



## Prevalence and Associated Factors of Neonatal Microcephaly in Thailand, 2014-2018

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### Abstract

Microcephaly became of high concern after Zika outbreaks occurred worldwide. An estimation of its prevalence is crucial for public health preparedness and response. The objectives of this study were to estimate the prevalence of neonatal microcephaly in Thailand during 2014-2018, describe its epidemiological characteristics, and identify associated factors. This study was a cross-sectional study using data from the Health Data Center, Ministry of Public Health, Thailand. Neonatal microcephaly, as defined in this study, is a condition where a newborn has a head circumference (HC) less than the 3<sup>rd</sup> percentile of the International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century standard head circumference charts for term newborn, and Fenton's growth charts for preterm newborn by gestational age and gender. Univariate and multivariate analysis were performed to identify associated factors. During 2014-2018, 121,448 newborns were identified and the prevalence of neonatal microcephaly was 14.5%. There were 9,871 boys and 7,687 girls. Multivariate analysis showed that small for gestational age (adjusted odds ratio (Adjusted OR) 5.34, 95% confidence interval (CI) 3.24, 8.81), birth length less than the 10<sup>th</sup> percentile (Adjusted OR 2.92, 95% CI 1.36, 6.29), elderly pregnancy (Adjusted OR 1.84, 95% CI 1.07, 3.18), and primigravida (Adjusted OR 2.01, 95% CI 1.37, 2.95) were significantly associated with neonatal microcephaly. The prevalence of neonatal microcephaly in Thailand was higher than expected. The international head circumference chart may not be suitable for Thai newborns suggesting that a head circumference growth standard for Thai newborns is needed.

**Keywords:** prevalence, neonatal, microcephaly, Thailand

### Introduction

Neonatal microcephaly is a condition where a newborn is born with a smaller than normal head, which is defined as a head circumference less than 2 standard deviations (SD) below the mean, or the 3<sup>rd</sup> percentile, compared with other newborns of the same gestational age and gender using a standard reference population.<sup>1-3</sup> Up to now, the cause of microcephaly remains unclear. Apart from a genetic predisposition, the most common causes are infection and exposure to toxic chemicals during pregnancy.<sup>1,3</sup> Newborn with microcephaly may have a normal development, delayed development or, in severe cases, die soon after birth.<sup>1,4</sup> The data from Latin America and the Caribbean showed that microcephaly can

cause a loss of almost 30 disability-adjusted life years per case and an expenditure of over US\$ 91,100 per patient-years.<sup>5</sup> The prevalence of microcephaly varies by region. It ranges from 20-120 cases per 100,000 live births in the United States, around 55 cases per 100,000 live births in Australia, 15.3 per 100,000 live births in Europe, and 4.36 per 100,000 live births in Thailand.<sup>1,6-8</sup>

The global concern of microcephaly rose in 2016 after the global Zika virus infection epidemic.<sup>9</sup> The increasing rate of congenital microcephaly in Brazil and potential association between microcephaly and other central nervous system abnormalities and Zika virus infection from 17 countries were reported to the World Health Organization (WHO) in 2015.<sup>9</sup>

Consequently, WHO declared that the cluster of microcephaly cases and other neurological disorders constituted a Public Health Emergency of International Concern.<sup>10</sup> Furthermore, a case-control study from Brazil confirmed an association between microcephaly and Zika virus infection.<sup>11</sup> Thailand was one of the 17 affected countries. In 2016, the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health (MoPH), Thailand reported more than 1,000 cases of Zika virus infection from many parts of the country, and two confirmed Zika-related microcephaly cases.<sup>12</sup>

Estimating the prevalence of microcephaly after the Zika virus epidemic is crucial for improvement of public health preparedness and response. Moreover, knowing the epidemiological characteristics of microcephaly in Thailand are vital for clinical management and development of clinical guidelines. Head circumference plays an important role in screening for genetic disorders, brain or neurological development abnormalities, and microcephaly. Measurement of head circumference is non-invasive, easy to perform and inexpensive.<sup>13</sup> However, the head circumference of a newborn requires proper standardization before it can be used as an indicator as it has been reported to be associated with many factors such as birth weight and length, maternal race, maternal age, maternal weight, maternal height, and parity.<sup>14-21</sup>

The objectives of this study were to estimate the prevalence of neonatal microcephaly in Thailand during 2014-2018, describe its epidemiological characteristics and identify associated factors.

## Methods

This was a cross-sectional study. The study population was all newborns who received a medical service in public hospitals under the jurisdiction of the Thai MoPH and other hospitals that sent their service data to the MoPH from 1 Jan 2014 to 31 Dec 2018. We excluded newborns who had no data on head circumference or gestational age.

The national health database from the Health Data Center, Thai MoPH, was used as the data source for this study. This database was established in 2012 and achieved nationwide coverage in 2014. The aim of this database is to collect health information among care seekers who received a medical service in public hospitals under the Thai MoPH for health strategic management and health policy planning.<sup>22</sup> The

database contains data from 1,076 public hospitals and 378 private hospitals throughout the country.<sup>23</sup>

The definition of neonatal microcephaly is a newborn with a head circumference less than the 3<sup>rd</sup> percentile when compared to a reference population of newborns with the same gestational age and gender. According to the Royal College of Pediatricians of Thailand, a newborn's head circumference should be measured within three days of birth and compared with the International Fetal and Newborn Growth Consortium for the 21<sup>st</sup> Century (INTERGROWTH 21<sup>st</sup>) standard head circumference charts for term newborns, and Fenton's growth chart for preterm infants.<sup>24-26</sup> Microcephaly was determined based on these reference charts and the prevalence is shown as a proportion with 95% confidence interval (CI).

Independent variables were neonatal factors (gender, birth weight, and length) and maternal factors (age, weight, height, nationality, gravida, and living in a Zika virus infected area). Birth weight was compared with standard references (INTERGROWTH 21<sup>st</sup> for term newborn, and Fenton growth chart for preterm infants) and classified as small for gestational age (a newborn who has a birth weight below the 10<sup>th</sup> percentile of the expected weight for their age and gender), appropriate for gestational age (a newborn who has birth weight between the 10<sup>th</sup> – 90<sup>th</sup> percentile of expected weight for their age and gender), and large for gestational age (a newborn with weight more than the 90<sup>th</sup> percentile of expected weight for their age and gender).<sup>27</sup> Similarly, birth length was classified as less than 10<sup>th</sup> percentile or more than or equal to 10<sup>th</sup> percentile.

There was a study showed that an advance maternal age ( $\geq 35$  years) have a relationship with pregnancy outcome so maternal age was divided into less than 35 years or more than or equal to 35 years.<sup>28</sup> Maternal weight and height were used to calculate body mass index ( $<18.5$  kg/m<sup>2</sup>= underweight; 18.5–22.9 kg/m<sup>2</sup>= normal range; 23–24.9 kg/m<sup>2</sup>= overweight;  $\geq 25$  kg/m<sup>2</sup>= obesity).<sup>29,30</sup> In previous study, mother with short stature ( $<145$  cm) was a risk factor of microcephaly so mother's height was grouped into less than 145cm and more than or equal to 145cm.<sup>19</sup> First gravida showed a relationship with newborn head size so gravidity was classified into two groups: primigravida and multigravida.<sup>15</sup> The residential address (province) of the mother and year of delivery were used to classify the mother as living in a Zika transmitted area or non-Zika transmitted area based on reports from the Bureau of Vector Borne Diseases, Department of Disease Control, Thai MoPH.<sup>31</sup> Any

province that had a confirmed case of Zika virus infection was categorized as being a Zika transmitted area from that year on.

Univariate analysis of independent variables associated with microcephaly was performed using Chi-square tests. Variables with a *P*-value less than 0.2 were included in a multiple logistic regression. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated to assess the statistical association.

## Results

During Jan 2014 – Dec 2018, a total of 2,335,320 newborns in Thailand were recorded in the Health Data Center database. Among these, 134,004 (5.7%) had head circumference recorded, of which 121,448 (90.6%) also recorded the gestational age. The prevalence of neonatal microcephaly, normal head size, and macrocephaly are shown in Table 1. There were 17,558 newborns (14.5%, 95% CI 14.3, 14.7%) with microcephaly.

**Table 1. Prevalence of neonatal microcephaly, normal head size, and macrocephaly, Thailand, 2014-2016**

Year	2014	2015	2016	2017	2018	Total
<b>Microcephaly</b>	2,700	3,565	5,717	2,415	3,161	17,558
<b>Prevalence of microcephaly (%)</b>	14.0	14.9	16.0	15.8	11.6	14.5
<b>95% Confidence interval</b>	13.5 - 14.5	14.5 - 15.7	15.6 - 16.6	15.2 - 16.3	11.3 - 12.0	14.3 - 14.7
<b>Macrocephaly</b>	1,958	1,925	2,324	865	1,298	8,370
<b>Prevalence of macrocephaly (%)</b>	10.1	8.1	6.5	5.6	4.8	6.9
<b>95% Confidence interval</b>	9.7 - 10.6	7.7 - 8.4	6.3 - 6.8	5.3 - 6.0	4.5 - 5.0	6.8 - 7.0
<b>Normal head size</b>	14,679	18,416	27,678	12,042	22,705	95,520
<b>Total</b>	19,337	23,906	35,719	15,322	27,164	121,448

In addition, 8,370 newborns (6.9%, 95% CI 6.8, 7.0%) had macrocephaly. The prevalence of neonatal microcephaly increased between 2014 and 2016, peaking (16.0%) in 2016 and then decreased over the next two years. The prevalence of neonatal microcephaly before (2014-2015) and after the Zika virus outbreak (2016-2018) were 14.5% and 14.4% (*P*-value 0.82), respectively. The epidemiological characteristics of newborns and their mother in this study are illustrated in Table 2. Most newborns with microcephaly were boys (56.2%). Most newborns had an appropriate weight for their gestational age (63.4% for those with microcephaly and 85.8% for those with normal head size). Approximately 86.3% and 97.6% of newborns had a length more than or equal to 10<sup>th</sup> percentile for the microcephaly and normal head size groups, respectively. The microcephaly condition was more likely among boys than girls, small for their gestational age and having a length less than 10<sup>th</sup> percentile were positively associated with microcephaly, in univariate analyses.

For maternal characteristics, most mothers were aged less than 35 years (98.2% in the microcephaly group and 97.6% in the normal head size group). The majority of mothers in both groups had a normal body mass index. However, microcephaly was more likely if

the mother was underweight (OR 1.23, 95% CI 1.16, 1.29) or obese (OR 1.09, 95% CI 1.04, 1.14). The height of majority of mothers in both groups were higher than 145 cm. Most (51.4%) were Thai nationals but mothers who were born in other countries were less likely to have a newborn with microcephaly (OR 0.47, 95% CI 0.42, 0.53). Multigravida was slightly more common for both groups and was protective for microcephaly. More than 50% of mothers in both groups lived in Zika transmission areas, although this was not a risk factor for microcephaly.

Results of the multiple logistic regression analysis is shown in Table 3. Factors significantly associated with microcephaly were birth weight, birth length, maternal age, and gravidity. Newborns whose weights were small for their gestational age were 5.34 times (95% CI 3.24, 8.81) more likely to have microcephaly. Newborns who had a birth length less than 10<sup>th</sup> percentile were 2.92 times (95% CI 1.36, 6.29) more likely to have microcephaly. Concerning maternal factors, mothers aged 35 years or more were more likely to have newborns with microcephaly (Adjusted OR 1.84, 95% CI 1.07, 3.18) and being primigravida also increased the risk of microcephaly (Adjusted OR 2.01, 95% CI 1.37, 2.95).

Table 2. Univariate analysis of epidemiological characteristic and microcephaly among Thai newborn, 2014-2018

	Microcephaly		Normal head size		Odds Ratio	95% CI		P- value
	n	%	n	%		Lower	Upper	
<b>Neonatal factors</b>								
<b>Gender (n= 113,078)</b>								
Boy	9,871	56.2	48,908	51.2	1.22	1.18	1.26	<0.001
Girl	7,687	43.8	46,612	48.8	ref.			
<b>Weight (n= 113,042)</b>								
SGA	6,341	36.1	5,974	6.3	7.82	7.51	8.14	<0.001
AGA	11,128	63.4	81,942	85.8	ref.			
LGA	81	0.5	7,576	7.9	0.08	0.06	0.10	<0.001
<b>Length (by Age and Gender) (n= 112,938)</b>								
<10 <sup>th</sup> percentile	2,401	13.7	2,319	2.4	6.38	6.01	6.77	<0.001
≥10 <sup>th</sup> percentile	15,110	86.3	93,108	97.6	ref.			
<b>Maternal factors</b>								
<b>Age (year) (n= 14,788)</b>								
≥35	43	1.8	295	2.4	0.75	0.54	1.03	0.08
<35	2,355	98.2	12,095	97.6	ref.			
<b>BMI (Kg/m<sup>2</sup>) (n= 80,506)</b>								
Underweight	2,543	19.1	11,207	16.7	1.23	1.16	1.29	<0.001
Normal range	4,679	35.1	25,280	37.6	ref.			
Overweight	1,521	11.4	7,890	11.7	1.04	0.98	1.11	0.21
Obesity	4,596	34.5	22,790	33.9	1.09	1.04	1.14	<0.001
<b>Height (centimeters) (n= 81,265)</b>								
<145	60	0.4	353	0.5	0.86	0.65	1.12	0.26
≥145	13,407	99.6	67,445	99.5	ref.			
<b>Nationality (n= 13,798)</b>								
Myanmar	310	14.2	1,752	15.1	0.70	0.61	0.80	<0.001
Laos	131	6.0	624	5.4	0.83	0.68	1.01	0.06
Cambodia	84	3.8	341	2.9	0.97	0.76	1.24	0.80
Other	536	24.5	4,476	38.5	0.47	0.42	0.53	<0.001
Thai	1,124	51.4	4,420	38.1	ref.			
<b>Gravida (n= 82,559)</b>								
1	6,192	47.9	29,402	42.2	1.26	1.21	1.31	<0.001
>1	6,723	52.1	40,242	57.8	ref.			
<b>Zika transmission area (n= 73,718)</b>								
yes	6,527	57.8	35,834	57.4	1.02	0.98	1.06	0.44
no	4,766	42.2	26,591	42.6	ref.			

BMI: body mass index. AGA appropriate for gestational age. LGA: large for gestational age. SGA: small for gestational age. CI: confidence interval. ref: reference group.

## Discussion

In this study, the definition of neonatal microcephaly is a newborn who had head circumference of less than the 3<sup>rd</sup> percentile of standard head circumference by age and gender.<sup>24</sup> This means that in a fictional but normal population the expected prevalence of neonatal microcephaly will be around 3%. The prevalence of neonatal microcephaly in this study was 14.5% or 14,457 per 100,000 live births which is much higher than a previous study (4.36 cases per 100,000

live-births).<sup>8</sup> The higher prevalence when compared with previous study was possibly from the different methods. In this study, we used head circumference compared with a standard reference population to identify microcephaly cases. However, in the previous Thai study, they used diagnosis code (ICD-10-CM = Q02) to identify microcephaly cases. The definition of Q02 is a congenital or acquired developmental disorder in which the circumference of the head is smaller than normal for the person's age and gender. It is the result of brain developmental delay.<sup>32</sup> Some

newborns with a small head but with normal brain development may not be diagnosed with microcephaly. In 2017, the Thai Bureau of Epidemiology, conducted a microcephaly reporting system evaluation using the national health database as a reporting system. They found that only 8 out of 5,796 (0.14%) newborns who

had a head circumference smaller than the 3<sup>rd</sup> percentile of the standard reference population were reported as microcephaly.<sup>33</sup> It is likely that using clinical diagnosis, recorded as ICD-10-Q02, may result in an underreporting of the magnitude of microcephaly.

**Table 3. Multivariate analysis of epidemiological characteristic and microcephaly among Thai newborn, 2014-2018 (n=1,009)**

Variables	Adjusted Odds Ratio	95% CI		P-value
		Lower	Upper	
<b>Neonatal factors</b>				
<b>Gender</b>				
Boy	1.03	0.72	1.49	0.87
Girl	ref.			
<b>Weight</b>				
SGA	5.34	3.24	8.81	<0.001
AGA	ref.			
LGA	0.41	0.13	1.36	0.15
<b>Length (by Age and Gender)</b>				
<10 <sup>th</sup> percentile	2.92	1.36	6.29	0.01
≥10 <sup>th</sup> percentile	ref.			
<b>Maternal factors</b>				
<b>Age (year)</b>				
≥35	1.84	1.07	3.18	0.03
<35	ref.			
<b>BMI (Kg/m<sup>2</sup>)</b>				
Underweight	0.63	0.12	3.22	0.58
Normal range	ref.			
Overweight	1.22	0.74	2.03	0.44
Obesity	0.67	0.42	1.08	0.10
<b>Nationality</b>				
Myanmar	1.38	0.13	14.07	0.79
Laos	1.77	0.17	18.71	0.63
Cambodia	2.22	0.21	23.00	0.50
Other	0.40	0.03	5.11	0.48
Thai	ref.			
<b>Gravida</b>				
1	2.01	1.37	2.95	<0.001
>1	ref.			

BMI: body mass index. AGA appropriate for gestational age. LGA: large for gestational age. SGA: small for gestational age. CI: confidence interval. ref: reference group.

Another reason for the high prevalence of microcephaly in this study may be due to the use of an international standard reference population which did not include countries from South East Asia where Thailand is located. A number of studies from

countries in South East Asia mentioned that international standard growth curves may not be suitable for their newborns.<sup>19,34-36</sup> When they made their own standard reference charts for head circumference based on their newborn data and

compared this with the international standard reference charts, they found that standard head circumferences in their countries were smaller than international standard head circumferences. We compared the 3<sup>rd</sup> percentile of head circumference of the population in this study with the standard international reference charts (INTERGROWTH 21<sup>st</sup> for term newborn, and Fenton growth chart for preterm infants) as shown in Table 4. We found that the 3<sup>rd</sup> percentile of head circumference in this population was smaller than the 3<sup>rd</sup> percentile of international standard head circumference. Therefore,

the high prevalence of microcephaly in our study is likely due to misclassification using the international standard head circumference, which may not be applicable in Thailand, and higher than the actual proportion. According to the national guideline, a newborn with microcephaly is one of the criteria to initiate congenital Zika syndrome investigation, which is costly.<sup>24</sup> Diagnosing microcephaly using international standard head circumference may result in unnecessary investigations and costs. Therefore, a local standard head circumference chart appropriate to Thai newborns is needed.

**Table 4. The 3<sup>rd</sup> percentile comparison of standard reference and study population**

GA	Standard 3 <sup>rd</sup> percentile	Male		Female		
		3 <sup>rd</sup> percentile in this study	n	Standard 3 <sup>rd</sup> percentile	3 <sup>rd</sup> percentile in this study	n
28	23	23	33	22.2	23	24
29	24	23	41	23	25	42
30	25	26	118	24	24.5	91
31	25.9	26.6	119	25	26	102
32	26.8	26.2	174	26	27	170
33	27.5	28	349	27	27	346
34	28.2	28	796	28	28	739
35	29	29	1,432	29	28	1,252
36	30	29	2,027	29.5	29	1,782
37	30.7	30	6,849	30.4	30	6,084
38	31.2	30	14,314	30.9	30	13,415
39	31.7	30	18,836	31.3	30	18,423
40	32.2	30	15,250	31.7	30	14,483
41	32.6	31	1,650	32.1	30	1,579
42	33	31	248	32.4	30	191
43	34	30	65	33	30	60
44	34.5	30	125	34	29.6	120

The prevalence of microcephaly increased between 2014 and 2016, peaking in 2016 (following the Zika virus outbreak in Thailand) then decreased. However, the difference in prevalence of neonatal microcephaly was not significant when we compared before and after Zika virus outbreak time periods. Although the association between Zika virus infection and microcephaly was confirmed in other countries, there was no association between mother's history of living in Zika transmission areas and microcephaly among newborns in this study.<sup>11</sup> However, our study had limited ability to verify the association between Zika infection and microcephaly in Thailand due to the low proportion of people who underwent specific Zika infection investigations among all microcephaly cases

diagnosed using international standard head circumference charts.

In this study, maternal weight and body mass index did not show an association with microcephaly, a result similar to previous studies.<sup>37-39</sup> Some studies showed that the weight-related factor was maternal gestational weight gain.<sup>38,40</sup> Unfortunately, gestational weight gain data is not recorded in the national health database.

There was a report about complication during pregnancy in advanced maternal age ( $\geq 35$  years).<sup>19</sup> Since parity is not included in the national health database, we used gravidity as a proxy. In this study, a primigravida woman was twice as likely to deliver a

newborn with microcephaly than multigravida women. The results of this study are similar to the result of a previous study by Shajari et al where the mean neonatal head circumference in the first parity group was smaller than the multiparity group.<sup>15</sup> The result may be explained by low birth weight. Terán et al found that a newborn with the first parity had a higher risk of low birth weight than a newborn with multiparity.<sup>41</sup> The explanation of low birth weight may come from poor uterine blood perfusion in primiparous mothers, which reduces the supply of oxygen and nutrients to the fetus.<sup>42</sup> In addition, newborns delivered in primigravida elderly mothers were likely to have small head circumference.

The strength of this study is the database. This study used data from the Health Data Center, which included data from 1,454 hospitals throughout Thailand. Since 2014, around 69% of live births in Thailand are included in this database.<sup>43</sup>

However, as this study used secondary data, we were unable to impute incomplete or missing data of crucial variables, such as head circumference (>95% were missing) and gestational age of the newborns, from the original data sources. This also prevent us from improving the representativeness of the group included in the multivariate analysis of our study, as a large proportion of records were excluded from the model due to missing data in one or more selected variables. Some head circumference measurements might have round-off errors which may have affected the results. However, due to the nature of secondary data analysis, we did not have a chance to validate all measurements. Moreover, some potential associated factors such as gestational weight gain, nutrition during pregnancy, socioeconomic status, environmental, and lifestyle factors (stress, smoking and alcohol use) were not available.

We recommend that a standard reference anthropometric chart for Thai newborns be developed to support health care providers to make proper diagnoses, investigations, and treatment of neonatal microcephaly. Health care facilities should ensure completeness and accuracy of the data before sending reports to the central level. The study on possible associated factors such as gestational weight gain, nutrition during pregnancy, socioeconomic status, environmental, and lifestyle factors (stress, smoking and alcohol use) should be considered.

### Suggested Citation

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