

Citation:

Chen BH, Carmichael SL, Selvin S, Abrams B, Shaw GM. NTD prevalences in central California before and after folic acid fortification. Birth Defects Res A Clin Mol Teratol. 2008 Aug; 82 (8): 547-552.

PubMed ID: [18496833](#)

Study Design:

Trend study

Class:

D - [Click here](#) for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine whether the declining pre-fortification (1989 to 1996) NTD prevalences continued into the post-fortification period (1998 to 2003) in selected California counties.

Inclusion Criteria:

- Eligible were live born infants, fetuses prenatally diagnosed and electively terminated and fetuses spontaneously aborted (defined as fewer than 20 weeks gestation)
- Cases were deliveries diagnosed with NTDs (British Pediatric Association [BPA] codes 740.0, 740.1, 741.0 and 741.9) (N=690)
- Anencephaly was defined as either anencephaly (BPA code 740.0) or craniorrachischisis (BPA code 740.1)
- Spina bifida included cases of spina bifida with or without hydrocephalus (BPA codes 741.0 and 741.9, respectively).

Exclusion Criteria:

Any live born infants, fetuses prenatally diagnosed and electively terminated and fetuses spontaneously aborted (defined as fewer than 20 weeks gestation) before 1989 or after 2003.

Description of Study Protocol:**Recruitment**

- All deliveries in eight central California counties
- Medical records were reviewed for data
- All live births and fetal deaths were included.

Design

Trend study. Study assessed whether the trend in NTD prevalences in the pre-fortification period (1989 to 1996) continued into the post-fortification period (1998 to 2003).

Dietary Intake/Dietary Assessment Methodology

Authors used data from a subset of the control group of a multi-state population-based birth defects study and found that folic acid supplementation appeared constant over the study period.

Intervention

1998 US-implemented compulsory folic acid fortification in cereal grain products.

Statistical Analysis

- Compared the slopes of two regression lines that summarized the annual change in NTD prevalence before (pre-fortification slope) and after (post-fortification slope) compulsory fortification
- Annual NTD prevalences were calculated by dividing the total number of cases in a single year by the total number of deliveries during the same year.

Data Collection Summary:

- *Timing of measurements:* Data collected for each subject at one time point (medical record review)
- *Dependent variables:* NTDs in infants or fetuses
- *Independent variables:* Folic acid fortification
- *Control variables:* None.

Description of Actual Data Sample:

- *Initial N:* 886,985 including live births and fetal deaths (cases N=690)
- *Attrition (final N):* No attrition, data collected at one time point per subject (886,985)
- *Age:* Newborn infant (N=880,945) or fetal death (N=6,040)
- *Ethnicity:* (Reported as Maternal race/ethnicity)
 - White, non-Hispanic (N=318,533)
 - US-born Hispanic (N=197,927)
 - Foreign-born Hispanic (N=243,880)

- Black (N=43,143)
- Asian (N=50,049)
- Other (N=30,665)
- Unknown (N=2,788)
- *Other relevant demographics*: Not applicable
- *Anthropometrics*: Not applicable
- *Location*: Eight central California counties (Tulare, Kern, Kings, San Joaquin, Merced, Madera, Fresno and Stanislaus).

Summary of Results:

Estimated Annual Change in NTD Prevalences Before and After Folic Acid fortification in Central California, 1989 to 2003

Defect	Pre-fortification (1989 to 1996)		Post-fortification (1998 to 2003)		
	N	Sloped (95% CI)	N	Sloped (95% CI)	Difference in slopes (95% CI)
All NTDs	395	-7.5 (-12.4, -2.5)	225	5.1 (-8.7, 19.0)	12.6 (2.6, 22.6)
Anecephaly	161	-4.5 (-6.1, -2.9)	83	3.9 (-5.7, 13.6)	8.4 (2.58, 14.1)
Spina Bifida	234	-3.0 (-7.1, 1.2)	142	1.2 (-4.06, 6.4)	4.2 (-2.3, 10.6)

Prevalence Ratios of NTDs Before and After Folic Acid Fortification in Central California, 1989 to 2003

Defect	Pre-fortification (1989 to 1996)		Post-fortification (1998 to 2003)		
	N	Prevalence	N	Prevalence	<u>95% CI</u>
All NTDs	395	85.23	225	72.16	0.85 (0.72, 1.00)
Anecephaly	161	34.74	83	26.62	0.77 (0.59, 1.00)
Spina Bifida	234	50.49	142	45.54	0.90 (0.73, 1.11)

Author Conclusion:

Annual NTD prevalences in central California did not continue to decrease after implementation of folic acid fortification.

Reviewer Comments:

- *Possible explanations for findings (each discussed at length in the Discussion section):*
 - *Changes in prenatal diagnosis and elective termination*

- *Case ascertainment*
- *NTD risk factors (i.e., maternal race/ethnicity, folic acid supplement use, maternal obesity)*
- *Limited geographic and demographic scope.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	Was the research question clearly stated?	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	Was the selection of study subjects/patients free from bias?	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	Were study groups comparable?	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	Yes

3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	Was method of handling withdrawals described?	Yes
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	Was blinding used to prevent introduction of bias?	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	Yes

6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	Were outcomes clearly defined and the measurements valid and reliable?	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A

8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	Are conclusions supported by results with biases and limitations taken into consideration?	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	Is bias due to study's funding or sponsorship unlikely?	Yes
10.1.	Were sources of funding and investigators' affiliations described?	No
10.2.	Was the study free from apparent conflict of interest?	Yes