

Folate and Clefts of the Lip and Palate—A U.K.-Based Case-Control Study: Part I: Dietary and Supplemental Folate

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Objectives: We sought to determine the associations between nonsyndromic cleft lip with or without cleft palate (CL±P) and cleft palate only (CP) and maternal intake of dietary folate and supplemental folic acid, in an area where the prevalence at birth of neural tube defects has been high and flour is not fortified with folic acid.

Methods: Interviews regarding periconceptual dietary intake and supplement use were completed with the mothers of 112 CL±P cases, 78 CP cases, and 248 unaffected infants. The data were analyzed by logistic regression methods.

Results: There was no overall association between CL±P and CP and either energy-adjusted total folate intake or supplemental folic acid use, irrespective of dosage.

Conclusion: Overall, higher intakes of total folate do not appear to prevent oral clefts in this population.

KEY WORDS: *case-control study, folate, folic acid, cleft lip, cleft palate, epidemiology*

Orofacial clefts (OFC) are among the most common types of congenital anomalies, occurring with a prevalence of about 1.7 per 1,000 live births (Mossey and Little, 2002). They are commonly divided into two etiologically distinct groups: cleft lip with or without cleft palate (CL±P) and cleft palate only (CP). A further division can be made within these groups into isolated clefts (those not associated with other malformations), syndromic clefts (those that are part of a recognized syndrome), and those associated with multiple defects that are not part of a recognized syndrome. Pierre Robin sequence (PRS) is a clinically defined subgroup of CP with a combination of micrognathia,

posterior U-shaped cleft palate, and glossoptosis (Holder-Epinasse et al., 2001) which accounts for 21% of CP cases without other malformations (FitzPatrick et al., 1994). The cleft palate in PRS is thought to be the result of abnormal development of lower jaw structures with cleft palate occurring as a secondary effect via physical obstruction of palatal shelf fusion from a retropositioned embryonic tongue. All individuals with any type of facial cleft require multidisciplinary care from birth until adulthood and they and their families may suffer psychological effects. The defects therefore pose a substantial burden to the individual and their family, and require significant expenditure in terms of health and related services. Thus, it is important to identify strategies for primary prevention, and this requires an understanding of etiology.

Studies in animals (Munger, 2002) have generated interest in a possible protective effect of improving maternal folate intake or status in the periconceptual period and the first trimester of pregnancy. Moreover, some established or putative risk factors for OFC—anticonvulsant drugs (Dansky and Finnell, 1991), tobacco smoking (Little et al., 2004b), high levels of alcohol intake (Werler et al., 1991; Munger et al., 1996a; Shaw and Lammer, 1999) are associated with poorer folate status (Herbert, 1987)—and there is possible overlap with the etiology of neural tube defects (NTD) (Czeizel, 1981; Khoury et al., 1989; Beaty et al., 1991; Little, 1995; Johnston and Bronsky, 1995; Shaw et al., 2004). However, direct evidence in humans is conflicting, reflecting the difficulties of teasing out the effects a specific nutrient from

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those of other nutrients, and differences between studies in methods and statistical power.

A large intervention study in the Czech Republic (Tolarova and Harris, 1995) suggested that in women with a family history of cleft lip or palate, use of a multivitamin supplement containing 10 mg of folic acid reduced the risk for these defects in the offspring. This was not conclusive; however, as the study was not randomized and the effects of specific vitamins could not be distinguished. Other small trials have been interpreted as suggesting that multivitamin supplementation during pregnancy that includes 0.5 to 5 mg folic acid per day, reduces the recurrence risk of OFC (Conway, 1958; Douglas, 1958; Peer et al., 1964; Briggs, 1976; von Kreybig and Stoeckenius, 1978; Schubert et al., 1990). However, these studies were not randomized, the possible effects of folic acid could not be distinguished from the possible effects of treatment with other vitamins, and the data presented are insufficient to evaluate the results (WHO Working Group, 2002).

In a randomized controlled trial of periconceptional vitamin supplementation in Hungary, there was no significant difference in the rate of first occurrence of OFC between a multivitamin mineral and trace element supplement and a supplement comprising trace elements only (Czeizel and Dudás, 1992). In a subsequent cohort study in which the same multivitamin and mineral supplement was used, no effect of the supplement on first occurrence of these defects was observed (Czeizel et al., 2004). However, neither the trial nor the subsequent cohort study had sufficient statistical power to detect a difference in the risk for OFC between the groups compared. The results of the few case-control studies of the association between OFC and maternal use of vitamin supplements containing folic acid (Shaw et al., 2006; Badovinac et al., 2007; Wilcox et al., 2007), maternal dietary folate intake (Shaw et al., 1995, 2006; Hayes et al., 1996; van Rooij et al., 2004; Wilcox et al., 2007) or biomarkers of folate intake (Munger et al., 1996b, 2004; Wong et al., 1999; van Rooij et al., 2003) are inconsistent. One case-control study suggests that medications that disrupt folate metabolism are associated with an increased risk for OFC as well as other types of congenital anomalies (Hernández-Díaz et al., 2000).

We sought to determine the associations between nonsyndromic CL±P and CP and maternal intake of dietary folate and supplemental folic acid, in an area where the prevalence at birth of NTD has been high and flour is not fortified with folic acid. Specifically, in the framework of a population-based study, the methods of which have been described (Little et al., 2004a), we set out to investigate maternal dietary and supplemental intake of folate in 112 cases of nonsyndromic CL±P, 78 cases of nonsyndromic CP, and 248 unaffected controls.

In addition, we investigated the relationship with biochemical markers of folate metabolism, and the *MTHFR* C677T polymorphism, and report the results of this research in a companion paper.

METHODS

A population-based case-control study was carried out between September 1, 1997, and January 31, 2001, and included 190 nonsyndromic OFC cases (112 CL±P and 78 CP) and 248 unaffected controls. Clinical records of cases were reviewed by experienced dysmorphologists in order to determine whether they were syndromic or nonsyndromic. Cases with isolated clefts or with other anomalies that were not part of a recognized syndrome were included. There were 12 such infants; 11 infants with cleft palate were classified as having PRS, and one child had micrognathia and isolated cleft palate, but was not diagnosed as having PRS. The diagnostic threshold between PRS and non-PRS in children who have micrognathia varies between clinicians, with some only including cases with all the features of micrognathia, glossoptosis, isolated cleft palate, and respiratory distress but others including cases with only some of these features. For these reasons we decided to include PRS without other malformations within nonsyndromal CP cases.

Subjects were recruited from predetermined postcode sector regions, selected to represent urbanized areas of Scotland and Manchester/Merseyside and used as geographical recruitment boundaries. Areas included from Scotland were Grampian, Tayside, Fife, Lothian, Forth Valley, Greater Glasgow, Ayrshire and Arran, Lanarkshire and Borders; from England, Manchester and Merseyside. Areas were selected by postcode.

All infants born with clefts in these areas are referred to specialist centers for treatment. Cases were ascertained via the regional cleft teams who informed the study coordinator or local research interviewer of any affected child born within the predetermined geographical boundaries. Scottish cases were verified against the CLEFTSiS register (formerly the Scottish Cleft Lip and Palate Association Register), to which all clinicians in Scotland involved in the care of OFC patients contribute, and which supports the management of care. This register has been validated against the National Birth Register for Scotland and has been found to have a high level of completeness for live-born infants (Clark et al., 2003). English cases were verified against the Craniofacial Anomalies Network (CRANE) register.

In Scotland, potentially eligible controls were identified from the Community Health Index (CHI), a register of the general population which allows assessment of capitation payments for general practitioners. The CHI is also used for the provision of primary care services such as breast and cervical cancer screening and recall, and in the organization of child health surveillance and immunization. It has been shown to have a high level of completeness (Roworth and Jones, 1988; Garton, 1993; Ramsay et al., 1999). In England, potentially eligible controls were identified by contacting general practitioners in the same postcode sector region as the recruited case infant. For each case, we sought to recruit two controls matched on region (postcode

sector), sex, and date of birth (± 1 month). Potentially eligible matched controls were randomly selected and approached; if a potentially eligible control declined to participate, another potential matched control was randomly selected and approached.

The initial approach, in which a study pack was either handed or posted to the index child's mother, was made by various agencies, depending on the region. The initial approach was made a mean of 5 months after the birth for cases and 6 months after birth for control infants. Completed consent forms were returned to the regional study interviewer, who was trained in interview techniques. The interviewer then telephoned to arrange a visit during which a structured interview was conducted.

Data Collection

A validated, semiquantitative food frequency questionnaire (Aberdeen FFQ, version 5.4 [Masson et al., 2003]) was sent to the mothers with the study pack and the mothers were asked to record their habitual diet at the time they completed the questionnaire. The questionnaire includes 150 food items and respondents were asked how often and how many "measures" they ate of each food item. Two weeks after the study pack was sent, the mothers were interviewed in person. They were asked to recall any dietary changes during the 3-month period before pregnancy and the first 3 months of pregnancy, henceforth referred to as the periconceptual period. This information was used to revise the data that had been provided on the food frequency questionnaire, so as to provide estimates of dietary intake during the periconceptual period. The mothers were asked about the type, period (3 months before pregnancy, first 3 months, second 3 months, last 3 months; information on time started and stopped within any of these periods was recorded) and frequency of use and dose of supplemental nutrients. Mothers were also asked about use of drugs that potentially affect folate metabolism in the period from 3 months before pregnancy through to the end of pregnancy; they were asked if they had undergone treatment for disorders which may be treated used by folic acid antagonists, and then about the specific agent (methotrexate, sodium valproate, phenytoin, phenobarbitone, primidone, sulphasalazine, carbamazepine, sulphonamides, trimethoprim, mefloquine, oral contraceptives) used. Sociodemographic data and information on factors that might confound the association between OFC and maternal folate intake or status, namely maternal age, previous reproductive history, previous medical history, smoking, alcohol consumption, and family history of OFC and NTD were also recorded.

Data Processing

Information from the food frequency questionnaire was converted into estimated nutrient intakes using the comput-

erized version of the U.K. food composition tables (Holland et al., 1991). These take into account changes in the fortification of cereals. Data on their composition of supplements taken by the mothers were obtained from the container labels or from the manufacturer, and formed the basis for a supplement composition table for this study. Average daily intake of folic acid from nutritional supplements during the periconceptual period was calculated as product of daily dose times the length of the period for which the supplements were taken, averaged over the entire 6 months of the periconceptual period. This was done to enable the dietary and supplemental intakes to be summed together. If a mother did not take nutritional supplements containing folic acid in the periconceptual period, she was categorized as being a "nonuser."

Statistical Analysis

The outcomes were CL \pm P and CP because there is evidence that these defects differ in etiology and pathogenesis. The primary analyses related to the association between these defects and reported total maternal intake of dietary folate and supplemental folic acid during the periconceptual period, assessed by case-control analysis. The timeframe of exposure in the primary analysis of dietary and supplemental folate intake was defined as the 3 months before and after conception as the development of the embryonic lip and palate is complete by the end of week 10 of gestation (Sperber, 2001). A secondary analysis was made of supplemental folic acid use at any time during pregnancy.

Unconditional logistic regression was used to estimate odds ratios (OR). We adjusted for the matching variables of sex and season of birth; adjustment for region and year of birth was not made because this had little effect on the results. To check that this analytical strategy was valid, the results of conditional and unconditional logistic regression analyses on the matched sets were compared. Potential confounders identified on the basis of previous studies of OFC were evaluated by assessing the *p* value for the change in likelihood ratio between models including the potential confounder and not including it; if this was less than .1, the factor was retained in the model. For all the logistic regression models the goodness-of-fit was determined (Hosmer and Lemeshow, 1989).

Since total and dietary folate intake were correlated with total energy intake, the nutrient residuals method was used to adjust for energy intake (Willett et al., 1997). Quantiles of folate intake (total, dietary) were then calculated on the basis of the combined distribution of cases and controls (Hsieh et al., 1991) and used as categorical variables in the analyses, with the lowest quantile being used as the reference group. This approach was used for each analysis (CL \pm P, CP, and OFC). For supplemental folic acid use, the reference group was defined as nonusers, and users were classified into tertiles.

TABLE 1 Reported Median Total and Dietary Folate Intake During the Periconceptual Period in Mothers of Cases with CL±P and CP, and Mothers of Control Infants

Folate	Median (interquartile range) Intake (µg/day) in Mothers of		
	CL±P cases	CP cases	Controls
Total	442 (299)	484 (324)	524 (318)
Dietary	291 (135)	301 (130)	292 (134)

Potential confounding by socioeconomic status was considered using three measures: maternal education; the child's ethnic group defined according to the country of birth of the parents; and the Carstairs index, an area-based measure of material deprivation (Carstairs and Morris, 1990). Maternal education and the child's ethnic group affected the results and were therefore included in the model; adjustment for the Carstairs index had little influence on the results. We also considered potential confounding by maternal age, previous reproductive history, previous medical history and use of medications, smoking, alcohol consumption, and family history of OFC and NTD. These did not influence the results. We decided *a priori* to categorize reported total and dietary folate intake in quartiles. To determine the sensitivity of the results to this categorization, we also analyzed these data in tertiles and quintiles. In sensitivity analysis, we examined the effect of excluding the 12 infants with anomalies that were not part of a recognized syndrome (see above); exclusion of these infants had no material effect on the associations observed. All statistical analyses were carried out using the Stata statistical package (StataCorp, 1999).

The study was originally designed to have more than 90% power to detect a relative risk of 0.7 per unit standard deviation increase in estimated intake or level of folate, with adjustment for a closely correlated ($r = .7$) nutrient (Hsieh, 1989); more than 80% power to detect a relative risk of 0.5 associated with a very conservative prevalence of supplement use of 10%, based on studies in Great Britain during the mid 1980s to 1990s (Bennett and McIlwaine, 1985; Best et al., 1989; Sutcliffe et al., 1993; Clark et al., 1994; Smith et al., 1994); and noting that this was expected

to increase following the launch of a campaign to increase public awareness of the importance of periconceptual folic acid intake (Health Education Authority, 1996).

This research was approved by the local research ethics committees for each Health Board region within Scotland and by the corresponding committees for Manchester and Merseyside. Approval was also obtained from GP subcommittees in Grampian.

RESULTS

The mothers of 190 of 349 eligible infants (54%) with OFCs (112 of 191 CL±P, 78 of 158 CP) were interviewed. Two hundred forty-eight mothers of control infants were interviewed, 75% of whom were the first controls approached, 25% the second, and 1% the third. The estimated median intakes of dietary and total folate intake during the periconceptual period are presented in Table 1. There was no association between CL±P or CP and either total folate intake (Table 2) or dietary folate intake (data not shown). These results were not substantially affected by sensitivity analysis.

Seventy-nine percent of mothers of infants with CL±P, 76% of mothers of infants with CP, and 81% of control mothers took a supplement containing folic acid during the periconceptual period. The majority of women only started to take supplements once they had become pregnant. There was no association between either CL±P or CP and use of supplements containing folic acid, irrespective of whether they contained other agents (Table 3) or the average daily intake of folic acid from supplements during the periconceptual period (Table 4). In addition, there was no association with reported use at any time during pregnancy. However, there was a suggestion of a positive association with use of folic acid antagonists in the periconceptual period (Table 3). Restriction of the analysis to women who did not take folic acid antagonists did not have a marked effect on the associations between either type of cleft, or both types combined and total folate, average daily intake of

TABLE 2 Association Between Oral Clefts and Maternal Total Folate (dietary and supplemental) Intake During the Periconceptual Period

Quartile	Total Folate Intake				<i>p</i> for Trend†
	Q1	Q2	Q3	Q4	
Median* (µg/day)	269	420	574	775	
CL±P versus controls					
CL±P/controls	29/61	35/55	25/65	23/67	
OR‡ (95% CI)	1.0 (ref)	1.7 (0.83–3.44)	1.1 (0.50–2.21)	0.9 (0.44–2.03)	.53
CP versus controls					
CP/controls	22/60	20/61	18/64	18/63	
OR‡ (95% CI)	1.0 (ref)	1.2 (0.54–2.82)	1.1 (0.49–2.63)	1.0 (0.43–2.36)	.93
OFC versus controls					
OFC/controls	50/60	61/48	41/69	38/71	
OR‡ (95% CI)	1.0 (ref)	1.4 (0.76–2.55)	1.0 (0.57–1.94)	0.9 (0.50–1.75)	.55

* OFC and controls combined. Values are similar for CL±P and controls combined, and CP and controls combined.

† χ^2 for trend across quartiles of reported intake.

‡ Adjusted for sex and season of birth (matching variables), maternal education, the child's ethnic group, and total energy intake.

TABLE 3 Oral Clefts and Use of Supplements and Folic Acid Antagonists During the Periconceptual Period

	<i>CL±P</i>		<i>CP</i>		<i>OFC</i>
	<i>Cases/controls</i>	<i>OR* (95%CI)</i>	<i>Cases</i>	<i>OR* (95%CI)</i>	<i>OR* (95%CI)</i>
Supplements					
None	22/40	1.0 (ref)	19	1.0 (ref)	1.0 (ref)
Folic acid only	64/136	1.3 (0.7–2.5)	38	0.8 (0.4–1.7)	1.0 (0.58–1.75)
Folic acid + other	25/64	0.9 (0.4–2.0)	21	0.9 (0.4–2.1)	0.9 (0.50–1.74)
Without folic acid	1/8	0.2 (0.02–1.5)	0	0.0 (<i>p</i> = .18)†	0.1 (0.01–1.03)
Folic acid antagonists					
No§	83/201	1.0 (ref)	59	1.0 (ref)	1.0 (ref)
Yes	16/26	1.8 (0.87–3.63)	11	1.3 (0.56–2.87)	1.6 (0.90–3.00)

* Adjusted for sex and season of birth (matching variables), maternal education, and child's ethnic group.

† Two-sided Fisher's exact test.

§ Excludes women who could not be classified as having taken a folic acid antagonist during the periconceptual period. When these women are included in the reference category, the odds ratios are for CL±P 1.7 (0.84–3.41), for CP 1.3 (0.57–2.83), and for OFC 1.6 (0.89–2.90).

supplemental folate, or type of supplement taken (data not shown). There was a suggestion of an inverse association between OFC and maternal use of supplements that did not contain folic acid (Table 3), but this was based on a small number of subjects.

DISCUSSION

In our study, higher intakes of total folate and supplemental folic acid did not appear to prevent OFC.

Strengths of the present study include the population-based design, the use of multiple measures of folate status in the same study subjects (see companion paper Little et al., 2008), and the detailed assessment of potential confounding. Potential limitations include incomplete participation, recall bias, and limited statistical power. Participation bias is possible in view of the incomplete participation of both cases and controls. However, the magnitude of the association observed between OFC and maternal smoking was similar to that found in other studies (Little et al., 2004b), which is indirect evidence suggesting that poor participation has not biased the study results. The information leaflet that was supplied with the consent form made no explicit mention of folate.

Recall bias is a potential concern with respect to the mother's ability to describe her diet and use of vitamin

supplements in early pregnancy. The evidence available specifically on recall of diet or use of vitamin supplements during pregnancy does not support the existence of any substantial recall bias (Klemetti, 1966; Mackenzie and Lippman, 1989). The present study was designed to minimize recall bias as much as possible, with standardized training for all interviewers, including the level and type of prompting that was permitted. If we were unsuccessful in our attempts to minimize recall bias we might expect mothers of cases to report higher intakes and recall more supplemental vitamin use than mothers of controls, biasing the results in a positive direction. However, the fact that we found no association suggests that recall bias, due to case mothers overreporting dietary intake or supplement use, was not a problem in this study.

The food frequency questionnaire had been extensively validated (Bolton-Smith and Milne, 1991; Lanham and Bolton-Smith, 1993; Masson et al., 2003). For folate, a high level of agreement (rank correlation coefficients .55 to .79) was found in a comparison between questionnaire responses and 4-day weighed records in 81 individuals (Masson et al., 2003). An additional issue is possible misclassification in the recall of the time during which supplements were taken in relation to the critical period for the occurrence of clefts in embryonic development. Nondifferential error in

TABLE 4 Association Between Oral Clefts and Average Daily Dose of Maternal Supplemental Folic Acid Intake During the Periconceptual Period

<i>Category*</i>	<i>Supplemental Folate Intake (µg/day)</i>			
	<i>None</i>	<i>T1</i>	<i>T2</i>	<i>T3</i>
CL±P versus controls				
Range (µg/day)	0	<200	200–342	350–10,000
CL±P/controls	23/50	38/66	27/61	24/71
OR† (95% CI)	1.0 (ref)	1.7 (0.85–3.48)	1.5 (0.70–3.12)	1.2 (0.56–2.51)
CP versus controls				
Range (µg/day)	0	<200	200–400	458–10,000
CP/controls	19/50	26/66	29/112	4/20
OR† (95% CI)	1.0 (ref)	1.4 (0.63–3.00)	0.9 (0.45–2.04)	0.7 (0.19–2.38)
OFC versus controls				
Range (µg/day)	0	<200	200–342	350–10,000
OFC/controls	42/50	64/66	40/61	44/71
OR† (95% CI)	1.0 (ref)	1.5 (0.82–2.61)	1.1 (0.57–2.00)	1.1 (0.60–2.02)

* Mothers who took supplements in the periconceptual period were categorized into three tertiles based on average daily intake during this period.

† Adjusted for sex and season of birth (matching variables), maternal education, and child's ethnic group.

recall of diet and supplemental vitamin use during pregnancy would be expected to bias the association with intake of folate (and other vitamins) towards the null. The companion paper presents data on the associations between clefts and other measures of folate status.

We did not find evidence of confounding of the associations with total or dietary folate intake, or supplement use, by smoking or alcohol consumption. Although we did not see any clear pattern of association between reported total energy intake and either defect, we took account of this in our analysis of total and dietary folate to minimize the impact of differential reporting (Willett, 1990). More recently, it has been noted that the impact of measurement error on energy-adjustment models is uncertain (Kipnis et al., 1997), and there is renewed debate about energy adjustment (Willett, 2002). However, our findings were similar when no adjustment for energy intake was carried out (data not shown).

Previous studies have evaluated the relation between OFC and dietary folate separately from use of supplements containing folic acid. In some, the relation with dietary folate (or sources of folate) has been assessed only in nonusers of supplements or stratified by supplement use. In the present study, the proportion of women who used supplements was high, and we lacked statistical power to make such an evaluation. Our finding of no association between CL±P and dietary folate intake is consistent with a large multistate study in the United States (Shaw et al., 2006) but not with studies in the Netherlands (van Rooij et al., 2004) or Norway (Wilcox et al., 2007). In the Norwegian study, low levels of dietary folate were weakly associated with CL±P whereas there was no association with intake of supplemental folic acid of less than 400 µg/day; this was interpreted as suggesting that other factors in diet correlated with folate might play a role in preventing CL±P (Wilcox et al., 2007). The lack of association between CP and dietary folate in our study is consistent with the Norwegian study (Wilcox et al., 2007). In the U.S. multistate study, the OR for the highest quartile compared with the lowest was 0.7 with adjustment for total energy intake only and 0.4 after adjusting for other nutrients in the diet (Shaw et al., 2006). Hayes et al. (1996) found no association between OFC and estimated maternal dietary folate intake during the 6-month interval prior to the last menstrual period, either in those who used supplements or in those who did not. In a study in California, Shaw et al. (1995) found that among the offspring of women who did not use multivitamins containing folic acid in the periconceptional period, those whose mothers reported daily cereal consumption (which was fortified in the United States, as it is in the United Kingdom) had a reduced risk of OFC. In Alberta and Ontario (Canada) and in Texas (United States), the prevalence at birth of OFC did not change between the period before and after the fortification of cereal grain products with folic acid (Ray et al., 2003; Hashmi et al., 2005; Sibbald and Lowry, 2005), although

the timing of a small decrease in OFC prevalence in aggregated data from the United States (45 states and Washington, DC) is consistent with the introduction of fortification (Yazdy et al., 2007).

Consistent with most (Shaw et al., 1995; Czeizel et al., 1996, 1999; Werler et al., 1999; Beaty et al., 2001; Itikala et al., 2001; Loffredo et al., 2001; Mitchell et al., 2003; Krapels et al., 2004) but not all (Saxen, 1975; Hill et al., 1988; Hayes et al., 1996; Kallen, 2003) previous studies, we found an inverse association between both CL±P and CP and maternal use of vitamin supplements during early pregnancy. However, this was not accounted for by supplements containing folic acid. With regard to maternal use of vitamin supplements containing folic acid, previous observational studies are inconsistent (Shaw et al., 2006; Badovinac et al. 2007; Wilcox et al., 2007). Our finding of a suggestion of a positive association with the use of folic acid antagonists in the periconceptional period is consistent with the study of Hernández-Díaz et al. (2000).

CONCLUSION

The findings of this study do not suggest that higher intakes of total folate would prevent OFC. As in most studies in other countries, we found an inverse association between both CL±P and CP and maternal use of vitamin supplements during early pregnancy. This did not appear to be accounted for by supplements containing folic acid.

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