



A Multisite Study of Oral Clefts and Associated Abnormalities in Thailand: The Epidemiologic Data

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Background: This study aimed to obtain epidemiological data of birth incidences of cleft lips and/or cleft palates (CLP) in the Thai population with associated risk factors.

Methods: The data were collected for a period of 12 months between 2003 and 2004 for infants' deliveries with CLP and associated risk factors in all hospitals of 6 provinces from 4 regions of Thailand. The birth incidence, related factors with cleft birth, and linkage with geographical area were analyzed by the geographic information system.

Results: Phitsanulok, Saraburi, and Khon Kaen had higher birth incidences for CLP of 2.01, 1.69, and 1.66 per 1000 live births, respectively, and the overall birth incidence was 1.51 per 1000 live births. There were a total of 112 cleft births (61 males and 51 females) with 43 cleft lips, 18 cleft palates, and 51 cleft lips + cleft palates. The northeast region had infants with different gestational ages at birth and mothers with higher intakes of vitamins and a use of vitamin A supplement or retinoic acid than others. A use of folic acid supplement was low in all 4 regions.

Conclusions: The varied incidence of CLP may reflect the incomplete accuracy of case ascertainment. A number of challenges were addressed. The geographic information system was helpful for more background investigation and planning of cleft care management. Our study enables future studies of etiological factors and future birth registries. (*Plast Reconstr Surg Glob Open* 2015;3:e583; doi: 10.1097/GOX.0000000000000570; Published online 18 December 2015.)

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The worldwide prevalence of isolated oral clefts varies with geography, ethnicity, and socioeconomic status.¹ A prospective study from Thailand reported a high incidence of 2.49 per 1000 live births.²⁻⁶ Problems to be anticipated and overcome for accurate epidemiologic data are the inclusiveness of the reporting system and confirmation of ascertainment, geographical accuracy of location of conception versus reporting and variation of diagnostic criteria, and accuracy of diagnosis and recording.⁷



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This study aimed to obtain birth incidence of cleft lip and/or cleft palate (CLP) and identify associated risk factors of infants with CLP and needs for improving healthcare services in Thai population.

METHODS

This study was one of the activities under the “Tawanchai Royal Granted Project” under Tawanchai Center in Sinagarind Hospital, Khon Kaen, with the gracious permission of Her Royal Highness Princess Maha Chakri Sirindhorn.⁸ It was a population-based study, conducted in 6 provinces representing 4 regions of Thailand: Khon Kaen, Loei, and Buriram (northeast, NE); Phitsanulok (north, N); Songkhla (south, S); and Saraburi (central, C; Fig. 1).

Preliminary workshops were conducted in all provinces to establish diagnostic criteria, consensus on treatment guidelines, referral system, data collection, and data reporting. The data included birth incidence and associated factors in all deliveries of infants with CLP from all hospitals in these provinces

for a total period of 12 months, between May 1, 2003 and April 30, 2004. Syndrome cases were excluded.

The study was divided into epidemiology study and case-control study. Three questionnaires were used to collect cleft births' data records, including the record for a case (the child born with CLP) and 2 control cases (2 following children born without CLP in the same hospital). Trained staff nurses interviewed and recorded the data and photographs. A co-principal investigator in each province made a confirmation of diagnosis and relayed data to the Tawanchai Centre. A nurse coordinator and the principal investigator in the center performed a review of case ascertainment and accuracy of the data with regular communication and required visits. The birth incidence, related factors with cleft birth, and linkage with geographical area were analyzed by the geographic information system (ArcView GIS, developed by Environmental Systems Research Institute, Inc., Redlands, Calif., from <http://www.esri.com>). The analyses of a case-control study of micronutrient and oral clefts were reported in another article.⁹

Ethics Approval

The Ethics Committee of Khon Kaen University approved this study.

RESULTS

There were a total of 112 cleft births (61 males and 51 females) with 43 cleft lips, 51 cleft lips + cleft palates, and 18 cleft palates. Associated craniofacial anomalies and other anomalies were 3.77% and 8.91%, respectively. There were 65.38% of mothers who had educational levels of secondary school and below. Poverty was reported in 51.92% of mothers (average household income <6000 baht/mo), and 19.42% of mothers had a family history of CLP. Demographic characteristics and related factors of patients with CLP by provinces were presented in Table 1. The data from Loei province were not included because of incompleteness of data.

The infant gestational age at birth was different in each region at P value = 0.044 (95% confidence interval). The NE region had infants with different gestational ages at birth significantly higher than others (Table 2). Mothers from the NE region had higher intakes of vitamins than others. The use of folic acid supplement was low in all 4 regions, whereas mothers from the NE region had the highest use of vitamin A and retinoic acid.

The total population and a number of live births were used for estimating CLP birth incidence.^{10,11} An average birth incidence was 1.51 per 1000 live births. Phitsanulok had the highest birth incidence for CLP of 2.01 per 1000 live births, whereas the lowest incidence of 1.06 CLP per 1000 live births was observed from Songkhla (Table 3).

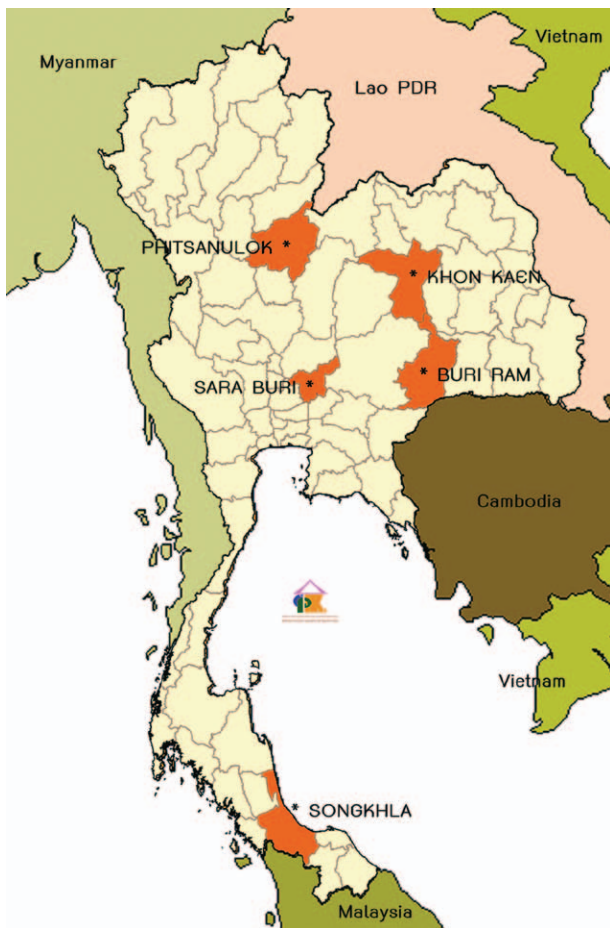


Fig. 1. Location of the study areas involving 6 provinces from 4 regions of Thailand: Khon Kaen, Loei, and Buriram (northeast); Phitsanulok (north); Songkhla (south); Saraburi (central).

Table 1. Demographic Characteristics and Related Factors of Patients with CLP by Provinces

| | Total (Cases) | Northeast | | North | South | Central |
|---|------------------|--------------|-------------|-----------------|--------------|--------------|
| | | Khon Kaen | Buri Ram | Phitsa Nulok | Song Khla | Sara Buri |
| Infant sex | 112 | 33 | 26 | 17 | 22 | 14 |
| Males | 61 | 15 | 15 | 10 | 11 | 10 |
| Females | 51 | 18 | 11 | 7 | 11 | 4 |
| Diagnosis | | | | | | |
| 1. CL | 43 | 14 | 11 | 9 | 6 | 3 |
| 2. CL + CP | 51 | 13 | 11 | 5 | 13 | 9 |
| 3. CP | 18 | 6 | 4 | 3 | 3 | 2 |
| Birth weight (g) | | | | | | |
| ≥2500 | 88 | 28 | 19 | 16 | 18 | 7 |
| <2500 | 19 | 4 | 7 | 1 | 4 | 3 |
| Missing | 5 | 1 | 0 | 0 | 0 | 4 |
| Infant gestational age at birth (wk) by last menstrual period | | | | | | |
| 37–41 | 75 | 22 | 18 | 11 | 18 | 6 |
| <37 | 15 | 4 | 6 | 1 | 0 | 4 |
| ≥42 | 3 | 2 | 0 | 1 | 0 | 0 |
| Missing | 19 | 5 | 2 | 4 | 4 | 4 |
| Infant with craniofacial anomalies | | | | | | |
| No | 106 | 33 | 23 | 16 | 20 | 14 |
| Yes | 4 | 0 | 2 | 1 | 1 | 0 |
| Missing | 1 | 0 | 0 | 0 | 1 | 0 |
| Infant with other anomalies | | | | | | |
| No | 101 | 30 | 22 | 15 | 20 | 14 |
| Yes | 9 | 3 | 4 | 1 | 1 | 0 |
| Missing | 2 | 0 | 0 | 1 | 1 | 0 |
| Mother's age (y) | | | | | | |
| <20 | 17 | 3 | 5 | 5 | 2 | 2 |
| 20–24 | 25 | 8 | 7 | 1 | 7 | 2 |
| 25–29 | 19 | 7 | 0 | 5 | 7 | 0 |
| 30–34 | 27 | 9 | 7 | 4 | 4 | 3 |
| ≥35 | 17 | 3 | 7 | 2 | 2 | 3 |
| Missing | 7 | 3 | 0 | 0 | 0 | 4 |
| Mother's educational level | | | | | | |
| None | 4 | 0 | 3 | 0 | 1 | 0 |
| Primary | 37 | 9 | 10 | 8 | 6 | 4 |
| Secondary | 27 | 5 | 6 | 6 | 7 | 3 |
| High school | 18 | 5 | 4 | 2 | 5 | 2 |
| Bachelor degree | 17 | 10 | 3 | 1 | 3 | 0 |
| Higher than Bachelor degree | 0 | 0 | 0 | 0 | 0 | 0 |
| Others | 1 | 0 | 0 | 0 | 0 | 1 |
| Missing | 8 | 4 | 0 | 0 | 0 | 4 |
| Household income (monthly in Baht) | | | | | | |
| ≤4000 | 34 | 7 | 14 | 8 | 4 | 1 |
| 4000–6000 | 20 | 8 | 3 | 4 | 3 | 2 |
| 6000–10,000 | 29 | 5 | 6 | 3 | 11 | 4 |
| >10,000 | 20 | 10 | 2 | 1 | 4 | 3 |
| Missing | 8 | 3 | 0 | 1 | 0 | 4 |
| Mother's drinking alcohol status | | | | | | |
| No | 89 | 25 | 22 | 12 | 20 | 10 |
| Yes 1–3 time(s)/wk | 12 | 5 | 3 | 2 | 2 | 0 |
| Yes 1–4 time(s)/wk | 2 | 0 | 1 | 1 | 0 | 0 |
| Missing | 8 | 3 | 0 | 1 | 0 | 4 |
| Mother's smoking status | | | | | | |
| No | 100 | 26 | 25 | 17 | 22 | 10 |
| Yes | 3 | 2 | 1 | 0 | 0 | 0 |
| Missing | 9 | 5 | 0 | 0 | 0 | 4 |
| Father, family's members or colleagues' smoking statuses | | | | | | |
| No | 38 | 16 | 7 | 6 | 5 | 4 |
| Yes | 66 | 13 | 19 | 11 | 17 | 6 |
| Missing | 8 | 4 | 0 | 0 | 0 | 4 |
| A total number of pregnancies | | | | | | |
| 1 | 27 | 7 | 8 | 4 | 5 | 3 |
| 2 | 51 | 20 | 9 | 9 | 11 | 2 |
| ≥3 | 26 | 3 | 8 | 4 | 6 | 5 |
| Missing | 7 | 3 | 0 | 0 | 0 | 4 |

(Continued)

Table 1. (Continued)

| | Total (Cases) | Northeast | | North | South | Central |
|---|------------------|--------------|-------------|-----------------|--------------|--------------|
| | | Khon Kaen | Buri Ram | Phitsa Nulok | Song Khla | Sara Buri |
| Vitamin uses | | | | | | |
| No | 8 | 0 | 0 | 2 | 6 | 0 |
| Yes | 96 | 30 | 26 | 14 | 16 | 10 |
| Missing | 8 | 3 | 0 | 1 | 0 | 4 |
| Folic acid supplement uses | | | | | | |
| No | 88 | 29 | 22 | 15 | 15 | 7 |
| Yes | 9 | 1 | 4 | 0 | 1 | 3 |
| Missing | 15 | 3 | 0 | 2 | 6 | 4 |
| Vitamin A supplement or retinoic acid uses during pregnancy | | | | | | |
| No | 86 | 23 | 22 | 17 | 16 | 8 |
| Yes | 17 | 7 | 2 | 0 | 6 | 2 |
| Missing | 9 | 3 | 2 | 0 | 0 | 4 |
| History of cleft in family | | | | | | |
| No | 83 | 23 | 22 | 14 | 15 | 9 |
| Yes | 20 | 5 | 4 | 3 | 6 | 2 |
| Missing | 9 | 5 | 0 | 0 | 1 | 3 |

CL, cleft lip; CP, cleft palate.

Table 2. Infant Gestational Age at Birth

| Infant Gestational Age at Birth (wk) | Total | NE | N | S | C | P Value |
|--------------------------------------|-------------|-------------|-------------|-------------|------------|---------|
| 37–41 | 75 (66.97%) | 40 (67.80%) | 11 (64.71%) | 18 (81.82%) | 6 (42.86%) | 0.044 |
| <37 | 15 (13.39%) | 10 (16.95%) | 1 (5.88%) | 0 | 4 (28.57%) | |
| ≥42 | 3 (2.68%) | 2 (3.39%) | 1 (5.88%) | 0 | 0 | |
| Missing | 19 (16.96%) | 7 (11.86%) | 4 (24.53%) | 4 (18.18%) | 4 (28.57%) | |

Table 3. Estimated CLP Birth Incidence by Provinces and Regions

| Province | Population in 2003 | No. of Hospitals* | No. of Live Births in 2003 | No. of Live Births in 2004 | Average No. of Births/Year in 2003–2004 | No. of Cleft Births During 12-Month Period in 2003–2004 | Estimated CLP Birth Incidence (per 1000 Live Births) | Incidence Rate Ratio (P Value = 0.112) |
|-------------------------------------|--------------------|-------------------|----------------------------|----------------------------|---|---|--|--|
| Khon Kaen | 1,770,605 | 31 | 19,344 | 20,479 | 19,912 | 33 | 1.66 | NE = 1.61 |
| Buriram | 1,544,009 | 24 | 15,374 | 18,043 | 16,709 | 26 | 1.56 | |
| Phitsanulok | 876,356 | 20 | 8333 | 8570 | 8452 | 17 | 2.01 | N = 2.01 |
| Songkhla | 1,294,442 | 30 | 20,246 | 21,357 | 20,802 | 22 | 1.06 | |
| Saraburi | 625,574 | 18 | 7331 | 9104 | 8218 | 14 | 1.69 | C = 1.69 |
| Average live births (all provinces) | | | | | 74,093 | 112 | 1.51 | |

*Included all government and private hospitals.

The NE, N, and C regions had the CLP incidence of 1.61, 2.01, and 1.69 per 1000 live births, which were higher than the S region where the incidence was 1.06. The proportions of incidence of periconceptional address in each province were tabulated into district areas (Fig. 2).

In Khon Kaen, 3.33% of cleft mothers lived outside the province, and 32.14% stayed outside the province during periconceptional period. There were 57.58% of CLP births in Khon Kaen delivered in Muang District where the University Hospital and Center Hospital were located, whereas only 26.67% had the addresses during periconceptional in this location (Fig. 3). There was a signifi-

cant percentage of the birth outside the district of periconceptional address and the birth outside the province of periconceptional address in all provinces (Table 4).

The case-control study was used to examine the relationships among micronutrients, supplements, and environmental risk factors. Cases were more likely to be low birth weight ($P < 0.01$), preterm, and have other anomalies and a family history of anomalies. There was statistically stable inverse association of 0.26 between liver intakes and CLP risk ($P < 0.01$). Mothers who took a menstrual regulation supplement were at a 5-fold increased risk of having an affected child ($P = 0.02$).⁹

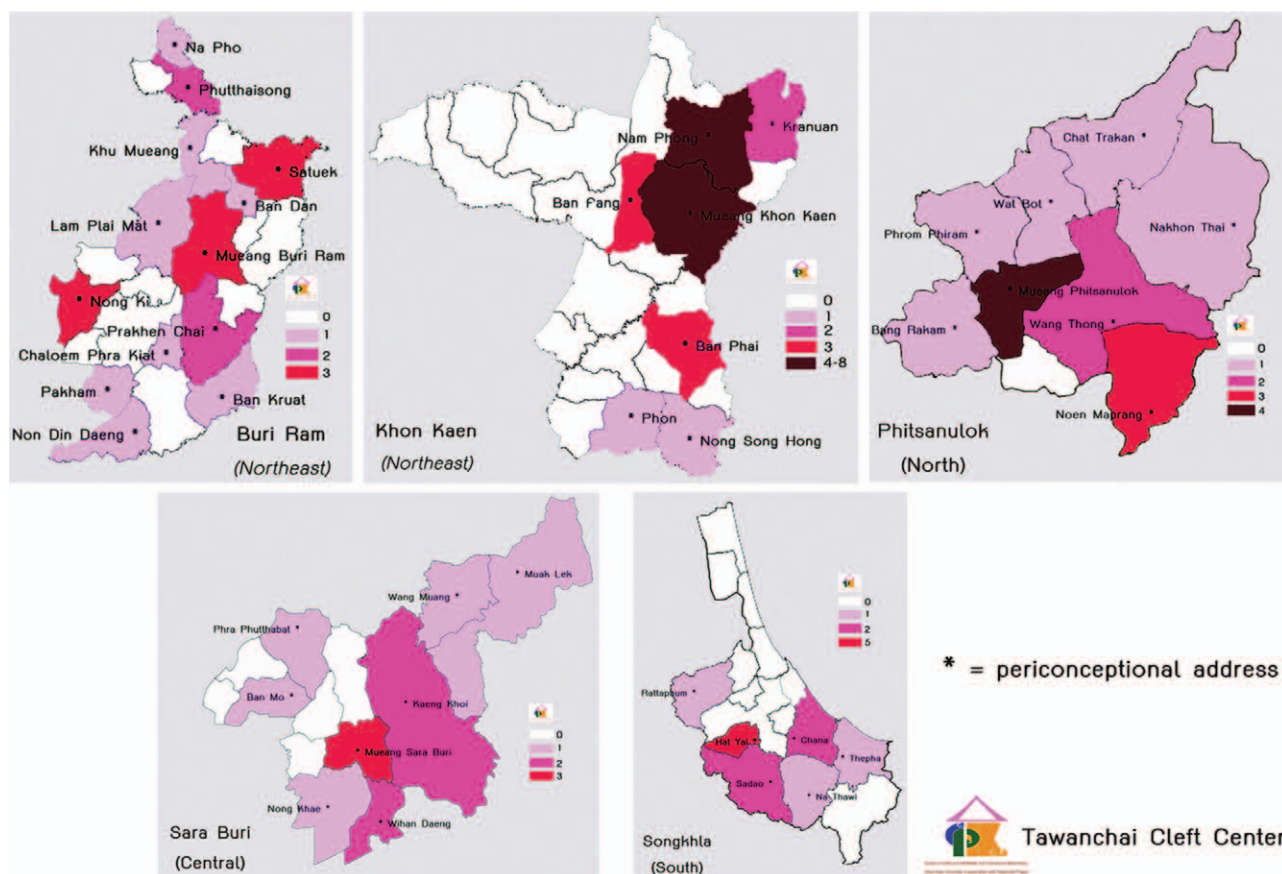


Fig. 2. The number of newborns with CLP in 5 provinces, with geographic distribution to location of periconceptual district in each province.

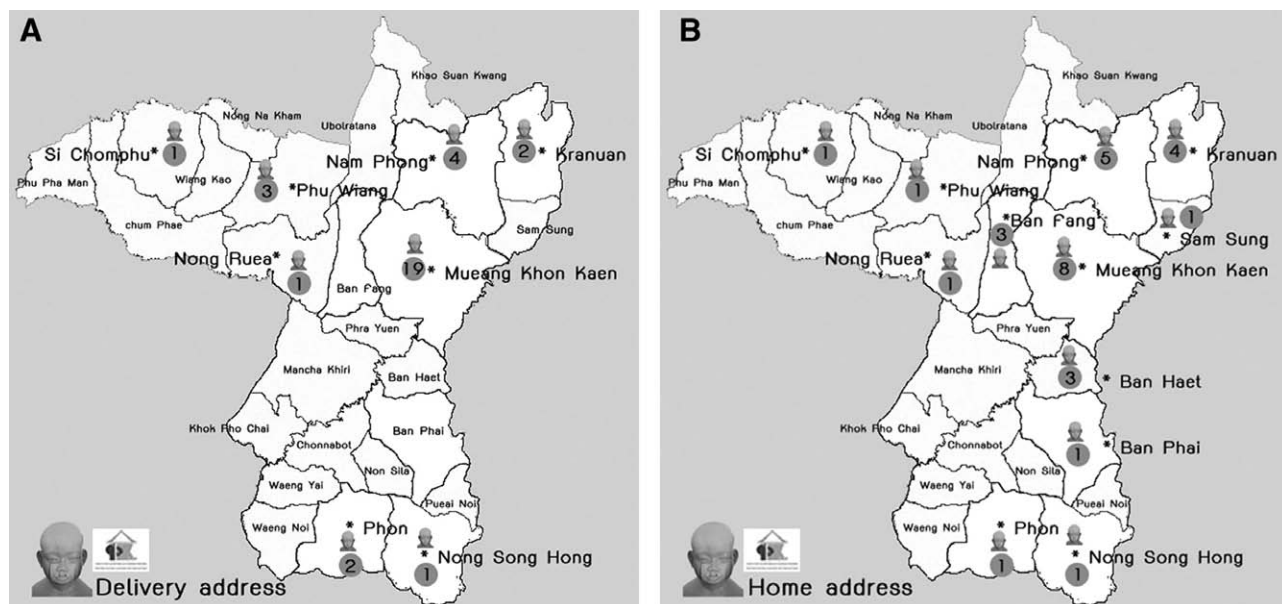


Fig. 3. Delivery hospital of CLP birth (A) and Home address during periconceptual of CLP birth (B) in Khon Kaen.

Table 4. The Relationship of the Birth Outside the District of Periconceptional Address and the Birth Outside the Province of Periconceptional Address

| Province | Birth Outside the District of Periconceptional Address | Birth Outside the Province of Periconceptional Address |
|-------------|--|--|
| Khon Kaen | 9 (39.13%) | 9 (39.13%) |
| Buri Ram | 10 (58.82) | 5 (29.41) |
| Phitsanulok | 5 (62.5%) | 1 (12.5%) |
| Songkhla | 5 (38.47%) | 7 (53.84%) |
| Saraburi | 6 (75.0%) | 1 (12.5%) |

DISCUSSION

The incidence of CLP is known to vary among races and regional geographic variability.¹² These differences among provinces from different regions from this study may reflect the accuracy of data from maximized case ascertainment, cooperation of local health authorities, unified cleft care, referral system, and geographic locations.

The geographic information system was helpful to join the tabulated infants' data to locate the areas of delivery and associated geographic data for more background investigation, planning of cleft care management, referral system, community outreach programs, and follow-ups.^{12,13} The high percentages (32.14% in Khon Kaen) of mothers who stayed outside the province during periconceptional period addressed the challenges of geographical accuracy of locations of conception versus confinement.⁷ The high percentages of CLP births delivered in Muang District (in Khon Kaen), whereas lower percentages had the addresses during periconceptional in this location should be considered in the planning of health care services.

A number of challenges were addressed in this study including the nature of anomalies, the inclusiveness of reporting system, maximal ascertainment, geographical accuracy of locations of conception versus confinement and reporting, and identifying geographical clustering of occurrences and environmental resources.¹² The syndrome cases had been excluded because of the different etiological backgrounds.¹⁴

Estimates of the genetic contribution ranged from 12 to 20%, whereas the remainder was attributed to environmental factors or gene–environmental interaction similar to previous studies^{15–21} with a great deal of interest in multivitamin uses in the periconceptional period.^{22–27} Fetuses with oral clefts are at elevated risk of having low and very low birth weight but not of having a premature birth.²⁸ The probability of mothers aged 35 years or over having a child with CLP was 20%.²⁹ There is a strong positive relationship of prevalence of CLP at birth with

increasing deprivation.³⁰ Mothers who took a menstrual regulation supplement were more likely to deliver a baby with CLP.³¹

This study recorded live births from all hospitals in the provinces. A study of prevalence rate of the neural tube defects in southern Thailand showed that failure to include stillbirths and termination of pregnancy but recording only registered live births and stillbirths in the registry system would result in inaccurately low neural tube defect prevalence rates, despite the fact that the frequency of termination of pregnancy after prenatal diagnosis of congenital anomaly has been increasing.³²

The results of case-control study⁹ suggest that micronutrients play a role in the cause of CLP. The future research can be developed as a community-based network system model³³ and established of diagnostic and treatment protocols.^{34,35} A study for a longer period of time may provide more data of incidences and analyses of oral clefts.

This study is among the first population-based epidemiologic studies in Southeast Asia. The limitations and challenges of epidemiologic study were addressed in the planning, such as the establishment of diagnostic criteria, protocol management, and recording data for the maximized case ascertainment. The majority of the births in Thailand were delivered in hospitals and most of the hospitals in the provinces participated in the study. Out of hospital births were subsequently reported and recorded in the hospital system. Given estimates of birth prevalence of oral clefts in Thailand and number of live births in the recruitment provinces, we suspected that some cases were missed during recruitment because of practical and logistic constraints. The establishment of central birth registries, including surveillance of aborted human fetuses and environmental monitoring, is needed.⁷

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