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Early neonatal mortality among babies born with spina bifida in Finland, 2000-2014

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ABSTRACT

Objectives: We examined early neonatal mortality risk, temporal trends, and selected infant and maternal factors associated with early neonatal mortality among all spina bifida-affected live births in Finland.

Study Design: We linked multi-registry population-based data from the national registers in Finland for infants born with spina bifida from 2000-2014. Early neonatal mortality was defined as death in 0-6 days after birth. Early neonatal mortality risk and 95% confidence intervals (CI) was estimated using the Poisson approximation of binomial distribution. Poisson regression was used to examine temporal trend in early neonatal mortality from 2000 to 2014 for spina bifida cases and all births in Finland. Selected infant and maternal characteristics were compared between cases that experienced early neonatal mortality and cases that did not. Exact logistic regression was used to estimate unadjusted odds ratios (uORs) and 95% confidence intervals (CIs).

Results: A total of 181 babies were born alive with spina bifida in Finland during the study period; 61% had isolated spina bifida. Pooling all study years, 7.2% (95% CI=4.2%, 12.4%) of all live-born cases experienced early neonatal death. There was a significant increase in early neonatal mortality among spina bifida births over the study period (p <0.0001). Low gestational age (<37 weeks) (uOR=6.96; 95% CI=1.86, 29.01), cases occurring as a part of a syndrome (uOR=125.67; 95% CI=14.90, >999.999), and advanced maternal age at gestation (≥35 years) (uOR=5.33; 95% CI=1.21, 21.87) were positively associated with early neonatal mortality.

Conclusions: Using national data from Finland, we found high early neonatal mortality with increasing trend over birth period spanning 15 years (2000-2014), and unadjusted positive associations with some infant and maternal factors. Future studies should pool data from Nordic countries to increase study size allowing multivariable analysis.

Key Words: Finland; myelomeningocele; neonatal mortality; open spina bifida; risk factors

Key Points:

- We conducted a large national multi-registry linked study in Finland.

- Early neonatal mortality in babies affected by spina bifida is 7% in Finland.

- Early neonatal mortality trend showed a significant increase from 2000 to 2014.

- Low gestational age and syndrome case status increased early neonatal mortality risk in spina bifida.

- Advanced maternal age increased the risk of early neonatal mortality in spina bifida.

INTRODUCTION

Open spina bifida is a type of neural tube defect characterized by incomplete closure of the spinal neural tube around fourth gestational week. Spina bifida leads to paralysis, loss of sensation, bowel and bladder dysfunction, pain, and depression associated with the persistent ill health status among those affected.[1-3] Recent advancements in medicine and surgery have resulted in an improved survival among spina bifida-affected individuals; however, mortality remains a significant concern at all ages, and especially during infancy.[4-9]

Mandatory staple food fortification programs to enrich commonly consumed foods with folic acid, an established prevention strategy for spina bifida, is not implemented as a public health policy in many European countries.[10, 11] Countries with mandatory fortification (e.g., US) report a significantly lower prevalence of spina bifida, less severe cases of spina bifida, and increased survival among those affected.[5, 10, 12] US studies on first-year mortality among spina bifida-affected infants have found significant positive associations with low birthweight, low gestational age, having multiple co-occurring major birth defects, multiple births, high level of spina bifida lesion (i.e., cervicothoracic lesions), and maternal factors including non-Hispanic black or Hispanic race/ethnicity, low education, and high pre-pregnancy body mass index.[7, 9, 13-15] The California Perinatal Quality Care Collaborative (CPQCC) study in the US reported that low birthweight and having multiple co-occurring birth defects increased the hazard ratios for early neonatal mortality in spina bifida-affected babies.[16] Studies examining predictors of early neonatal mortality for spina bifida are not available in Europe, which has a different profile compared to the US, mainly with regards the proportion of elective terminations of pregnancy for fetal anomalies (ETOPFA) in pregnancies affected by spina bifida, and universal healthcare.

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The objective of our study was to examine the early neonatal mortality risk, temporal trends, and factors associated with early neonatal mortality among all live born infants with spina bifida in Finland. Because of the publicly funded universal healthcare system in the country, Finland documents all births, and provides an opportunity to examine all cases of spina bifida in the country using linked multi-registry data sources capturing several infant and maternal clinical variables. Findings from the study can inform education, resource allocation, and screening for early interventions to prevent mortality among newborns with spina bifida in Finland and in other countries with similar demographic and health profile in Europe.

MATERIALS AND METHODS

Study Design and Data Sources

We conducted a retrospective cohort study. Data were obtained from linking multiple national registries in Finland. The first data source was the Register of Congenital Malformations (RCM) that collects data on congenital chromosomal and structural anomalies in live births, stillbirths and pregnancy terminations due to congenital anomaly in Finland.[17] We used RCM to access all live born cases of spina bifida. Diagnoses in RCM have been determined using the extension of *International Statistical Classification of Diseases and Related Health Problems,* 9th Edition, beginning in 1993 and have been retrospectively applied to all cases since 1987.[18] Our second data source was the Finnish Hospital Discharge Register (FHDR), a national repository of all hospital discharges and identification codes providing information on maternal inpatient and outpatient care in hospitals and primary health care centers.[19] FHDR also includes information on the patient's area of residence, admission and discharge days, patient diagnosis, and surgical procedures. As a third data source, we used the Finnish Medical Birth Register (MBR) which provided information on maternal demographics and health.[20] The MBR, supported by the

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Finnish Institute for Health and Welfare, includes information on live births and stillbirths dating

back to 1987. We used as our fourth data source, the administrative registers from Statistics

Finland, which provided information on each parturient's disposable income[21] and educational

attainment.[22] We linked above four data sources using unique identification codes for individuals

determined to be citizens and permanent residents of Finland. We achieved a nationally

representative analytic sample for the study as 99.8% of women in Finland have valid

identification code, and we achieved 99.9% linkage among the four data sources.

Case Selection

The analysis included all live births with spina bifida in Finland delivered between 2000 through

2014. We identified spina bifida cases from the RCM using Centers for Disease Control and

Prevention – British Pediatric Association (CDC-BPA) codes 741000-741999. An 'isolated case'

was defined as a case of spina bifida, and with no other co-occurring major malformations. Cases

that co-occurred with one or more additional major birth defects, unrelated to spina bifida, were

included in our analysis, and defined as 'multiple cases', and those that presented as a part of a

known chromosomal or genetic syndrome were defined as 'syndrome cases'. Clinical geneticists

reviewed, validated, and classified all birth defects in RCM. Birth defects case definitions and

classifications of other major congenital anomalies in multiple cases are based on criteria defined

by EUROCAT as mentioned in the RCM.[23]

Early neonatal mortality in spina bifida cases

Data from the MBR was used to identify early neonatal deaths, defined as death occurring during

0-6 days after birth, among those born with spina bifida. Within MBR, spina bifida cases

resulting in deaths beyond ≥7 days of life were not linked with information on other congenital

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anomalies and therefore not examined in the current analysis. We dichotomized early neonatal

death outcomes as 'yes' or 'no'.

Covariables

Study covariables were selected based on the literature review of factors previously associated

with mortality among children with spina bifida. Several covariables identified were available in

one of the four data sources available for the study. The infant variables examined included: sex

(male/ female); gestational age (<37 / ≥37 weeks); congenital anomaly pattern (isolated /

multiple / syndrome); congenital hydrocephalus (yes / no); breech presentation (yes / no);

plurality (i.e., multiple births) (singleton / plural). Maternal variables examined included: age at

delivery (<20 / 20-34 / ≥35 years); highest attained education (basic or no education / upper

secondary or pre-bachelors education / bachelors or greater); marital or cohabiting status

(married and cohabiting / unmarried without cohabiting); household income level (<20th / 20th-

80th / >80th percentile); nativity (Finnish background, born in Finland / other); body mass index

(BMI) (underweight, <18.5 / normal weight, 18.5-24.9 / overweight, 25-29.9 /obese, ≥30 kg/m^2);

gravidity (i.e., number of all previous pregnancies) (none / 1 or more), parity (none / 1 or more);

previous miscarriages (none / 1 or more); previous induced abortions (none / 1 or more); total

number of prenatal care visits (none / 1-14 / ≥15 visits); week of first prenatal care visit (no

prenatal care visit / before 12 weeks of gestation / at or after 12 weeks gestation); anemia during

pregnancy (defined as hemoglobin <100 g/L) (yes / no); smoking status during pregnancy (never

smoker / smoker); mode of delivery (vaginal / Cesarean section); pregestational diabetes (yes /

no); gestational diabetes (yes / no); pre-existing hypertension (yes / no); gestational hypertension

(yes / no); and preeclampsia (yes / no).

Statistical Analysis

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Early neonatal mortality risk for all infants with spina bifida was calculated using the number of

deaths at age 0-6 days among infants with spina bifida divided by the number of total live births

with spina bifida during the study period. Because of the rarity of outcome, mortality risk and the

95% confidence interval (CI), were estimated using the Poisson approximation of binomial

distribution. Based on the rare outcome assumption, Poisson regression was used to quantify

time trends in mortality from 2000-2014. We smoothed random variability in our temporal trend

lines by pooling data for an overlapping sequence of three consecutive years. Mortality trends

were examined for early neonatal deaths in spina bifida cases as well as the general population of

live births. The trend was considered to be significant using Poisson regression analysis (p value

<0.05).

We made two groups in our study: 1) spina bifida cases that died between day 0-6 after

birth; and 2) spina bifida cases that were alive during day 0-6 after birth. We compared the

differences in selected infant and maternal characteristics between the two groups using Pearson

Chi square test or Fisher exact test (when cell sizes were less than 5). Because of low

frequencies, we used non-parametric methods and conducted Exact logistic regression to

estimate unadjusted odds ratios (uOR) and 95% CIs to study the association between selected

infant and maternal factors and early neonatal mortality. Multivariable analysis was not

undertaken because of small cell sizes in some variable categories. All analyses were performed

using the SAS version 9.4 (SAS Institute Inc Cary, NC). Finnish Institute for Health and Welfare

and Statistics Finland approved and granted data access for the study. As data spanned 15 years,

all data were permitted to be presented in the results tables without suppressing small cells.

RESULTS

A total of 181 live-born infants were identified in the RCM during the study period (2000-2014).

Overall, 111 (61%) of cases were classified as isolated, 52 (29%) as multiple, and 18 (10%) as

syndrome cases. Thirteen of these 181 infants died during day 0-day 6 of their life, with an early

neonatal mortality risk of 7.2% (95% CI=4.3%, 11.9%). Ten out of the 13 infants that

experienced early neonatal death had spina bifida as a part of a known syndrome. There was a

statistically significant increasing trend in mortality among cases between years 2000 and 2014

(p < 0.0001). **Figure 1** shows trends in early neonatal mortality among spina bifida cases and

total population births in Finland during the study period.

Descriptive analysis results examining selected infant and maternal characteristics by

early neonatal mortality are presented in **Table 1**. Preterm birth (<37 weeks) (uOR=6.96; 95%

CI=1.86, 29.01) and increased maternal age at delivery (≥35 years) (uOR=5.33; 95% CI= 1.21,

21.87) were positively associated with early neonatal mortality. Additionally, spina bifida

occurring as a part of a syndrome also increased the risk of early neonatal mortality significantly

(uOR=125.67; 95% CI=14.90, >999.99).

Anemia during pregnancy was another characteristic that was recorded in a higher

proportion of mothers of infants with spina bifida who died in the early neonatal period

compared to mothers of infants with spina bifida who were alive in that same period (15.4% vs.

1.2%), with a marginally significant positive association (uOR=14.52; 95% CI=0.97, 218.14).

DISCUSSION

Using national multi-registry linked dataset for all births between years 2000 and 2014, our study

found that 7.2% of all liveborn infants with spina bifida experienced early neonatal mortality in

Finland. We found an increasing trend in mortality during the study period as well as a

significantly high proportion of mortality among spina bifida cases compared to all livebirths in

the population during early neonatal period. Preterm gestation, syndrome case status, and increased maternal age were positively and significantly associated with early neonatal death in spina bifida-affected infants. Maternal anemia during pregnancy also indicated some risk, though not statistically significant, and is a novel finding that should be explored further.

The total prevalence of spina bifida, including live births, stillbirths and ETOPFA varies worldwide, and is estimated to be 8.63 per 10,000 live births for births in year 2015 (95%CI=6.80, 10.47) in the European region.[24] A meta-analysis by Johnson et al. (2012) estimated about 66% of cases of spina bifida result in ETOPFA (range: 41%-89%).[25] Stillbirths among pregnancies affected by spina bifida in Europe are rare (<5%).[26] In Finland, the average live birth prevalence of spina bifida is 2 per 10,000 total births (range: 1.8 - 2.4) for birth years 2000-2018.[23] The live birth prevalence of spina bifida in Finland is similar to an estimate obtained by pooling data from all EUROCAT registries during the same time period is similar, i.e., 1.9 per 10,000 total births (range: 1.8 - 2.0).[27] There are approximately 60,000 live births each year in Finland, and it is expected that 11 to 15 live births are affected by spina bifida every year.

In the US, a population-based birth defects registry in New York, examining children born with spina bifida between years 1983 and 2006, reported 7% of babies born with spina bifida died by age 7 days.[8] The CPQCC study in the US linked vital records and hospital discharge data for births recorded in California between years 2006 and 2011, and showed 4% mortality during first 7 days of life.[16] An older population-based surveillance registry study in metropolitan Atlanta, US, examining births between 1979 and 1994, reported early neonatal mortality among spina bifida-affected infants to be 10% (95% CI = 5.9%, 13.5%).[9] The proportion of stillbirths and elective terminations are very different in the US compared to

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Finland, and thus the case characteristics (e.g., spina bifida severity as measured through higher lesion level) and maternal and healthcare system characteristics, are different between the countries, and limit direct comparison of findings.

Studies on early neonatal mortality among infants affected by spina bifida are scarce in European countries. A multi-country analysis by the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), which included many European birth defects registries, reported that 6.9% (95% CI=6.3%, 7.7%) of infants born with spina bifida during 2001-2012 died within the first week of life, and that spina bifida cases with other co-occurring birth defects or those occurring as a part of a syndrome, constituted a higher proportion of early neonatal deaths compared to isolated cases.[26] The Danish Spina Bifida Patient Database study reported that a high proportion of mortality occurred during the first three months of life,[28] while a hospital-based study in Poland, with 47 live born infants with spina bifida, reported that 10 died on the first day of life; early neonatal mortality was not reported.[29] Glinianaia et al. (2020) conducted a systematic review and meta-analysis of studies examining mortality in spina bifida; however, this review only included studies with survival at age one year and higher.[30] Other studies from European countries looked at a long-term survival among individuals with spina bifida, reporting on mortality at ages 1 year and higher.[31, 32] Our study only examined mortality in early neonatal phase when most of the infant deaths were recorded; deaths among infants with spina bifida from ages 7 to 365 days were scarce (n<5) in Finland and hence could not be examined. Within Europe, studies from Denmark, Poland, Norway and United Kingdom examined mortality in the post-early neonatal phase among individuals with spina bifida and hence not comparable to current study findings.[28, 29, 31-38]

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The impact of mandatory folic acid fortification of staples on spina bifida prevalence and mortality is relevant for discussion in the context of the current study. There were significant reductions in the prevalence of spina bifida in the US after food fortification with folic acid.[39] Studies comparing infant mortality among birth cohorts born pre-, interim- and post-fortification periods in the US show that the pre-fortification prevalence of infant mortality risk was 10-12% during pre-fortification period,[5, 9] and dropped to 4-8% after fortification.[5, 7, 16] Contrary to the US, Finland and other European countries do not have policies on mandatory folic acid fortification of staple foods.[11] Instead, Europe relies on folic acid supplement intake recommendations which encourage women of reproductive age to take folic acid pills before and during pregnancy to prevent neural tube defects.[40] The impact of the supplement pill programs on early neonatal mortality in European region should be examined in future studies, as folic acid has been found to decrease the severity of spina bifida among those affected, and severity is an important predictor of mortality among spina bifida-affected individuals.[5, 14]

Our study has several strengths. We conducted a national, population-based, multi-register study with clinically confirmed cases of spina bifida in Finland. We were able to examine associations between early neonatal mortality and several infant and maternal variables which were not explored in any of the previous studies, including birth order, breech presentation, and maternal health and obstetric history, prenatal care, and maternal smoking during pregnancy. Data quality, reliability, completeness, and validity of data linkages of Finnish registers are well established, and these data sets have been used consistently in the past to conduct robust epidemiological analyses.[41-45] Spina bifida diagnosis is validated at the RCM. Various infant and maternal variables in the study were abstracted from medical records, without a potential for recall or reporting bias. Congenital anomalies are tracked until the child reaches

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age one year, thus improving the validity of capturing other co-occurring major birth defects among spina bifida cases.[19,46]

MBR implemented data collection on folic acid supplement use beginning in 2017, which was not within our study period. Hence, we were unable to examine the association between pre-conception and perinatal folic acid supplement use and early neonatal mortality. Deaths beyond early neonatal period could not be examined as they were not linked to the congenital anomaly registry. We were also unable to examine causes of early neonatal mortality due to lack of information.

In conclusion, early neonatal mortality risk among infants born with spina bifida is a concern in Finland. Some of the risk factors noted in our study for early neonatal mortality in those with spina bifida, such as preterm birth, syndrome case status, increased maternal age, and potentially maternal anemia during pregnancy, can be used for screening and early identification of cases that could be at a high risk of early neonatal death. Pre-planned interventions should be in place to minimize health complications and prevent deaths in the first seven days of life.[47, 48] Nordic countries with comparable healthcare systems and population characteristics should pool data to achieve a higher sample size, and employ multivariable regression methods to better understand preventable risk factors for early neonatal mortality in spina bifida-affected infants.

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FIGURE LEGENDS

Figure 1. Trends in Early neonatal mortality (0-6 days of age) in the population of all live births and among infants with spina bifida in Finland, 2000-2014

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Table 1. Infant and Maternal characteristics of individuals with spina bifida, by early neonatal death (defined as death between 0-6 days after birth) status, in Finland, 2000-2014

Characteristics	Early Neonatal Death No (n=168)	Early Neonatal Death Yes (n=13)	Unadjusted Odds Ratio (95% Confidence Interval)
	n (%)	n (%)	
Infant			
Sex			
Male	94 (55.95)	6 (46.15)	Reference
Female	74 (44.05)	7 (53.85)	1.48 (0.41, 5.57)
Gestational age*			
≥37 weeks	137 (81.55)	5 (38.46)	Reference
<37 weeks	31 (18.45)	8 (61.54)	6.96 (1.86, 29.01)
Congenital anomaly pattern*			
Isolated	110 (65.48)	1 (7.69)	Reference
Multiple	50 (29.76)	2 (15.38)	4.36 (0.22, 261.89)
Syndrome	8 (4.76)	10 (76.92)	124.67 (14.90, >999.99)
Congenital hydrocephalus			
No	167 (99.40)	13 (100.00)	Reference
Yes	1 (0.60)	0 (0.00)	NC
Breech presentation			
No	147 (87.50)	10 (76.92)	Reference
Yes	21 (12.50)	3 (23.08)	2.09 (0.34, 9.04)
Plurality			
Singleton	156 (92.86)	11 (84.62)	Reference

Plural	12 (7.14)	2 (15.38)	2.35 (0.23, 12.83)
Maternal			
Age at delivery (years)*			
<20	5 (2.98)	1 (7.69)	4.05 (0.08, 44.53)
20-34	144 (85.71)	7 (53.85)	Reference
≥35	19 (11.31)	5 (38.46)	5.33 (1.21, 21.87)
Highest attained education			
Basic or no education	75 (44.64)	7 (53.85)	1.72 (0.42, 8.36)
Upper secondary or Pre-Bachelors	74 (44.05)	4 (30.77)	Reference
Bachelors or greater	19 (11.31)	2 (15.38)	1.93 (0.16, 14.68)
Marital or cohabiting Status			
Married and cohabiting	158 (94.05)	12 (92.31)	Reference
Unmarried without cohabiting	8 (4.76)	1 (7.69)	1.64 (0.03, 14.14)
Household income level			
<20th percentile	18 (10.71)	1 (7.69)	0.64 (0.01, 5.17)
20th-80th percentile	104 (61.90)	9 (69.23)	Reference
>80th percentile	24 (14.29)	1 (7.69)	0.48 (0.01, 3.79)
Nativity			
Finnish background, born in Finland	146 (86.90)	12 (92.31)	Reference
Other	20 (11.90)	1 (7.69)	0.61 (0.01, 4.56)
Body Mass Index (kg/m^2)			
<18.5 (underweight)	2 (1.19)	0 (0.00)	NC
18.5-24.9 (normal weight)	51 (30.36)	5 (38.46)	Reference

25-29.9 (overweight)	23 (13.69)	1 (7.69)	0.45 (0.01, 4.33)
≥30 (obese)	23 (13.69)	1 (7.69)	0.45 (0.01, 4.33)
Gravidity			
None	55 (32.74)	3 (23.08)	Reference
1 or more	113 (67.26)	10 (76.92)	1.62 (0.40, 9.52)
Parity			
None	65 (38.69)	3 (23.08)	Reference
1 or more	103 (61.31)	10 (76.92)	2.10 (0.51, 12.29)
Previous miscarriages			
None	134 (79.76)	8 (61.54)	Reference
1 or more	34 (20.24)	5 (38.46)	2.45 (0.59, 9.14)
Previous induced abortions			
None	153 (91.07)	12 (92.31)	Reference
1 or more	15 (8.93)	1 (7.69)	0.85 (0.02, 6.55)
Total number of prenatal care visits			
No prenatal care visits	0	0	NC
1-14 visits	64 (38.10)	8 (61.54)	2.54 (0.70, 10.31)
15 or more visits	102 (60.71)	5 (38.46)	Reference
Week of first prenatal care visit			
No prenatal care visits	0	0	NC
<12 weeks of gestation	142 (84.52)	9 (69.23)	Reference
At or after 12 weeks gestation	22 (13.10)	4 (30.77)	2.85 (0.59, 11.34)
Anemia during pregnancy (<100 g/l)*			

Yes	2 (1.19)	2 (15.38)	14.52 (0.97, 218.14)
No	166 (98.81)	11 (84.62)	Reference
Smoking status during pregnancy			
Never smoker	142 (84.52)	8 (61.54)	Reference
Smoker	21 (12.50)	3 (23.08)	2.52 (0.40, 11.61)
Mode of delivery			
Vaginal	96 (57.14)	5 (38.46)	Reference
Cesarean section	55 (32.74)	4 (30.77)	1.39 (0.27, 6.77)
Pregestational diabetes			
Yes	4 (2.38)	0 (0.00)	NC
No	164 (97.62)	13 (100.00)	Reference
Gestational diabetes			
Yes	7 (4.17)	0 (0.00)	NC
No	161 (95.83)	13 (100.00)	Reference
Pre-existing hypertension			
Yes	1 (0.60)	0 (0.00)	NC
No	167 (99.40)	13 (100.00)	Reference
Gestational hypertension			
Yes	2 (1.19)	0 (0.00)	NC
No	166 (98.81)	13 (0.00)	Reference
Preeclampsia			
Yes	0 (0.00)	0 (0.00)	NC
No	168 (100.00)	13 (100.00)	Reference

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n=Frequency; NC=Not Calculated (due to 0 exposure cells)
*p value <0.05; Fisher exact p-value was examined when cell sizes were less than 5
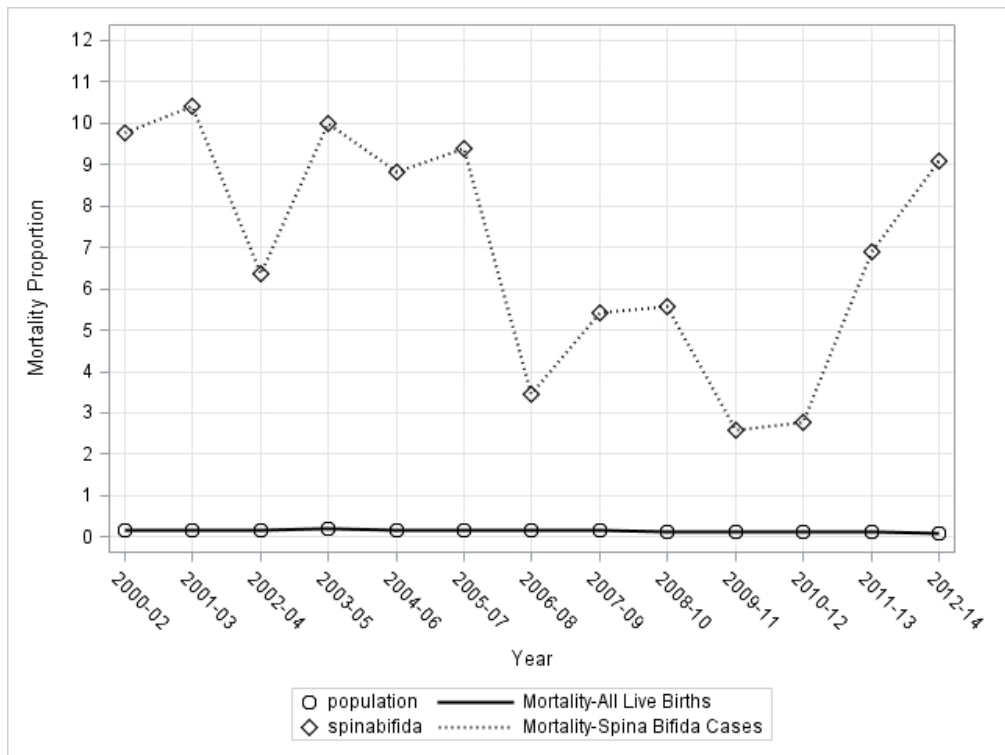Frequencies and percentages may not equal total and 100% due to missing or unknown data

Figure 1. Trends in Early neonatal mortality (0-6 days of age) in the population of all live births and among infants with spina bifida in Finland, 2000-2014

Early neonatal mortality among babies born with spina bifida in Finland, 2000-2014

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Data Availability Statement: The data that support the findings of this study are available in multiple data sources with permission from the Finnish Institute for Health and Welfare and Statistics Finland. The Finnish register data have been given for this specific study, and the data cannot be shared without authorization from the register keepers. More information on the authorization application to researchers who meet the criteria for access to confidential data can be found at https://www.findata.fi/en/services/services-for-customers/ (Health and Social Data Permit Authority Findata), https://thl.fi/fi/web/thlfi-en/statistics/information-for-researchers/authorisation-application (THL) and https://www.stat.fi/meta/tietosuoja/kayttolupa_en.html (Statistics Finland)

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ABSTRACT

Objectives: We examined early neonatal mortality risk, temporal trends, and selected infant and maternal factors associated with early neonatal mortality among all spina bifida-affected live births in Finland.

Study Design: We linked multi-registry population-based data from the national registers in Finland for infants born with spina bifida from 2000-2014. Early neonatal mortality was defined as death in 0-6 days after birth. Early neonatal mortality risk and 95% confidence intervals (CI) was estimated using the Poisson approximation of binomial distribution. Poisson regression was used to examine temporal trend in early neonatal mortality from 2000 to 2014 for spina bifida cases and all births in Finland. Selected infant and maternal characteristics were compared between cases that experienced early neonatal mortality and cases that did not using Chi square or Fisher's Exact test (when cell sizes were less than 5). Exact logistic regression was used to estimate unadjusted odds ratios (uORs) and 95% confidence intervals (CIs).

Results: A total of 181 babies were born alive with spina bifida in Finland during the study period; 61% had isolated spina bifida. Pooling all study years, 7.2% (95% CI=4.2%, 12.4%) of all live-born cases experienced early neonatal death. There was a significant increase in early neonatal mortality among spina bifida births over the study period (p <0.0001). Low gestational age (<37 weeks) (uOR=6.96; 95% CI=1.86, 29.01), cases occurring as a part of a syndrome (uOR=125.67; 95% CI=14.90, >999.999), and advanced maternal age at gestation (≥35 years) (uOR=5.33; 95% CI=1.21, 21.87) were positively associated with early neonatal mortality.

Conclusions: Using national data from Finland, we found high early neonatal mortality with increasing trend over birth period spanning 15 years (2000-2014), and unadjusted positive associations with some infant and maternal factors. Future studies should pool data from Nordic countries to increase study size allowing multivariable analysis.

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Key Words: Finland; myelomeningocele; neonatal mortality; open spina bifida; risk factors

Key Points:

- We conducted a large national multi-registry linked study in Finland.

- Early neonatal mortality in babies affected by spina bifida is 7% in Finland.

- Early neonatal mortality trend showed a significant increase from 2000 to 2014.

- Low gestational age and syndrome case status increased early neonatal mortality risk in spina bifida.

- Advanced maternal age increased the risk of early neonatal mortality in spina bifida.

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INTRODUCTION

Open spina bifida is a type of neural tube defect characterized by incomplete closure of the spinal neural tube around fourth gestational week. Spina bifida leads to paralysis, loss of sensation, bowel and bladder dysfunction, pain, and depression associated with the persistent ill health status among those affected.[1-3] Recent advancements in medicine and surgery have resulted in an improved survival among spina bifida-affected individuals; however, mortality remains a significant concern at all ages, and especially during infancy.[4-9]

Mandatory staple food fortification programs to enrich commonly consumed foods with folic acid, an established prevention strategy for spina bifida, is not implemented as a public health policy in many European countries.[10, 11] Countries with mandatory fortification (e.g., US) report a significantly lower prevalence of spina bifida, less severe cases of spina bifida, and increased survival among those affected.[5, 10, 12] US studies on first-year mortality among spina bifida-affected infants ~~has~~ have ~~been~~ found significant positive ~~associated~~ associations with low birthweight, low gestational age, having multiple co-occurring major birth defects, multiple births, high level of spina bifida lesion (i.e., cervicothoracic lesions), and maternal factors including ~~and~~ non-Hispanic black or Hispanic ~~maternal~~ race/ethnicity, low education, and high pre-pregnancy body mass index.[7, 9, 13-15] The California Perinatal Quality Care Collaborative (CPQCC) study in the US reported that low birthweight and having multiple co-occurring birth defects increased the hazard ratios for early neonatal mortality in spina bifida-affected babies.[16] ~~But US studies may not be generalizable to other countries due to characteristics that are unique to the country (i.e., mandatory fortification of staple foods, ETOPFA prevalence, and prenatal care utilization and access to health services).~~ Studies examining predictors of early neonatal mortality for spina bifida are not available in Europe, which has a different profile compared to

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the US, mainly with regards ~~of~~ the proportion of <u>elective terminations of pregnancy for fetal anomalies (</u>ETOPFA<u>)</u> in pregnancies affected by spina bifida<u>,</u> ~~and universal healthcare environment~~. ~~This gap in the knowledge of factors associated with early neonatal mortality in the European region can be addressed using national health registries in most Nordic countries, which efficiently capture all vital events and many known infant and maternal risk factors.~~

The objective of our study was to examine the early neonatal mortality risk<u>,</u> ~~and~~ temporal trends<u>, and factors associated with</u> ~~in~~ early neonatal mor<u>t</u>ality among all live born infants with spina bifida in Finland. Because of the publicly funded universal healthcare system in the country, Finland documents all births, and provides an opportunity to examine all cases of spina bifida in the country using linked multi-registry data sources <u>capturing</u>. ~~Additionally, through data linkages between different registries, Finland provides a unique opportunity to examine~~ several infant and maternal clinical variables ~~and their association with early neonatal mortality among spina bifida-affected births, which is difficult to achieve in the US and other countries~~. ~~Thus, our second objective was to examine a wide range of infant and maternal variables and their association with early neonatal mortality.~~ Findings from the study can inform education, resource allocation, and screening for early interventions to prevent mortality among newborns with spina bifida in Finland and in other countries with similar demographic and health profile in Europe.

MATERIALS AND METHODS

Study Design and Data Sources

We conducted a retrospective cohort study. Data were obtained from linking multiple national registries in Finland ~~for the study~~. The first data source was the Register of Congenital Malformations (RCM) that collects data on congenital chromosomal and structural anomalies in

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live births, stillbirths and pregnancy terminations due to congenital anomaly in Finland.[17] We used RCM to access all live born cases of spina bifida. Diagnoses in RCM have been determined using the extension of *International Statistical Classification of Diseases and Related Health Problems,* 9th Edition, beginning in 1993 and have been retrospectively applied to all cases since 1987.[18] Our second data source was the Finnish Hospital Discharge Register (FHDR), a national repository of all hospital discharges and identification codes providing information on maternal inpatient and outpatient care in hospitals and primary health care centers.[19] FHDR also includes information on the patient's area of residence, admission and discharge days, patient diagnosis, and surgical procedures. As a third data source, we used the Finnish Medical Birth Register (MBR) which provided information on maternal demographics and health.[20] The MBR, supported by the Finnish Institute for Health and Welfare, includes information on live births and stillbirths dating back to 1987. ~~Finally, we~~We used as our fourth data source, the administrative registers from Statistics Finland, which provided information on each parturient's disposable income[21] and educational attainment.[22] We linked ~~all~~ above four data sources ~~mentioned above~~ using unique identification codes for individuals determined to be citizens and permanent residents of Finland. We achieved a nationally representative analytic sample for the study as 99.8% of women in Finland have valid identification code, and we achieved 99.9% linkage among the four data sources ~~used for our analysis~~.

Case Selection

~~This~~The analysis included all live births with spina bifida in Finland delivered between 2000 through 2014. We identified spina bifida cases from the RCM using Centers for Disease Control and Prevention – British Pediatric Association (CDC-BPA) codes 741000-741999. An 'isolated case' was defined as a case of spina bifida, and with no other co-occurring major malformations.

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Cases that co-occurred with one or more additional major birth defects, unrelated to spina bifida, were included in our analysis, and defined as 'multiple cases', and those that presented as a part of a known chromosomal or genetic syndrome were defined as 'syndrome cases'. Clinical geneticists reviewed, validated, and classified all birth defects in RCM. Birth defects case definitions and classifications of other major congenital anomalies in multiple cases are based on criteria defined by EUROCAT as mentioned in the RCM.[23]

~~Outcome –~~Early neonatal mortality in spina bifida cases

Data from the ~~Finnish~~ MBR was used to identify early neonatal deaths, defined as death occurring during 0-6 days after birth, among those born with spina bifida. Within MBR, spina bifida cases resulting in deaths beyond ≥7 days of life were not linked with information on other congenital anomalies and therefore not examined in the current analysis. We dichotomized early neonatal death outcomes as 'yes' or 'no'.

Covariables

Study covariables were selected based on the literature review of factors previously associated with mortality among children with spina bifida. Several covariables identified were available in one of the <u>four</u> data sources available for the study ~~(see Section 2.1)~~. The infant variables examined included: sex (male/ female); ~~birthweight (<2500 / 2500-3999 / ≥4000 grams);~~ gestational age (<37 / ≥37 weeks); congenital anomaly pattern (isolated / multiple / ~~syndromie~~<u>syndrome</u>); congenital hydrocephalus (yes / no); breech presentation (yes / no); plurality (<u>i.e.,</u> ~~number of fetuses~~<u>multiple births</u>) (singleton / ~~twins or higher~~<u>plural</u>). ~~The following infant variables were examined as continuous variables: 1-minute and 5-minute Apgar scores.~~ Maternal variables examined included: age at delivery (<20 / 20-34 / ≥35 years); highest attained education (basic or no education / upper secondary <u>or</u>~~,~~ pre-bachelors education / bachelors or

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greater); marital or cohabiting status (married and cohabiting / unmarried without cohabiting /
unknown); household income level (<20th / 20th–80th / >80th percentile); nativity (Finnish
background, born in Finland / other); body mass index (BMI) (underweight, <18.5 / normal
weight, 18.5-24.9 / overweight, 25-29.9 /obese, ≥30 kg/m²); gravidity (i.e., number of all
previous pregnancies) (none / 1 or more), parity (none / 1 or more); previous miscarriages (none
/ 1 or more); previous induced abortions (none / 1 or more); total number of prenatal care visits
(none / 1-14 / ≥15 visits); week of first prenatal care visit (no prenatal care visit / before 12 weeks of
gestation / at or after 12 weeks gestation); anemia during pregnancy (defined as hemoglobin <100
g/L) (yes / no); smoking status during pregnancy (never smoker / smoker); mode of delivery
(vaginal / Cesarean section); pregestational diabetes (yes / no); gestational diabetes (yes / no);
pre-existing hypertension (yes / no); gestational hypertension (yes / no); and preeclampsia (yes /
no).

Statistical Analysis

Early neonatal mortality risk for all infants with spina bifida was calculated using the number of
deaths at age 0-6 days among infants with spina bifida divided by the number of total live births
with spina bifida during the study period. Because of its the rarity of outcome, mortality risk and
the 95% confidence interval (CI), was were estimated using the Poisson approximation of
binomial distribution. Based on the rare outcome assumption, Poisson regression was used to
quantify time trends in mortality from 2000-2014. We smoothed random variability in our
temporal trend lines by pooling data for an overlapping sequence of three consecutive years.
Mortality trends were examined for early neonatal deaths in spina bifida cases as well as the
general population of live births. The trend was considered to be significant using Poisson
regression analysis (p value <0.05).

For our analytic study~~We,~~ we made two groups in our study: 1) spina bifida cases that died between day 0-6 after birth; and 2) spina bifida cases that were alive during day 0-6 after birth. We compared the differences in selected infant and maternal characteristics between the two groups using Pearson Chi square test or Fisher exact test (when cell sizes were less than 5). Because of low frequencies, we used non-parametric methods and conducted Exact logistic regression to estimate unadjusted odds ratios (uOR) and 95% CIs to study the association between selected infant and maternal factors and early neonatal mortality. Multivariable analysis was not undertaken because of small cell sizes in some ~~of~~ variable categories. All analyses were performed using the SAS version 9.4 (SAS Institute Inc Cary, NC). Finnish Institute for Health and Welfare and Statistics Finland approved and granted data access for ~~this~~ the study. As data spanned 15 years, all data were permitted to be presented in the ~~Results~~ results ~~Tables~~ tables without suppressing small cells~~; however, we were unable to report effect estimates for associations where one of the cell sizes was zero~~.

RESULTS

A total of 181 live-born infants were identified in the RCM during the study period (2000-2014). Overall, 111 (61%) of cases were classified as isolated, 52 (29%) as multiple, and 18 (10%) as syndrome cases. Thirteen of these 181 infants died during day 0-day 6 of their life, with an early neonatal mortality risk of 7.2% (95% CI=4.3%, 11.9%). Ten out of the 13 infants that experienced early neonatal death had spina bifida as a part of a known syndrome. ~~Overall, 111 (61%) of cases were classified as isolated, 52 (29%) as multiple, and 18 (10%) as syndrome cases.~~ There was a statistically significant increasing trend in mortality among cases between years 2000 and 2014 (p < 0.0001). **Figure 1** shows trends in early neonatal mortality among

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spina bifida cases and total population births in Finland ~~between 2000 and 2014~~during the study period.

Descriptive analysis results examining selected infant and maternal characteristics by early neonatal mortality are presented in **Table 1**. Preterm birth (<37 weeks) (uOR=6.96; 95% CI=1.86, 29.01) and increased maternal age ~~during~~ at delivery (≥35 years) (uOR=5.33; 95% CI= 1.21, 21.87) were positively associated with early neonatal mortality. Additionally, spina bifida occurring as a part of a syndrome also increased the risk of early neonatal mortality significantly (uOR=125.67~~3~~; 95% CI=14.90, >999.99~~9~~).

Anemia during pregnancy was another characteristic that was recorded in a higher proportion of mothers of infants with spina bifida who died in the early neonatal period compared to mothers of infants with spina bifida who were alive in that same period (15.4% vs. 1.2%), with a marginally significant positive association (uOR=14.52; 95% CI=0.97, 218.14).

DISCUSSION

Using ~~Finnish~~ national multi-registry linked dataset for all births between years 2000 and 2014, our study found that 7.2% of all liveborn infants with spina bifida experienced early neonatal mortality in Finland. We found an increasing trend in mortality during the study period as well as a significantly high proportion of mortality among spina bifida cases compared to all livebirths in the population during early neonatal period. ~~The data source, with various infant and maternal variables, including many clinical variables abstracted from medical records, allowed us to examine several important risk factors in relation to early neonatal mortality among spina bifida-affected newborns for the first time. We found that P~~preterm gestation, syndrome case status, and increased maternal age were positively and significantly associated with early neonatal death in spina bifida-affected infants. Maternal anemia during pregnancy also indicated some risk,

though not statistically significant, and is a novel finding that should be explored further. ~~The positive associations reported were not adjusted for confounding due to small frequencies; however, our study captures all live born cases of spina bifida in Finland. Some significant and marginally significant findings in our study are hypothesis generating.~~

The total prevalence of spina bifida, including live births, stillbirths and ~~elective terminations for fetal anomalies~~ (ETOPFA~~)~~ varies worldwide, and is estimated to be 8.63 per 10,000 live births for births in year 2015 (95%CI=6.80, 10.47) in the European region.[24] A meta-analysis by Johnson et al. (2012) estimated about 66% of cases of spina bifida result in ETOPFA (range: 41%-89%).[25] Stillbirths among pregnancies affected by spina bifida in Europe are rare (<5%).[26] In Finland, the average live birth prevalence of spina bifida is 2 per 10,000 total births (range: 1.8 - 2.4) for birth years 2000-2018.[23] The live birth prevalence of spina bifida in Finland is similar to an estimate obtained by pooling data from all EUROCAT registries during the same time period is similar, i.e., 1.9 per 10,000 total births (range: 1.8 - 2.0).[27] There are approximately 60,000 live births each year in Finland, and it is expected that 11 to 15 live births are affected by spina bifida every year.

~~Studies on early neonatal mortality among infants affected by spina bifida are scarce in European countries. Multi-country data from International Clearinghouse for Birth Defects Surveillance and Research member registries (ICBDSR) for births between 2001-2012 reported that 6.9% (95% CI=6.3%, 7.7%) of infants born with spina bifida die within the first week of life, and that multiple or syndromic cases constituted a higher proportion of early neonatal deaths compared to isolated cases.[26]~~ In the US, a population-based birth defects registry ~~study~~ in New York, examining children born with spina bifida between years 1983 and 2006, reported 7% of babies born with spina bifida died by age 7 days.[8] The CPQCC study in the US linked vital

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records and hospital discharge data for births recorded in California between years 2006 and

2011, and showed 4% mortality during first 7 days of life.[16] An older population-based

surveillance registry study in metropolitan Atlanta, US, examining births between 1979 and

1994, reported early neonatal mortality among spina bifida-affected infants to be 10% (95% CI =

5.9%, 13.5%).[9] The proportion of stillbirths and elective terminations are very different in the US

compared to Finland, and thus the case characteristics (e.g., spina bifida severity as measured

through higher lesion level) and maternal and healthcare system characteristics, are different

between the countries, and limit direct comparison of findings.

Studies on early neonatal mortality among infants affected by spina bifida are scarce in

European countries. A multi-country analysis by the International Clearinghouse for Birth

Defects Surveillance and Research (ICBDSR), which included many European birth defects

registries, reported that 6.9% (95% CI=6.3%, 7.7%) of infants born with spina bifida during

2001-2012 died within the first week of life, and that spina bifida cases with other co-occurring

birth defects or those occurring as a part of a syndrome, constituted a higher proportion of early

neonatal deaths compared to isolated cases.[26] The Danish Spina Bifida Patient Database study

reported that a high proportion of mortality occurred during the first three months of life,.[28] A

while a hospital-based study in Poland, with 47 live born infants with spina bifida, reported that

10 died on the first day of life; early neonatal mortality was not reported.[29] Glinianaia et al.

(2020) conducted a systematic review and meta-analysis of studies examining mortality in spina

bifida; however, this review only included studies with survival at age one year and higher.[30]

Other studies from European countries looked at a long-term survival among individuals with

spina bifida, reporting on mortality at ages 1 year and higher.[31, 32] Our study only examined

mortality in early neonatal phase when most of the infant deaths were recorded; deaths among

infants with spina bifida from ages 7 ~~days~~ to 365 days were ~~very~~ scarce (n<5) in Finland and hence could not be examined.

~~The ICBDSR conducted a multi-national study based largely on European birth defects surveillance registries examining a similar study period (2001-2012) as the current study (2000-2014).[26] The pooled early neonatal mortality risk among spina bifida-affected infants in the ICBDSR study was 6.9% (95% CI=6.3%, 7.7%), and this statistic varied by region, especially between Europe and the Americas.[26] Our finding is also consistent with a single state (New York), population-based registry study in the United States for births between 1983 and 2006, with 7% early neonatal death[8]; however, the proportion of stillbirths and elective terminations are very different in the US compared to Finland, and thus the case characteristics (e.g., severity) and maternal and healthcare system characteristics, are very different between the countries, and limit direct comparison. A study from California, US, which was also population-representative, reported a much lower prevalence of early neonatal mortality (4%).[16] California has a diverse mix of race/ethnic and socio-economic strata, and thus not directly reflective of Finnish demographic characteristics. An older population-based surveillance registry study in metropolitan Atlanta, US, examining births between 1979 and 1994, reported early neonatal mortality among spina bifida-affected infants to be 10% (95% CI = 5.9%, 13.5%).[9]~~ Within Europe, ~~there were~~ studies from Denmark, Poland, Norway and United Kingdom ~~that~~ examined mortality _in the post-early neonatal phase_ among individuals with spina bifida _and hence not comparable to current study findings_~~; however, they are very old, not population-based, and/or not on mortality during the early neonatal period as the current study examined~~.[28, 29, 31-38]

The impact of mandatory folic acid fortification of staples on spina bifida prevalence and mortality is relevant for discussion in the context of the current study. ~~There are more studies on~~

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infant mortality (i.e., mortality by age one year) compared to studies on early neonatal mortality, even though it is shown that majority of deaths in spina bifida occur in the first week of life.[26] Factors associated with first year mortality in spina bifida include birthweight, gestational age, having multiple birth defects, level of spina bifida lesion, and maternal race/ethnicity, education, and pre-pregnancy BMI.[7, 9, 13-15] Some factors that were significant for early neonatal mortality noted in the current study also matched with the factors listed above for infant mortality. The CPQCC study was the only large population-based study which examined risk factors for early neonatal mortality; low birthweight and having multiple co-occurring birth defects were associated with a the risk of early neonatal mortality in infants with spina bifida.[16] The current study examined many new factors that were not studied in the CPQCC study.

An interesting aspect we want to highlight is the impact of folic acid fortification of staple foods on both the prevalence of spina bifida, and mortality among infants born with spina bifida; and by extension, we opine a similar effect may be seen for early neonatal mortality, which none of the studies have examined yet. Fortification is a public health intervention for primary prevention of spina bifida, and implemented in the US in 1998. There were significant reductions in the prevalence of spina bifida in the US after food fortification with folic acid.[39] Studies comparing infant mortality among birth cohorts born pre-, interim- and post-fortification periods in the US show a clear drop in infant mortality in spina bifida-affected infants born after fortification went into effect. that Prethe pre-fortification prevalence of infant mortality risk was higher about 10% to 12% during pre-fortification period,[5, 9] and dropped to 4%-8% after fortification.[5, 7, 16] Contrary to the US, Finland and other European countries do not have policies on mandatory folic acid fortification of staple foods.[11] Instead, most European countries, including Finland, haveEurope relies on folic acid supplement intake recommendations, which

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encourage women of reproductive age to take folic acid pills before and during pregnancy to prevent neural tube defects.[40] The impact of ~~these programs~~the supplement pill programs on early neonatal mortality in European region should be examined in future studies, as folic acid has been found to decrease the severity of spina bifida among those affected, and severity is an important predictor of ~~infant~~ mortality among spina bifida-affected individuals.[5, 14]

~~Having co-occurring congenital hydrocephalus is known to increase the risk of infant mortality in some previous studies[9]; however, our study did not have cases with co-occurring hydrocephaly, and crude Exact odds ratios did not show any association between congenital hydrocephalus and early neonatal mortality. It is possible that due to high prenatal care availability and utilization in Finland, congenital hydrocephaly is identified *in utero* through early and periodic prenatal ultrasound screenings, and managed clinically immediately after birth, which reduces the risk of mortality through shunt related complications. Early management of congenital hydrocephaly among infants with spina bifida in Finland needs further investigation. It was interesting to note that variables indicative of socio-economic disadvantage, including maternal education, marital status, and household income level, did not predict early neonatal mortality in the current study. A similar observation was reported by Kancherla et al. (2020) using CPQCC data in the US.[16]~~

~~Some degree of variation in findings on both early neonatal mortality risk and factors associated with it in Finland compared to other studies could be a result of the impact of time periods examined (more recent studies have improved care and early surgical interventions), inherent variations in study data sources, data linkage methods and probabilities, surveillance and vital record follow-up for mortality tracking. Folic acid fortification is also an important consideration leading to differences in prevalence of spina bifida, its severity, and mortality~~

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outcomes among those affected.[5, 39] Overall, we found that studies on prevalence and predictors of early neonatal mortality among infants with spina bifida are scarce in Europe. In that regard, it was difficult to compare current study findings with studies from the US. Finland has a much higher prevalence of elective terminations for fetal anomalies after prenatal diagnosis,[41] and a much lower prevalence of stillbirths among affected pregnancies.[26, 27] In the current study, there were no stillbirths among spina bifida-affected fetuses.

Our study has several strengths. We conducted a national, population-based, multi-register study with clinically confirmed cases of spina bifida in Finland. Linkage between various data registers was near complete and allowed us to examine both demographic and clinical risk factors comprehensively. The study population was homogenous in terms of racial and ethnic distribution. We were able to examine associations between early neonatal mortality and several infant and maternal variables which were not explored in any of the previous studies, including birth order, breech presentation, and maternal health and obstetric history, prenatal care, and maternal smoking during pregnancy. The study included recent births covering a time span of 15 years and allowed us to examine temporal trends in early neonatal mortality for all live born infants with spina bifida comparing with all livebirths in the general population in Finland. Data quality, reliability, completeness, and validity of data linkages of Finnish registers are well established, and these data sets have been used consistently in the past to conduct robust epidemiological analyses.,[42][41-46][45] including a recent study on the association between maternal pregestational diabetes and spina bifida.[47] Spina bifida diagnosis is made using standardized procedures using ICD-9 and ICD-10 codes validated at the RCM. Various infant and maternal variables in the study are based on a comprehensive population-based birth and hospital registers, whichwere abstracted details from medical records, without a potential for recall or

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reporting bias ~~generally influencing observational studies negatively~~. Congenital anomalies are tracked until the child reaches age one year, thus improving the validity of capturing other co-occurring major birth defects among spina bifida cases.[19, ~~48~~ 46]

~~There was one important limitation to our study.~~ MBR implemented data collection on folic acid supplement use beginning in 2017, which was not within our study period. Hence, we were unable to examine the association between pre-conception and perinatal folic acid supplement use and early neonatal mortality. Deaths beyond early neonatal period could not be examined as they were not linked to the congenital anomaly registry. We were also unable to examine causes of early neonatal mortality due to lack of information.

In conclusion, early neonatal mortality risk among infants born with spina bifida is a concern in Finland. Some of the risk factors noted in our study for early neonatal mortality in those with spina bifida, such as ~~low birthweight,~~ preterm birth, syndrome case status, increased maternal age, and potentially maternal anemia during pregnancy, can be used for screening and early identification of cases that could be at a high risk of early neonatal death. Pre-planned interventions should be in place to minimize health complications and prevent deaths in the first seven days of life.[4~~79~~, ~~50~~ 48] Nordic countries with comparable healthcare systems and population characteristics ~~with publicly funded and organized healthcare systems, robust birth defects surveillance, successful multi-registry linkage capacity, and with similar characteristics related to the proportion of spina bifida-affected pregnancies terminated through elective terminations and the proportion resulting in stillbirths,~~ should pool data to achieve a higher sample size, and employ multivariable regression methods to better understand preventable risk factors for early neonatal mortality in spina bifida-affected infants.

FIGURE LEGENDS

Figure 1. Trends in Early neonatal mortality (0-6 days of age) in the population of all live births and among infants with spina bifida in Finland, 2000-2014

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Table 1. Infant and Maternal characteristics of individuals with spina bifida, by early neonatal death (defined as death between 0-6 days after birth) status, in Finland, 2000-2014

Characteristics	Early Neonatal Death No (n=168)	Early Neonatal Death Yes (n=13)	Unadjusted Odds Ratio (95% Confidence Interval)
	n (%)	n (%)	
Infant			
Sex			
Male	94 (55.95)	6 (46.15)	Reference
Female	74 (44.05)	7 (53.85)	1.48 (0.41, 5.57)
Gestational age*			
≥37 weeks	137 (81.55)	5 (38.46)	Reference
<37 weeks	31 (18.45)	8 (61.54)	6.96 (1.86, 29.01)
Congenital anomaly pattern*			
Isolated	110 (65.48)	1 (7.69)	Reference
Multiple	50 (29.76)	2 (15.38)	4.36 (0.22, 261.89)
Syndrome	8 (4.76)	10 (76.92)	124.67 (14.90, >999.99)
Congenital hydrocephalus			

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No	167 (99.40)	13 (100.00)	Reference
Yes	1 (0.60)	0 (0.00)	NC
Breech pPresentation			
No	147 (87.50)	10 (76.92)	Reference
Yes	21 (12.50)	3 (23.08)	2.09 (0.34, 9.04)
Plurality			
Singleton	156 (92.86)	11 (84.62)	Reference
Plural	12 (7.14)	2 (15.38)	2.35 (0.23, 12.83)
Maternal			
Age at delivery (years)*			
<20	5 (2.98)	1 (7.69)	4.05 (0.08, 44.53)
20-34	144 (85.71)	7 (53.85)	Reference
≥35	19 (11.31)	5 (38.46)	5.33 (1.21, 21.87)
Highest attained eEducation			
Basic or no education	75 (44.64)	7 (53.85)	1.72 (0.42, 8.36)
Upper secondary or Pre-Bachelors	74 (44.05)	4 (30.77)	Reference
Bachelors or greater	19 (11.31)	2 (15.38)	1.93 (0.16, 14.68)
Marital or cCohabiting Status			
Married and cohabiting	158 (94.05)	12 (92.31)	Reference
Unmarried without cohabiting	8 (4.76)	1 (7.69)	1.64 (0.03, 14.14)
Household income level			
<20th percentile	18 (10.71)	1 (7.69)	0.64 (0.01, 5.17)
20th-80th percentile	104 (61.90)	9 (69.23)	Reference

>80th percentile	24 (14.29)	1 (7.69)	0.48 (0.01, 3.79)
Nativity			
Finnish background, born in Finland	146 (86.90)	12 (92.31)	Reference
Other	20 (11.90)	1 (7.69)	0.61 (0.01, 4.56)
Body Mass Index (kg/m^2)			
<18.5 (underweight)	2 (1.19)	0 (0.00)	NC
18.5-24.9 (normal weight)	51 (30.36)	5 (38.46)	Reference
25-29.9 (overweight)	23 (13.69)	1 (7.69)	0.45 (0.01, 4.33)
≥30 (obese)	23 (13.69)	1 (7.69)	0.45 (0.01, 4.33)
Gravidity			
None	55 (32.74)	3 (23.08)	Reference
1 or more	113 (67.26)	10 (76.92)	1.62 (0.40, 9.52)
Parity			
None	65 (38.69)	3 (23.08)	Reference
1 or more	103 (61.31)	10 (76.92)	2.10 (0.51, 12.29)
Previous miscarriages			
None	134 (79.76)	8 (61.54)	Reference
1 or more	34 (20.24)	5 (38.46)	2.45 (0.59, 9.14)
Previous induced abortions			
None	153 (91.07)	12 (92.31)	Reference
1 or more	15 (8.93)	1 (7.69)	0.85 (0.02, 6.55)
Total number of prenatal care visits			
No prenatal care visits	0	0	NC

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1-14 visits	64 (38.10)	8 (61.54)	2.54 (0.70, 10.31)
15 or more visits	102 (60.71)	5 (38.46)	Reference
Week of first prenatal care visit			
No prenatal care visits	0	0	NC
<12 weeks of gestation	142 (84.52)	9 (69.23)	Reference
At or after 12 weeks or latergestation	22 (13.10)	4 (30.77)	2.85 (0.59, 11.34)
Anemia during pregnancy (<100 g/l)*			
Yes	2 (1.19)	2 (15.38)	14.52 (0.97, 218.14)
No	166 (98.81)	11 (84.62)	Reference
Smoking status during pregnancy			
Never smoker	142 (84.52)	8 (61.54)	Reference
Smoker	21 (12.50)	3 (23.08)	2.52 (0.40, 11.61)
Mode of delivery			
Vaginal	96 (57.14)	5 (38.46)	Reference
Cesarean section	55 (32.74)	4 (30.77)	1.39 (0.27, 6.77)
Pregestational diabetes			
Yes	4 (2.38)	0 (0.00)	NC
No	164 (97.62)	13 (100.00)	Reference
Gestational diabetes			
Yes	7 (4.17)	0 (0.00)	NC
No	161 (95.83)	13 (100.00)	Reference
Pre-existing hypertension			
Yes	1 (0.60)	0 (0.00)	NC

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No	167 (99.40)	13 (100.00)	Reference
Gestational hypertension			
Yes	2 (1.19)	0 (0.00)	NC
No	166 (98.81)	13 (0.00)	Reference
Preeclampsia			
Yes	0 (0.00)	0 (0.00)	NC
No	168 (100.00)	13 (100.00)	Reference

n=Frequency; NC=Not Calculated (due to 0 exposure cells)
*p value <0.05; Fisher exact p-value was examined when cell sizes were less than 5
Frequencies and percentages may not equal total and 100% due to missing or unknown data