WHAT IS ALREADY KNOWN ON THIS TOPIC

Damp, cold, and mouldy houses are associated with poor health

WHAT THIS STUDY ADDS

Insulating existing houses makes the indoor environment significantly warmer and drier, while lowering energy use

Fitting insulation significantly improves occupants' self rated health, self reported wheezing, days off school or work, and visits to general practitioners, and results in fewer hospital admissions for respiratory conditions

teams; and all the householders who took part in our study. We are grateful to our community coordinators the late Ruth Nepia, Pounamu Skelton, and Jo-Ani Robinson. We also thank the general practitioners, the National Health Information Service, the energy companies who supplied us with utilisation data, and June Atkinson, who carried out the randomisation.

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Folic acid supplements and risk of facial clefts: national population based case-control study

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EDITORIAL by Billie et al

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ABSTRACT

Objective To explore the role of folic acid supplements, dietary folates, and multivitamins in the prevention of facial clefts.

Design National population based case-control study.

Setting Infants born 1996-2001 in Norway.

Participants 377 infants with cleft lip with or without cleft palate; 196 infants with cleft palate alone; 763 controls.

Main outcome measures Association of facial clefts with maternal intake of folic acid supplements, multivitamins, and folates in diet.

Results Folic acid supplementation during early pregnancy (≥400 µg/day) was associated with a reduced risk of isolated cleft lip with or without cleft palate after adjustment for multivitamins, smoking, and other potential confounding factors (adjusted odds ratio 0.61, 95% confidence interval 0.39 to 0.96). Independent of supplements, diets rich in fruits, vegetables, and other high folate containing foods reduced the risk somewhat (adjusted odds ratio 0.75, 0.50 to 1.11). The lowest risk of cleft lip was among women with folate rich diets who also took folic acid supplements and multivitamins (0.36, 0.17 to 0.77). Folic acid provided no protection against cleft palate alone (1.07, 0.56 to 2.03).

Conclusions Folic acid supplements during early pregnancy seem to reduce the risk of isolated cleft lip (with or without cleft palate) by about a third. Other vitamins and dietary factors may provide additional benefit.

INTRODUCTION

Folic acid deficiency is known to produce facial clefts in rodents.[1] However, studies of an association with facial clefts in humans have provided inconsistent results,[2-7] and the question remains unresolved.[8] This question is especially relevant in countries where fortification of foods with folic acid has not been allowed. One of these is Norway, which has one of the highest rates of facial clefts in Europe.[9] We assessed possible effects of folic acid on facial clefts in Norway through a population based case-control study.

METHODS

Study design

Infants born in Norway with orofacial clefts are treated in one of two surgical centres (Oslo and Bergen). We contacted the families of all newborn infants born from 1996 to 2001 who had been referred for surgical treatment of a cleft (either cleft lip with or without cleft

Crude and adjusted odds ratios (95% confidence intervals) for cleft lip with and without cleft palate and cleft palate only, for three categories of folic acid supplementation

Folic acid supplement (μg/day)	All cases: crude risk	Isolated clefts		
		Crude risk	Crude risk (restricted to subset with complete data)	Adjusted risk*
Cleft lip with or without cleft palate				
	(n=377)	(n=314)	(n=287)	(n=287)
0	1.0	1.0	1.0	1.0
1-399	0.98 (0.73 to 1.33)	0.97 (0.70 to 1.35)	0.97 (0.69 to 1.36)	1.17 (0.75 to 1.84)
≥400	0.66 (0.47 to 0.95)	0.58 (0.39 to 0.86)	0.57 (0.38 to 0.85)	0.65 (0.40 to 1.05)
Cleft palate only				
	(n=196)	(n=118)	(n=114)	(n=114)
0	1.0	1.0	1.0	1.0
1-399	1.06 (0.72 to 1.56)	1.02 (0.63 to 1.66)	1.09 (.067 to 1.79)	0.98 (0.51 to 1.90)
≥400	0.81 (0.53 to 1.26)	0.90 (0.54 to 1.52)	0.92 (0.55 to 1.57)	1.07 (0.56 to 2.03)

*Adjusted for mother's education (less than high school, high school or more), mother's employment in early pregnancy (yes or no), mother's consumption of alcohol in early pregnancy (four categories), mother's smoking (ordinal linear, five categories: none; passive only; 1-5, 6-10, and ≥11 cigarettes a day), dietary folate (continuous), periconceptional multivitamin use (yes or no), and year of birth.

palate or cleft palate only). During the same years, we randomly selected an average of four per 1000 live births through the medical birth registry of Norway as controls.

Data collection

The main questionnaire collected data on demographic characteristics; reproductive history; and smoking, alcohol, drugs, and other exposures during early pregnancy. The median time from the baby's delivery to completion of the main questionnaire was 14 weeks for cases and 15 weeks for controls (interquartile range 13-17 weeks).

In a quantitative food frequency questionnaire,[10-12] we asked women to recall their diet during the first three months of pregnancy. We identified non-cleft birth defects among cases through the medical birth registry, medical records at the hospital doing the corrective surgery, and the mothers' questionnaire. Both questionnaires are available on line (dir.niehs.nih.gov/direb/studies/ncl/question.htm).

Intake of folic acid supplements—We defined a three month exposure window for folate intake comprising the month before the last menstrual period and the first two months of pregnancy. We counted women as exposed if they took folic acid for at least one month during this window. We were able to confirm intake for 99% by using the product name or pill bottle label. Women were asked similar questions about multivitamins. We estimated each woman's total folic acid intake from folic acid supplements and multivitamins. We categorised perinatal folic acid intake into three groups: none, less than the current recommended daily dose (1-399 μg), and the recommended daily dose (≥400 μg).

Intake of dietary folates—We estimated dietary folate intake by applying official Norwegian food composition tables to mothers' responses on the food frequency questionnaire.

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RESULTS

Participants

Among the 300 000 women who delivered in Norway during the time of our study (1996-2001), 676 mothers had a baby with an orofacial cleft referred for corrective surgery. After exclusions, there were 652 eligible case mothers. Of these, 88% (573) agreed to participate (377 with cleft lip with or without cleft palate and 196 with cleft palate only). We randomly selected 1022 live births within six weeks of delivery to serve as controls. After exclusions,1006 control mothers were eligible, of whom 76% (763) agreed to participate. Ten per cent of control mothers took ≥400 μg folic acid supplements as well as multivitamins in early pregnancy, 9% took folic acid alone, and 26% took multivitamins alone.

Folic acid supplement

The table shows odds ratios for clefts with folic acid supplements. The crude odds ratio with folic acid of ≥400 μg/day was 0.66 (95% confidence interval 0.47 to 0.95) for cleft lip with or without cleft palate and 0.81 (0.53 to 1.26) for cleft palate only. Associations were present only among the cases with isolated clefts (that is, those with no other birth defects). We restricted subsequent analyses to the isolated clefts. After restrictions and adjustment for potential confounding factors (diet and multivitamins, mother's education, mother's employment during early pregnancy, smoking, alcohol consumption, and year of baby's birth) the association between folic acid and cleft lip with or without cleft palate did not change but the association with cleft palate only was no longer present.

None of the analyses suggested any association of low dose folic acid (<400 μg/day) with clefting. In the dichotomous analysis of folic acid (<400 μg/day *v* ≥400 μg/day), the adjusted odds ratio for isolated cleft lip with or without cleft palate was 0.61 (0.39 to 0.96).

Dietary folates

The estimated median intake of dietary folates was 205 (interquartile range 160-260) μg/day. Dietary folate intake across quarters was moderately associated with the crude risk of cleft lip with or without cleft palate (P for trend=0.03) (see bmj.com). The odds ratio for women above the median compared with those below was 0.78 (0.61 to 1.01). After adjustment for covariates it was 0.80 (0.60 to 1.08).

Multivitamins

Intake of multivitamins around conception showed a similarly modest association with reduced risk of cleft lip with or without cleft palate. The crude odds ratio was 0.77 (0.57 to 1.03); after adjustment for covariates (including folic acid) it was 0.75 (0.50 to 1.11).

Combining three sources of folic acid and vitamins

The figure shows adjusted odds ratios for eight groups of mothers, categorised by whether the mothers were above or below the median for dietary folate, whether they were taking multivitamins around conception, and whether they were taking ≥400 μg folic acid around conception. Women with lower measures in all three categories are the reference group. The groups at lowest risk were those who took ≥400 μg of folic acid in combination with multivitamins or good diet. The esti-

WHAT IS ALREADY KNOWN ON THIS TOPIC

Folic acid supplementation in the periconceptional period reduces the risk of neural tube defects

Benefits from folates in the prevention of other birth defects have not been established

WHAT THIS STUDY ADDS

The risk of cleft lip with or without cleft palate seems to be substantially reduced by folic acid supplements during the month before pregnancy and the first two months of pregnancy

Similar benefits are not apparent for cleft palate

mated relative risk among women with all three (≥400 µg folic acid plus multivitamins and healthy diet) was 0.36 (0.17 to 0.77).

DISCUSSION

We found evidence that folic acid supplementation of 400 µg or more a day reduces the risk of isolated cleft lip with or without cleft palate by a third, with no apparent effect on the risk of cleft palate alone. Separate findings for the two types of orofacial clefts are consistent with embryological and epidemiological data that show distinct causal mechanisms for these two types of defects.[13] Multivitamins and a diet rich in vegetables and fruits may also be protective for cleft lip with or without cleft palate, although these effects (if real) are weaker.

Strengths and weaknesses

Study design—Cases were drawn from a large and well defined population, with virtually complete ascertainment, and a high participation rate (88%). Although the participation rate was lower for controls (76%), the controls were drawn randomly from the entire population of births. Women were contacted as soon as possible after delivery to reduce the recall interval. The collection of pill labels allowed us to correct some errors in self report.

Data quality—Folic acid dosage is estimated more reliably than dietary folates. Our measure of dietary folate (based on recalled intake of fruit and vegetables) probably captures many aspects of good nutrition, and the observed association with dietary folate could reflect the effects of other vitamins in addition to folates.

Bias—We sent the main questionnaire to women around three months after delivery, earlier than in many previous studies. Concerns about recall bias were further reduced by the specificity of the findings. Our findings are consistent with previous positive studies, which have found associations more often with cleft lip with or without cleft palate than with cleft palate only.[2 5 6]

Confounding—Adjustments for social factors, alcohol, smoking, and other potential confounding variables had little impact on the estimates. We cannot rule out the presence of unmeasured confounders, although such confounders would have to be strongly related to cleft lip with or without cleft palate in order to produce the observed results.

Comparisons with previous human studies

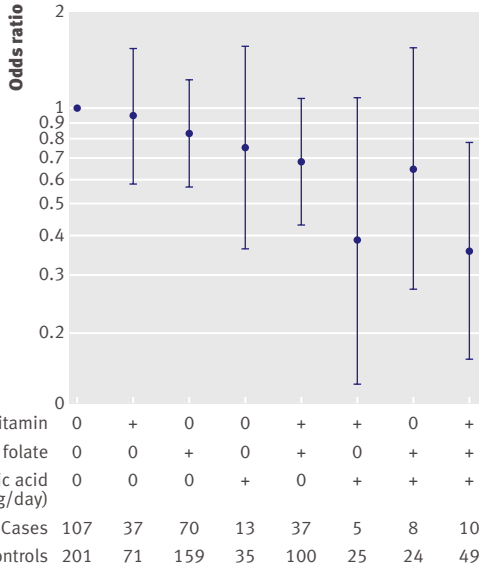
Previous evidence from epidemiological studies of folic acid and clefts has been mixed.[3-7] Some ambiguity in previous studies may reflect the relatively weaker association of folic acid with clefts compared with neural tube defects. Most of the earlier clefts studies were not specifically designed to test the folic acid hypothesis, few were able to distinguish intake of folic acid from intake of multivitamins, and none sought documentation of reported intake. Recently, van Rooij and colleagues reported a protective effect on isolated cleft lip with or without cleft palate with folic acid supplement alone,[6] although this study was limited by a small sample and a haphazard set of controls.

Contribution of other vitamins

The finding that the relatively low levels of dietary folates (which are less bioavailable than folic acid) seemed to be weakly protective against cleft lip with or without cleft palate, even though we saw no evidence for a protective effect of low dose folic acid supplements (<400 µg/day), is curious. Other nutritional factors correlated in diet with the folates may have a role in preventing cleft lip with or without cleft palate. We saw a stronger effect when dietary folate and multivitamins were combined, even in the absence of folic acid supplement (figure).

Prevalence of birth defects and population attributable risk

Given the current levels of folic acid supplementation in Norway, and the estimated reduction in risk from folic acid, we estimate that an additional 22% of isolated cases of cleft lip with or without cleft palate could be averted if all pregnant women took ≥400 µg of folic acid a day.



Odds ratios for cleft lip with or without cleft palate in women divided into eight categories according to their intake of folic acid (≥400 µg folic acid *v* all others), dietary folate (above or below the median), and multivitamins (yes or no). Numbers of women in each category are shown beneath the figure

Conclusion

Intake of 400 µg a day or more of folic acid in the periconceptional period seems to reduce the risk of isolated cleft lip with or without cleft palate in Norway by about a third. This possible benefit should be considered when weighing the risks and benefits of fortifying foods with folic acid.[14]

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BMJ UPDATES

Micronutrient supplements may improve neonatal health

Research question

Does a micronutrient supplement help undernourished pregnant women give birth to healthier babies?

Answer

Probably

Why did the authors do the study?

A micronutrient supplement given to pregnant women could be a simple and cheap way to improve neonatal health in the developing world. But at least five randomised trials have produced mixed results. These authors wanted to clarify the evidence by focusing on those most likely to benefit—pregnant women who were already underweight and anaemic.

What did they do?

They recruited 200 pregnant women from one of the poorest areas in Delhi, India, to a randomised controlled trial. All had a body mass index below 18.5 or a haemoglobin concentration of 70-90 g/l. During the third trimester, 98 of the women took a supplement containing 29 micronutrients (including vitamins A, B, C, and D, minerals, and trace elements). The rest took an identical placebo. All participants took extra iron (60 mg/day) and folic acid (500 µg/day). The trial was double blind.

The authors followed up the women until they gave birth, and then followed up their babies for seven days. They were particularly interested in the effects of the supplement on the babies' birth weight, length, mid-arm circumference, and neonatal illnesses. They compared the intervention and control groups using intention to treat analysis.

What did they find?

Women given the supplement were 70% less likely than controls to have a baby weighing less than 2500 g (16% (12/74) v 43% (31/72), relative risk 0.3 (95% CI 0.13 to 0.71)). Their babies were 0.80 cm (0.03 to 1.57 cm) longer on average and 0.20 (0.04 to 0.36) cm larger in mid-arm circumference. But the difference in birth weight was not significant (2667 *v* 2511 g, adjusted difference 98 (–16 to 213) g, P=0.09).

Babies born to mothers who took the supplement were also significantly less likely to become ill during the first week of life (15% (13/88) *v* 28% (23/82), adjusted relative risk 0.42 (0.19 to 0.94)). Sepsis was the commonest illness in both groups.

What does it mean?

This unconventional supplement had a measurable impact on the wellbeing of the infants in this study, when compared with iron and folic acid supplements alone. But the large number of dropouts means that the study was not as powerful as it should have been. The authors had data on birth weight for only 146 out of a possible 200 babies, and as a result the findings on birth weight are inconclusive.

The authors deliberately studied a select group of particularly poor and undernourished women, so their results are unlikely to apply to less vulnerable women in India or elsewhere in the developing world. We still don't know if micronutrient supplements can help save lives.

Gupta et al. Multimicronutrient supplementation for undernourished pregnant women and the birth size of their offspring: a double-blind, randomized, placebo-controlled trial. *Archives of Pediatric and Adolescent Medicine* 2007;161:58-64