Idiopathic Congenital Talipes Equinovarus in Wisconsin Newborns: Incidence and Associated Risk Factors

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ABSTRACT

Introduction: Clubfoot, also known as idiopathic congenital talipes equinovarus, is one of the most common pediatric deformities affecting 1 to 2 in every 1,000 live births. We sought to provide the first known analysis of incidence of clubfoot diagnoses in the most populous region of Wisconsin as well as risk factors associated with the deformity.

Methods: We conducted a retrospective study on children treated for clubfoot at Children's Wisconsin from January 1, 2004, through December 31, 2018. To examine trends, we performed a linear trend of annual clubfoot births for each county covered as well as the southeastern region of Wisconsin. We also analyzed common risk factors associated with clubfoot.

Results: The study population included 760 patients diagnosed with clubfoot: 497 males and 263 females. Most patients were non-Hispanic/Latino (76.8%) and White (72.2%). A total of 414 patients (54.4%) had no family history of clubfoot, 130 patients (17.1%) had a positive family history of clubfoot, and family history was unknown for 216 patients (28.4%). The southeastern region of Wisconsin contained the largest patient population (n = 523) and, among counties studied, Milwaukee County had the largest patient population (n = 269). Linear trends for Milwaukee County and the southeastern region of Wisconsin showed a statistically significant increase in clubfoot births from 2004 through 2017 ($P < 0.001$).

Conclusions: In this study of children diagnosed with clubfoot, high population areas showed a statistically significant increase in the number of children affected over time, with a low evidence of family history. This study provides further insight into the possible etiology of clubfoot being influenced by an exogenous, environmental factor.

INTRODUCTION

Idiopathic congenital talipes equinovarus, also known as clubfoot, is one of the most common pediatric deformities, affecting 1 to 2 newborns in every 1,000 live births.[1] While an effective treatment method has been established, the prevalence of clubfoot in the newborn population has given rise to concerns regarding the possible etiologies of the deformity. Multiple theories have been proposed, including aspects of genetics, maternal demographics, and some environmental factors, with no single hypothesis predominating in literature.

Myriad risk factors have been associated with clubfoot, including male sex, family history, maternal smoking, and amniocentesis. Studies exploring the role of population density in the development of clubfoot are relatively rare in the literature. While changes in incidence of clubfoot births may not be related entirely to population density, as there may be multiple factors of influence, it is valuable to look at this trend to assess if changes have occurred. Whether they are demographic, environmental, or unknown, any factor affecting the diagnosis and development of clubfoot is worth noting.

The objective of this study is to provide the first known analysis of incidence of clubfoot diagnoses over a defined time period in the most populous region of Wisconsin. We hypothesize that if there are no exogenous factors of influence, incidence of clubfoot births over time should remain relatively unchanged. This study also provides an analysis of certain risk factors associated with clubfoot diagnosis, comparing our findings to current published literature.

METHODS

This study was a retrospective analysis utilizing electronic medical records (Epic Systems, Verona, Wisconsin) to collect infor mation

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on all clubfoot diagnoses encountered at Children's Wisconsin from January 1, 2004, through December 31, 2018. This includes diagnoses made at the institution's MAIN campus in Milwaukee, Wisconsin, as well as Children's Wisconsin-affiliated locations throughout Wisconsin. A clubfoot diagnosis code was utilized to search for charts of interest. Risk factor data were collected via the patient's medical record. Data collection was limited by availability of variables within a patient's record. To evaluate the incidence of clubfoot births, annual birth rates were collected via the Wisconsin Department of Health Services for the years 2004 through 2017 per county and region. (Population data were available only through 2017, despite data collection through 2018). The institutional review board approved this study and waived the parental consent requirement since the study analyzed previously collected data.

Study Population

To be eligible for inclusion in this study, patients had to be born in Wisconsin with a documented diagnosis of idiopathic congenital talipes equinovarus. Subjects were required to have at least 1 encounter at one of the Children's Wisconsin locations between January 1, 2004, and December 31, 2018. Medical records of more than 1,300 children were reviewed. A total of 760 patients fit the required population criteria and were included in this study.

Variables Collected

To evaluate incidence of clubfoot births by county/region, patients' addresses at birth—including ZIP code and county—were collected. Demographic data collected from chart review included date of birth, sex, ethnicity/race, address, laterality, preterm vs term delivery, birth weight (kg), and family history of clubfoot. Ethnicity was reported as non-Hispanic/Latino or Hispanic/Latino, and race was reported as White, Black, Asian, American Indian/Alaskan Native, American Indian, and other. Laterality of clubfoot was reported as bilateral or unilateral. Preterm delivery was defined as delivery before 32 weeks gestation. Less than 32 weeks gestation was chosen to define prematurity, as this is considered very preterm and is associated with higher rates of death and disability. Researchers wanted to ensure that subjects born before 32 weeks gestation could have a diagnosis more reliably accountable to their pre-term delivery. Family history was reported as yes (positive family history of clubfoot), no (negative family history of clubfoot), or unknown.

Statistical Analysis

Simple linear regression analyses were used to examine linear trends in annual rates of clubfoot births over the 14-year data collection time period. Linear trends were estimated for the entire southeastern region of Wisconsin as well as each county within the region. Observed annual rates were plotted with mean and 95% confidence intervals. Demographic data were summarized by frequencies, and birth weight was further characterized by boxplot. Statistical significance was determined at P value < 0.05.

Table 1. Clubfoot Encounters at Children's Wisconsin per County, 2004-2018

Counties	No. of Clubfoot Births
Brown	47
Clark	1
Columbia	2
Dane	3
Dodge	11
Door	5
Fond Du Lac	25
Grant	1
Green Lake	8
Jefferson [a]	13
Kenosha [a]	27
Kewaunee	4
Manitowoc	24
Marathon	2
Marinette	9
Milwaukee [a]	269
Oconto	7
Outagamie	27
Ozaukee [a]	24
Racine [a]	42
Rock	6
Shawano	4
Sheboygan	20
Vilas	1
Walworth [a]	18
Washington [a]	31
Waukesha [a]	92
Waupaca	3
Waushara	3
Winnebago	30
Wood	1

[a] Counties within the southeastern region of Wisconsin.

RESULTS

Location Data

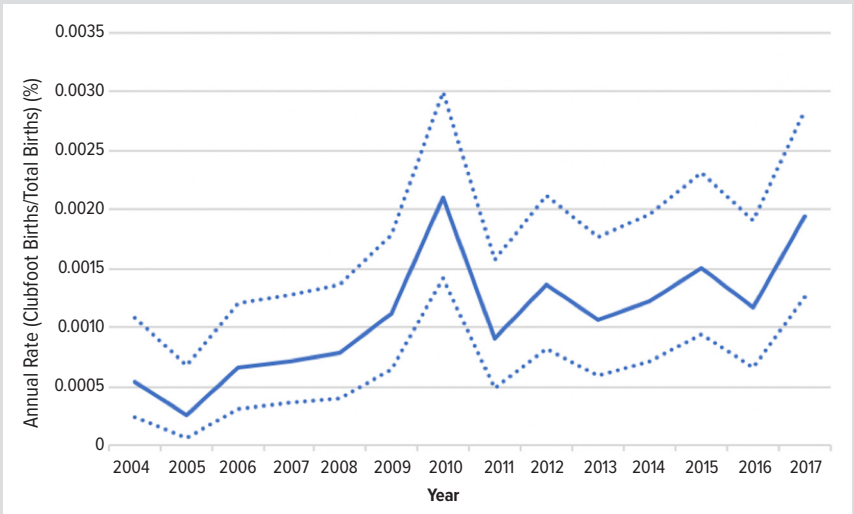
Out of Wisconsin's 72 counties, final population data reached 31 of these counties with coverage of all 5 regions. The majority of clubfoot births (n=523) were recorded in the southeastern region of Wisconsin, with most (n=236) occurring in Milwaukee County (Table 1).

Incidence of Clubfoot Births

Linear trends were plotted for each county in the southeastern region of Wisconsin. Milwaukee County was found to have a statistically significant increase in the incidence of annual clubfoot birth rates from 2004 through 2017 (P for trend < 0.001, $R^2 = 0.5185$) (Figure 1). The linear regression model shows that the annual rate of clubfoot among all births increased by approximately 0.0004 every year. In 2004, approximately 1 in every 2,000 births in Milwaukee County was diagnosed with clubfoot. In 2017, the incidence increased to 4 in every 2,000 births. Overall, there was a 245% increase in the rate of clubfoot births in Milwaukee County from 2004 through 2017.

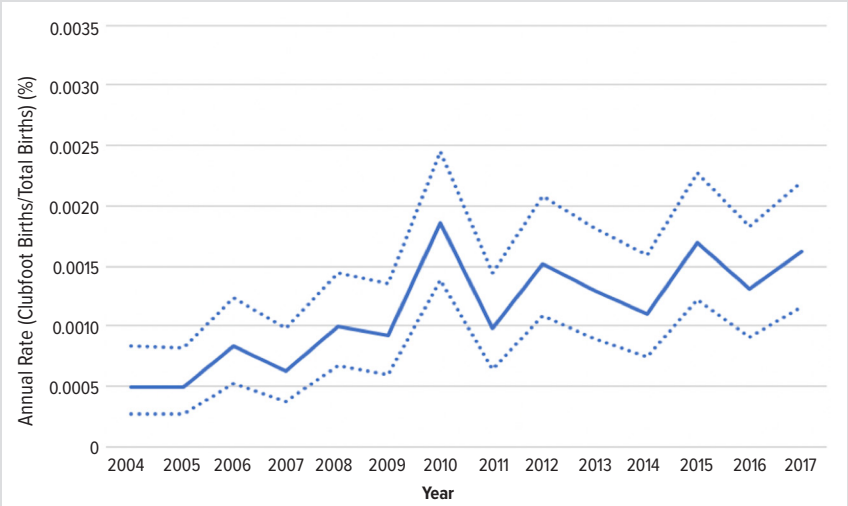
The southeastern region of Wisconsin also experienced a statisti-

Figure 1. Significantly Increased Incidence of Clubfoot Births in Milwaukee County, 2004-2017



Solid line: mean value; dotted lines: 95% CI; *P* value < 0.001

Figure 2. Significantly Increased Incidence of Clubfoot Births in the Southeastern Region of Wisconsin, 2004-2017



Solid line: mean value; dotted lines: 95% CI; *P* value < 0.001

cally significant increase in the incidence of annual clubfoot births over this time period (*P* for trend < 0.001, $R^2 = 0.5958$) (Figure 2). In 2004, approximately 1 in every 2,000 births in the southeastern region of Wisconsin was diagnosed with clubfoot, a rate similar to that of Milwaukee County. In 2017, the incidence rose to 3 in every 2,000 births. Overall, there was a 224% increase in the rate of clubfoot births in the region from 2004 through 2017.

Population Demographics

This study included a population of 760 patients with clubfoot: 497 males (65.4%) and 263 females (34.6%). The majority of patients were non-Hispanic/Latino (76.8%) and White (72.2%). Most (81.1%) were born at term, and unilateral vs bilateral clubfoot birth rates were nearly equal. Average birthweight was 3.068 kg (median 3.180 kg) (Figure 3). A total of 414 patients (54.4%) had no family history of clubfoot, 130 patients (17.1%) had a positive family history of clubfoot, and family history was unknown for 216 patients (28.4%). Populations demographics are shown in Table 2 and Figure 3.

DISCUSSION

This retrospective study showed a significantly increasing annual rate of clubfoot births over a 14-year period, specifically in the most populous areas in Wisconsin. The data do not support the hypothesis that clubfoot birth rates remained stable in Wisconsin from 2004 through 2017. We hypothesized that if clubfoot is a purely genetic phenomenon with no exogenous, environmental factors of influence, then the annual clubfoot birth rate should not change significantly over time. Moreover, a majority of our population reported no family history of the deformity.

Interestingly, a recent report analyzing trends of the most common birth defects in the United States found that the prevalence of clubfoot remained relatively stable from 2010 through 2014.[2] However, Wisconsin data were not included in this study, and one must consider if the southeastern region of Wisconsin has been subject to factors that impact the diagnosis and development of clubfoot.

In a comprehensive 2018 meta-analysis and systematic review on the etiology of clubfoot, family history was noted as the strongest predictor of clubfoot diagnosis.[1] Studies have reported that 24% to 50% of all patients with isolated clubfoot report a positive family history.[3] Our study, while limited by the unknown percentage (28.4%), reports a positive family history in 17.1% of our population (Table 2). Yet even if the unknown percentage of family history were considered, most of the study population still reports a negative family history of clubfoot. Family history points toward clubfoot being dependent on genetic predisposition. While genetics have been studied in reference to clubfoot development, only associations have been made; no sole genetic cause of clubfoot has been identified.[4] Genetics certainly may play a role in the pathogenesis of clubfoot,

but our analysis suggests that the etiology may be multifactorial.

Our study is not the first to suggest that exogenous factors impact clubfoot pathogenesis. Maternal smoking, maternal selective serotonin reuptake inhibitor (SSRI) use, and regional and seasonal variation have been linked to clubfoot development. Chen et al noted that maternal smoking has been shown to have a strong gene-environment association, having a significant association with clubfoot.[1] Multiple studies support this finding.[5-13] Prescription drug use also has been explored as a possible risk factor for clubfoot development. One of the most common complications during pregnancy is the development of depression, with up to 70% of women reporting symptoms of depression during pregnancy.[14] SSRIs are the most commonly prescribed antidepressant in pregnant women and have been found to have an association with clubfoot.[1,15-17] It is hypothesized that this may be due to the vasoconstrictive effects of serotonin compromising uterine blood flow.[18]

Literature on possible environmental factors associated with clubfoot is limited. A similar study conducted in Denmark by Krogsgaard et al reported an incidence of clubfoot that was significantly correlated with population density.[19] This is consistent with findings reported in our study. Milwaukee County is the most populous county in Wisconsin and the city of Milwaukee is the 31st most populous in the United States.[20] It is well known that areas of higher population density are more exposed to environmental stressors, such as pollution, viral illness, noise, crowding, and air quality. Generally, areas of higher population density also are associated with increased use of alcohol, tobacco, and illicit drugs. Galiatsatos et al concluded that tobacco store density and neighborhood socioeconomic factors were associated with the prevalence of maternal smoking while pregnant, a well-known risk factor correlated with clubfoot.[21] Higher population density areas are also associated with increased stress of daily living and higher rates of mental illness.[22] Specifically, living in areas characterized by ethnic segregation has been associated with greater risks of depression and anxiety,[23] and based on 2013-2017 data, Milwaukee is the most segregated city in the nation.[24] Increased rates of anxiety and depression come with increased use of SSRIs as a treatment method—another risk factor significantly associated with clubfoot.

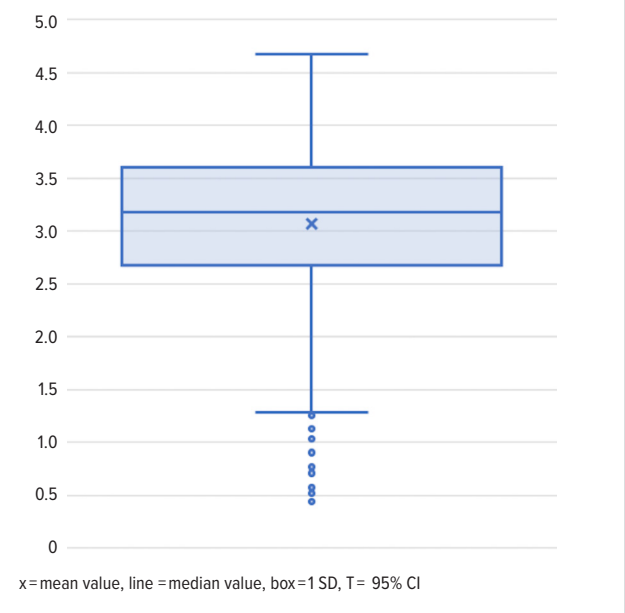
Our study's demographic data show a male-to-female ratio of 1.89:1. Male preponderance with a male-to-female ratio near 2:1 in the diagnosis of clubfoot is a well-known finding that has been reported consistently in literature.[4,5,8] Our study also found a nearly 50:50 ratio on unilateral vs bilaterally affected clubfeet—another common finding that has been reported consistently in literature.[25] Preterm birth was not a predominant finding in our study. Our population's mean and median birthweight values were considered normal and healthy. Additionally, while the literature does not consistently report a specific ethnicity/race as a predisposing risk factor, a majority of our population was non-Hispanic/Latino and White.

Given that this is an observational study, the scope of our findings is limited as we cannot demonstrate definitive causality. The increase in incidence of clubfoot diagnoses could be explained by myriad factors not mentioned in our study. Our study was also limited by the inability to gather information on the mothers of our subjects, which would have provided more data and helped us to better understand our population's exposures. In the future, a prospective study with a survey of mothers would be needed to

Table 2. Risk Factor and Laterality Data

Sex	**n=760, n (%)**
Male	497 (65.4%)
Female	263 (34.6%)
Laterality	**n=760, n (%)**
Unilateral	384 (50.5%)
Bilateral	376 (49.5%)
Term vs Preterm	**n=718, n (%)**
Term	582 (81.1%)
Preterm	136 (18.9%)
Race	**n=760, n (%)**
White	549 (72.2%)
African American	120 (15.8%)
Unknown	51 (6.7%)
Asian	19 (2.5%)
White/African American	12 (1.6%)
American Indian/Alaskan Native	4 (0.5%)
Other	3 (0.4%)
Asian/African American	1 (0.1%)
White/American Indian	1 (0.1%)
Ethnicity	**n=760, n (%)**
Non-Hispanic/Latino	584 (76.8%)
Hispanic/Latino	89 (11.7%)
Unknown	87 (11.4%)
Family History	**n=760, n (%)**
No	414 (54.4%)
Yes	130 (17.1%)
Unknown	216 (28.4%)

Figure 3. Boxplot of Clubfoot Births (kg), n = 483



gather this information. We were also limited in our ability to collect data from hospitals not affiliated with Children's Wisconsin. While Children's Wisconsin has multiple locations throughout the state, it cannot be assumed that all diagnoses of clubfoot were treated at a Children's Wisconsin institution. This would have provided us with a larger, more comprehensive patient population.

CONCLUSION

This study found a significantly increasing rate of clubfoot births in the most populous areas of Wisconsin, with a negative family history in the majority of patients. Notably, other regions of the country reported a stable prevalence of clubfoot during a portion of our study's timeframe. Our investigation provides further insight into the possible etiology of clubfoot relating to exogenous, environmental factors. These possible exogenous determinants are not known at this time but could be related to myriad factors, including population density, changes in the prevalence of maternal smoking or SSRI use, and age of conception. This is speculative and further research is needed to investigate what these possible factors of influence may be.

This study also provides an analysis of commonly studied risk factors associated with the diagnosis of clubfoot, including support for male preponderance. Future research should provide additional analyses of clubfoot birth rates in other highly populous cities, along with further geographical characterization to pinpoint highly affected areas. Future research is also needed to further explore possible exogenous factors of influence in the development of clubfoot, which could account for the significantly increasing incidence found in our study.

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