area and assessed trends over the study period.

Results: The incidence of DD in children under 6 years old displayed an increasing trend over the study period, ranging from 7.0 to 16.3 per 1000 person-year. Boys had higher incidence throughout all 14 years, and the boy-to-girl rate ratios had an increasing trend over time with some fluctuations, ranging from 1.84 (95% confidence interval: 1.77-1.92) to 1.99 (1.93-2.06). In addition, rural areas had higher incidence rates, and the rural-to-urban rate ratios ranged from 0.98 (0.94-1.03) to 2.00 (1.94-2.06) without apparent time trends. Girls had a higher proportion of early reporting (<3 year) throughout all years, but the difference in the proportion of early reporting between rural and urban areas were not consistent.

Conclusions: Male sex appeared to be a risk factor for development delays, which is unlikely to be due to more attention received by boys because girls had a higher proportion of early reporting. We also found that children lived in rural areas appeared to have a higher risk of having DD.

Keywords: Developmental delays; Geographic distribution; Incidence; Registry; Sex; Taiwan

Strengths and limitations of this study

- The Taiwanese registry of children with developmental delays in included only new cases , which provides incidence data that are rarely available at the national level.
- The law in Taiwan mandates the reporting of cases, which minimizes under-reporting.
- Using nationwide registry data, this study has a large sample size, with a population of more than 1 million each year.
- The duration of data collection in this study was 14 years, and the assessment of time trends over such a long period of time at the national level has rarely been achieved in previous studies.
- The major limitation of our study is that the government does not release data on individual cases, which make it impossible to conduct the analysis in further detail.

INTRODUCTION

Developmental delays (DD) are generally defined as a child does not reach expected developmental milestones at the age.[1] Although DD are prevalent among children, data on its incidence at the national level are limited. For the identification of risk factors, incidence data are generally more useful than prevalence data. However, the majority of previous studies on DD used prevalence data, most likely because incidence data were more difficult to obtain.[2] As a result, changes in epidemiologic characteristics over time are seldom assessed, because such studies would require incidence data.

A child's development is affected by many biological and environmental factors.[1] Among biological ones, male sex is a strong risk factor.[3] Many studies found that the prevalence rate for DD was higher in boys than in girls.[3 4] Also, residents of rural areas have reported more health-related problems than those of urban areas in general,[5] and this disparity might also be true for DD. However, studies on this topic are limited and have reported inconsistent results. For example, the Multiple Indicator Cluster Survey conducted by the United Nations Children's Fund in countries with low and middle incomes did not observe consistent results in terms of differences between rural and urban areas across various countries.[6]

Under the Children Welfare Law, local governments in Taiwan have established Early Intervention Reporting and Referral Centers (EIRRCs) to register and provide services to children with DD.[7] The Children and Youth Welfare Law also mandates that institutions of welfare, education, and medicine report all children with suspected DD to the EIRRC.[8] Using data collected at the EIRRCs, the central government has constructed a national registry of children with DD. This registry provides researchers with a unique resource with which to conduct nationwide epidemiological studies. In a previous study, we analyzed the national

registry data from 2003 to 2008.[2] However, since it is difficult to precisely evaluate the trends of incidence with only 6 years' worth of data, we extended the time range from 2003 to 2008 to a 14-year period till 2016 as more data became available. This better suited our purposes of studying epidemiological characteristics of incident cases of DD and assessing time trends.

METHODS

Case definition

The Enforcement Rules of the Children and Youth Welfare Law of Taiwan[9] defined "developmental delays" as "allegedly or expected abnormal development in respect of cognitive development, physiological development, language and communication development, psycho-social development or self-governing skills that have been judged and confirmed by the accredited medical institutes under health authority." In order to be registered as a case of DD, the child requires an assessment performed by a physician at an accredited hospital, or by a trained social worker in an EIRRC,[10] who generally used the Taipei City Developmental Checklist for Preschoolers, 2nd version as the assessment tool.[11]

Data Collection

The EIRRCs collect data on newly reported cases and report such cases to the central government, which maintains a registry of cases and publishes a yearbook each year. Before the re-organisation of the government in 2013, the registry was maintained by the Ministry of the Interior. After 2013, this responsibility fell to the Ministry of Health and Welfare. This yearbook includes the total numbers of newly reported cases by age at reporting, sex, and

area.[12] We analysed the data from 2003 to 2016.

We divided the cases into two groups, < 3 years and 3–5years, according to the age at the time of reporting and defined the group < 3 years as "early reporting".[13] Although the yearbook includes statistics on a age group "≥ 6 years," we did not include this group in our analyses because it only includes children who have not yet entered the primary school, not all children who are 6 years of age or older.

In the stratified analyses by geographic area, we divided the administrative regions in Taiwan into two groups: "urban areas" and "rural areas." An urban area is one in which more than 50% of the population live in metropolitan areas (as defined by the Directorate-General of Budget, Accounting and Statistics of Taiwan).[14] Consequently, a rural area is one in which 50% or less of the population live in metropolitan areas. In a re-organisation of administrative regions in 2011, the original Tainan City (an urban area) and Tainan County (a rural area) were merged into the new Tainan City. Data on the two original administrative regions has been unavailable since this merging, so they were both excluded from this part of the analyses.

To calculate incidence rates, we obtained data on the numbers of boys, girls, and the total population in each age group for each administrative region from the Monthly Bulletin of Interior Statistics.[15]

Data analysis

We estimated age-specific incidence rates in a given year by dividing the number of newly reported cases by the number of individuals in a specific age group. Likewise, the

sex-specific incidence rates of each year were estimated by dividing the number of newly reported cases by the number of individuals of each sex. We evaluated the differences between the two sexes by using the incidence rate ratio calculated through dividing the incidence rate in boys by the incidence rate in girls. To evaluate the geographic differences, we estimated the incidence rate in rural or urban areas in each year by first dividing the number of newly reported cases by the number of individuals in each type of area, and then obtaining the incidence rate ratio by dividing the incidence rate in rural areas by the incidence rate in urban areas. A 95% confidence interval was constructed for each rate ratio to evaluate its statistical significance.

To evaluate the difference in early reporting between boys and girls, we calculated the proportion of early reporting in boys or girls each year by dividing the number of cases under 3 years of age by the number of cases under 6 years of age in each sex. We then obtained the boy-to-girl proportion ratio of early reporting by dividing the proportion in boys by the proportion in girls. A 95% confidence interval was constructed for each proportion ratio to evaluate its statistical significance.

Likewise, to evaluate the difference of early reporting between rural and urban areas, we calculated the proportion of early reporting in rural or urban areas in each year by dividing the number of cases under 3 years of age by the number of cases under 6 years of age in each area. We then obtained the rural-to-urban proportion ratio of early reporting by dividing the proportion in rural areas by the proportion in urban areas. A 95% confidence interval was constructed for each proportion ratio to evaluate its statistical significance.

We reported descriptive statistics as numbers or percentages and used linear regressions to evaluate the trends of changes in incidence rates, incidence rate ratios, and proportion ratios over time. All the analyses were conducted using SAS 9.1, and all the statistical tests

were performed at the two-tailed significance level of 0.05.

RESULTS

During the study period of 2003 to 2016, 211661 new cases of DD under 6 years of age were registered, and the overall incidence rate was 7.0 to 16.3 per 1000 person-year. The rate was 5.7 to 15.3 per 1000 person-year in children under 3 years of age and 7.9 to 18.0 per 1000 person-year in children 3–5 years of age. We observed a general increasing trend over time in all three age groups (p <0.01 for all) (Table 1).

With data on 14 years, we were able to compare the incidence among four mutually exclusive birth cohorts. Using the 2001-2003 cohort (those who were in the <3 year group in 2003) as the baseline, we observed an increasing trend in the estimated overall incidence rates in children under 6 years old. Specifically, the estimated overall incidence before 6 years of age rate was 7.5 per 1000 in the 2001-2003 birth cohort, 11.1 per 1000 in the 2004-2006 birth cohort, 13.5 per 1000 in the 2007-2009 birth cohort, and 13.9 per 1000 in the 2010-2012 birth cohort. The trend was similar to that observed in the year-by-year overall incidence rates.

The overall incidence rate ranged from 9.0 to 21.3 per 1000 person-year in boys and from 4.9 to 11.0 per1000 person-year in girls. The rate was constantly higher in boys than in girls, and the boy-to-girl rate ratios had an increasing trend over time (p < 0.01) with some fluctuations, ranging from 1.84 to 1.99 (Table 2). All the rate ratios were statistically significant.

Table 1 The overall incidence rate of developmental delays in children under 6 years of age

Year	Reported number of cases		Population		Incidence (per 1000 person-year)		
	<3 year	3-5 year	<3 year	3-5 year	<3 year	3-5 year	<6 year
2003	4139	7557	720897	856546	5.7	8.8	7.4
2004	4058	6682	680737	846130	6.0	7.9	7.0
2005	4512	6672	641095	809663	7.0	8.2	7.7
2006	5098	6798	619354	730819	8.2	9.3	8.8
2007	6201	7273	606840	692164	10.2	10.5	10.4
2008	6655	7439	599674	654179	11.1	11.4	11.2
2009	6103	8789	587219	633676	10.4	13.9	12.2
2010	6957	9122	551334	621318	12.6	14.7	13.7
2011	5850	8816	551707	612443	10.6	14.4	12.6
2012	6270	9921	589053	600984	10.6	16.5	13.6
2013	7474	9644	622140	564244	12.0	17.1	14.4
2014	9618	9711	634646	566056	15.2	17.2	16.1
2015	9372	10319	613735	608119	15.3	17.0	16.1
2016	9160	11451	627470	636735	14.6	18.0	16.3

Table 2 The overall incidence rate and rate ratio of developmental delays in children under 6 years of age by sex

Year	Reported number of cases		Population		Incidence (per 1000 person-year)		Rate ratio [95% C.I.][a]
	Boy	Girl	Boy	Girl	Boy	Girl	
2003	7837	3859	823435	754008	9.5	5.1	1.86 [1.79, 1.93]*
2004	7183	3557	797949	728918	9.0	4.9	1.84 [1.77, 1.92]*
2005	7550	3634	758014	692744	10.0	5.2	1.90 [1.83, 1.98]*
2006	7998	3898	705549	644624	11.3	6.0	1.87 [1.80, 1.95]*
2007	9053	4421	679395	619609	13.3	7.1	1.87 [1.80, 1.94]*
2008	9463	4631	655736	598117	14.4	7.7	1.86 [1.80, 1.93]*
2009	9981	4911	637773	583122	15.6	8.4	1.86 [1.80, 1.92]*
2010	10968	5111	612072	560580	17.9	9.1	1.97 [1.90, 2.03]*
2011	9969	4697	607034	557116	16.4	8.4	1.95 [1.88, 2.02]*
2012	11069	5122	619396	570641	17.9	9.0	1.99 [1.93, 2.06]*
2013	11578	5540	616451	569933	18.8	9.7	1.93 [1.87, 1.99]*
2014	13122	6207	622626	578076	21.1	10.7	1.96 [1.90, 2.02]*
2015	13419	6272	633460	588394	21.2	10.7	1.99 [1.93, 2.05]*
2016	13939	6672	654986	609219	21.3	11.0	1.94 [1.89, 2.00]*

[a]CI: confidence interval

*$p < 0.05$.

With the exclusion of Tainan City and County, there were 6 cities and 17 counties in Taiwan. All 6 cities and 5 of the counties were classified as urban areas, and the remaining 12 counties were classified as rural areas. The overall incidence rate ranged from 7.2 to 25.5 per 1000 person-year in rural areas and from 6.1 to 14.7 per 1000 person-year in urban areas. The incidence rates were generally higher in rural than in urban areas, except for the year 2003, in which the rural-to-urban rate ratio was not statistically significant (Table 3). In other years, the ratio fluctuated from 1.10 to 2.00 and all reached statistical significance. There was no apparent trend in the changes over time.

The proportion of early reporting had an increased trend from 2003 to 2008 and then showed fluctuations afterwards (Table 4). Girls had a higher proportion of early reporting than boys throughout all years, with the boy-to-girl proportion ratios ranging from 0.85 to 0.94. All the proportion ratios were statistically significant, but there was no apparent trend in the changes over time. The difference in the proportion of early reporting between rural and urban areas fluctuated over time. The rural-to-urban proportion ratios ranged from 0.79 to 1.19, and there was no apparent trend in the changes over the years (Table 5).

Table 3 The overall incidence rate and rate ratio of developmental delays in children under 6 years of age by area[a]

Year	Reported number of cases[a]		Population[a]		Incidence (per 1000 person-year)		Rate ratio [95% C.I.][b]
	Rural	Urban	Rural	Urban	Rural	Urban	
2003	3016	7651	417597	1041508	7.2	7.3	0.98 [0.94, 1.03]
2004	3499	6161	401360	1010972	8.7	6.1	1.43 [1.37, 1.49]*
2005	3275	7031	379954	962324	8.6	7.3	1.18 [1.13, 1.23]*
2006	3401	7580	350937	898852	9.7	8.4	1.15 [1.10, 1.20]*
2007	3688	8794	331562	871125	11.1	10.1	1.10 [1.06, 1.14]*
2008	4843	8177	312880	847893	15.5	9.6	1.61 [1.55, 1.66]*
2009	4306	9515	298839	831537	14.4	11.4	1.26 [1.22, 1.31]*
2010	5108	9881	280108	806265	18.2	12.3	1.49 [1.44, 1.54]*
2011	5074	8779	268296	808844	18.9	10.9	1.74 [1.68, 1.80]*
2012	5829	9336	266682	833418	21.9	11.2	1.95 [1.89, 2.02]*
2013	5339	10124	261442	835199	20.4	12.1	1.68 [1.63, 1.74]*
2014	6629	10838	259828	850302	25.5	12.7	2.00 [1.94, 2.06]*
2015	5531	12576	257152	872878	21.5	14.4	1.49 [1.45, 1.54]*
2016	5591	13365	261055	908526	21.4	14.7	1.46 [1.41, 1.50]*

[a] Tainan City and Tainan County were excluded in the analyses due to a re-organization of administrative regions in 2011.

[b] CI: confidence interval

* $p < 0.05$.

Table 4 The proportion of early reporting of developmental delays in children under 6 years of age by sex

Year	Reported number of cases									Boy-to-girl proportion ratio of early reporting [95% C.I.] [a]
	Total			Boy			Girl			
	< 3 year	< 6 year	%	< 3 year	< 6 year	%	< 3 year	< 6 year	%	
2003	4139	11696	35.4	2660	7837	33.9	1479	3859	38.3	0.89 [0.84, 0.93]*
2004	4058	10740	37.8	2648	7183	36.9	1410	3557	39.6	0.93 [0.88, 0.98]*
2005	4512	11184	40.3	2881	7550	38.2	1631	3634	44.9	0.85 [0.81, 0.89]*
2006	5098	11896	42.9	3321	7998	41.5	1777	3898	45.6	0.91 [0.87, 0.95]*
2007	6201	13474	46.0	3953	9053	43.7	2248	4421	50.8	0.86 [0.83, 0.89]*
2008	6655	14094	47.2	4310	9463	45.5	2345	4631	50.6	0.90 [0.87, 0.93]*
2009	6103	14892	41.0	3995	9981	40.0	2108	4911	42.9	0.93 [0.90, 0.97]*
2010	6957	16079	43.3	4627	10968	42.2	2330	5111	45.6	0.93 [0.89, 0.96]*
2011	5850	14666	39.9	3896	9969	39.1	1954	4697	41.6	0.94 [0.90, 0.98]*
2012	6270	16191	38.7	4153	11069	37.5	2117	5122	41.3	0.91 [0.87, 0.95]*
2013	7474	17118	43.7	4818	11578	41.6	2656	5540	47.9	0.87 [0.84, 0.90]*
2014	9618	19329	49.8	6320	13122	48.2	3298	6207	53.1	0.91 [0.88, 0.93]*
2015	9372	19691	47.6	6066	13419	45.2	3306	6272	52.7	0.86 [0.83, 0.88]*
2016	9160	20611	44.4	5944	13939	42.6	3216	6672	48.2	0.88 [0.86, 0.91]*

[a] CI: confidence interval

* $p < 0.05$.

Table 5 The proportion of early reporting of developmental delays in children under 6 years of age by area[a]

Year	Reported number of cases						Rural-to-urban proportion ratio of early reporting [95% C.I.][b]
	Rural			Urban			
	< 3 year	< 6 year (total)	< 3 year (%)	< 3 year	< 6 year (total)	< 3 year (%)	
2003	1159	3016	38.4	2475	7651	32.3	1.19 [1.12 1.26]*
2004	1215	3499	34.7	2393	6161	38.8	0.89 [0.85 0.94]*
2005	1140	3275	34.8	2959	7031	42.1	0.83 [0.78 0.87]*
2006	1353	3401	39.8	3415	7580	45.1	0.88 [0.84 0.93]*
2007	1423	3688	38.6	4294	8794	48.8	0.79 [0.75 0.83]*
2008	2472	4843	51.0	3578	8177	43.8	1.17 [1.12 1.21]*
2009	1845	4306	42.8	3646	9515	38.3	1.12 [1.07 1.17]*
2010	2211	5108	43.3	4152	9881	42.0	1.03 [0.99 1.07]
2011	1888	5074	37.2	3555	8779	40.5	0.92 [0.88 0.96]*
2012	2054	5829	35.2	3715	9336	39.8	0.89 [0.85 0.92]*
2013	2271	5339	42.5	4366	10124	43.1	0.99 [0.95 1.02]
2014	3318	6629	50.1	5175	10838	47.7	1.05 [1.02 1.08]*
2015	2772	5531	50.1	5712	12576	45.4	1.10 [1.07 1.14]*
2016	2482	5591	44.4	5730	13365	42.9	1.04 [1.00 1.07]

[a]Tainan City and Tainan County were excluded in the analyses due to a re-organization of administrative regions in 2011.

[b]CI: confidence interval

*p< 0.05.

DISCUSSION

The overall incidence rate of DD in children under 6 years of age generally increased during the study period, which is consistent with the observation in our preliminary study.[2] We believe the increase cannot be attributed to an increase in the number of cases, because the major risk factors for DD such as genetic constructs, medical care, and socioeconomic status[1, 16] did not undergo remarkable changes over the 14-year period. In fact, there were no changes in the diagnostic and reporting criteria of DD, neither. Therefore, the increased incidence rate of DD is more likely to be due to the improvement in reporting of cases, which may be in turn attributable to the improvement in the awareness of the developmental abnormalities in children, lower discrimination against the patients, better service of the related agencies, more willingness demonstrated by parents and guardians to register their children, etc.[17, 18] These were generally gradual changes, and therefore we did not observe any abrupt changes in the incidence of DD over time, indicating the lack of an obvious period effect.

In addition to cases confirmed by physicians, the registry also includes cases identified by trained social workers in the EIRRCs. This would lead to overestimation of the incidence rates. However, the registry ascertains cases through reporting rather than thorough active screenings in the communities or schools, and therefore the candidates who receive the screening generally have shown certain symptoms or signs of DD which draw the attention of care givers. Consequently, the proportion of confirmed cases in the registry is very high. Although the government never provides the statistics on the proportion of cases excluded after reporting, from our experience of running the EIRRC in the Chia-Yi City (an urban area) and Chia-Yi County (a rural are), we notice that the proportion of cases confirmed by physicians at reporting

has been increasing. Therefore, the effect of overestimating the incidence should have been decreasing and thus would not affect our conclusion of an increasing trend over time.

Since the critical period of treatment for DD is before the child reaches 3 years of age, an early diagnosis is crucial.[19] Therefore, the Taiwanese government has been promoting the reporting and intervention in cases of children with DD under 3 years of age,[2, 13] when intervention procedures are most cost effective. In fact, it is generally believed that the earlier the intervention, the better the prognosis.[20] Although we observed an increased trend in early reporting from 2003 to 2008, the trend did not persist after 2008. This might indicate that the existing measures of promotion have reached their limits of effectiveness, additional efforts and approaches are required, especially since the proportion of early reporting has never risen beyond 50%.

Previously, we used the data from the national disability registry of Taiwan, a different nationwide source of information than that used in the current study, to conduct a series of studies on major developmental disabilities, including autism spectrum disorders (ASD), intellectual disability, and speech and language disability.[17, 18, 21] We found that the prevalence rates were consistently higher in boys than in girls. Those developmental disabilities are all major risk factors for DD. Therefore, the finding of a higher incidence of DD in boys in the current study is compatible with the findings of our previous studies. Many theories have been proposed to explain the sex difference, including both biological and sociological factors. Biologically, the higher risk in boys is often attributed to hereditary factors such as X-linked conditions.[22, 23] The central nervous system of young boys is also found to be more susceptible to damage.[22] In terms of social factors, in Asian countries, families generally display a male gender preference, and thus pay more attention to boys.[22, 23] In addition, boys are more likely to

demonstrate impulsive and aggressive behaviors than girls and therefore are more likely to be referred for diagnosis. [23]

In this study, however, we found that girls had a higher proportion of early reporting than boys. This does not support the theory that the higher level of attention received by boys is a major factor contributing to the higher incidence rate of DD. In fact, a review of literature concluded that boys are more likely to have DD, but when such conditions arise in girls, a more severe form is usually manifest.[24] Our finding of a higher proportion of early reporting in girls is compatible with this conclusion. Furthermore, as the birth rate has been decreasing in Taiwan, [15] the difference in the attention received by boys and girls should be decreasing, but we found the sex difference had an increasing trend instead of a decreasing trend. Therefore, we believe biological factors contribute more than social factors to the sex difference in DD in early childhood.

In the preliminary study, we failed to identify the time trend in the sex difference (no significant trend in boy-to-girl rate ratio).[2] The current study has the advantage of a longer follow-up period. In a separate study, which used data from the national disability registry, we found that there was a 497.30% increase in the prevalence rate of childhood ASD from 2000 to 2011in Taiwan, which is much higher than the 54.40% increase in all reported disabilities combined.[25] In addition, the boy-to-girl ratio of ASD was found to be the highest among the major conditions contributing to DD.[4, 17] Therefore, we believe the increasing trend in the boy-to-girl incidence rate ratio of DD in Taiwan can largely be attributable to the increasing trend in the number of cases of ASD.

Studies on the differences in DD between rural and urban areas are limited. There are

relatively more data on childhood disabilities. The Multiple Indicator Cluster Survey conducted by the United Nations Children's Fund in developing countries did not observe a consistent result.[6] Munro reviewed several studies of intellectual disability in the U.S.A. and also found results to be inconsistent.[23] A nationwide study of childhood disability in China, however, found a higher prevalence rate in rural areas,[26] which is consistent with our finding on DD in this study. Moreover, according to the national disability registry of Taiwan, some major childhood disabilities leading to DD, including intellectual disability and speech and language disability,[18, 21] as well as all disabilities combined[27] were more prevalent in rural areas. While the lower socioeconomic status of rural residents in Taiwan should be a major factor,[28, 29] the difference might also be explained by environmental factors such as lower quality of child care, lower parental education, and limited educational and cultural opportunities.[5, 22, 30]

The registry of children with DD in Taiwan has some unique features. First of all, it included new cases only, which provides incidence data that are rarely available at the national level and are more reliable for identifying risk factors.[31] Secondly, Taiwanese law mandates that cases be reported, and therefore, instances of under-reporting are rare. The registry also has the advantage of a large number (more than 200000) of cases. Lastly, the duration of data collection is long, which makes assessing time trends possible.

The major limitation of our study is that the government does not release data on individual cases, and therefore we were unable to conduct more detailed analyses. For example, while we believe the increasing trend in the boy-to-girl incidence rate ratio of DD can largely be attributable to the increasing trend in the number of cases of ASD, we could not perform analyses to verify this. Likewise, we were unable to adjust for the geographical difference while evaluating the effects of sex or age, or study the interaction between sex and geographical

difference. In addition, the government does not provide data on the prevalence of DD, and therefore we were unable to study the prevalence of DD directly. Nonetheless, a study that used the National Health Insurance Research Database of Taiwan to estimate the prevalence of DD in children aged 0-6 years and found that the prevalence gradually increased from 0.16% to 3.25% from 1997 to 2008.[32] Even though the case definition was not exactly the same as in the current study and the source of information was different, the study also observed an increasing trend in the annual prevalence and a higher risk in boys than in girls. Geographic differences were not evaluated in that study. Our study is also limited by the range of age under observation. A likely reason of observing a significant increasing trend in the incidence without a remarkable actual increase in the number of cases is that there was a trend of cases being diagnosed (and thus reported) at an earlier age. Although this hypothesis can be tested by evaluating if there was a decreasing trend in the order population, such as 6 to 12 years old, we did not include cases diagnosed later than 6 years old because the registry only includes cases who had not yet entered the primary school, not all the cases. In the current study, we adopted the "administrative" data from a national registry which obtains the information on all persons receiving or qualifying for the services, and such an approach was found to generally result in underestimation because it does not include persons who do not receive or not qualify for the services.[33] However, the administrative data we used have the advantage of providing information on incidence. Although incidence data are preferable to prevalence for investigating risk and etiology, such data on DD are rare, and therefore epidemiology of DD has generally to be inferred from cross-sectional data.[31] It has been proposed that incidence data need to be obtained by longitudinal studies from conception or birth to death.[31] Whereas our study did not apply an active case ascertainment approach such as a house-by-house screening survey, it is a longitudinal study that followed the population from birth and thus can provide the incidence data that some researchers once

believed to be unattainable in any population.[31]

CONCLUSIONS

The incidence rates of young children with DD have been increasing in Taiwan, which is likely to be attributable to improvements in the reporting of cases. The incidence rates are higher in boys than in girls, which is unlikely to be due to more attention received by boys because girls had a higher proportion of early reporting. In addition, the boy-to-girl rate ratio has an increasing trend of over the years, and we believe the increasing number of cases of ASD is an important factor. Rural areas had higher incidence than urban areas, which calls for further studies to identify the contributing factors.

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Acknowledgements

We would like to thank the Department of Statistics of Ministry of the Interior and the Department of Statistics of the Ministry of the Health and Welfare for providing the registry data and Miss Chao-Hui Weng for her assistance in statistical analysis.

Contributors

All the authors approved the contents of the submitted article. Y-CT and H-RG contributed

equally to this work. D-CL and Y-CT conceived and designed the experiments. D-CL and H-RG collected and analysed the data. D-CL and H-RG wrote the paper. D-CL, Y-CT, and H-RG contributed in the final approval of manuscript.

Funding

This research was supported by Ditmanson Medical Foundation Chia-Yi Christian Hospital Research Program through Grant R105-006.

Competing interests

None declared.

Ethics approval

This study has been reviewed and approved by the Institution Review Board of the Ditmanson Medical Foundation Chia-Yi Christian Hospital (CYCH-IRB No. 104016).

Data sharing statement

No additional data are available.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-9
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Not applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.