

Haberg SE, London SJ, Stigum H, Nafstad P, Nystad W. Folic acid supplements in pregnancy and early childhood respiratory health. *Arch Dis Child* (published online 5 December 2008)

The paper does not show that folic acid supplements in pregnancy cause early childhood respiratory illness. It shows a weak association that is unlikely to be causal and could even have arisen by chance because the associations reported are of borderline statistical significance.

1. The weak association is illustrated by the following results:

Childhood illness	Anytime in pregnancy		In early pregnancy	
	Relative risk	95% confidence interval	Relative risk	95% confidence interval
Wheeze	1.06	1.03-1.08	1.07	1.03-1.12
Lower respiratory tract infection (LRTI)	1.05	1.001-1.11	1.10	1.01-1.20
Hospitalization for LRTI	1.11	1.05-1.17	1.28	1.07-1.53

2. These results, though, statistically significant, could easily have arisen by chance because there is no strong hypothesis that taking folic acid around conception caused childhood respiratory illness.

3. If one accepts the association as real (ie, not due to chance, which could easily be the case in the absence of a strong prior hypothesis) there are two possible explanations:

(i) First possible explanation: "Confounding"

The following two propositions are widely accepted:

(a) Women who are more likely to take folic acid in pregnancy, particularly immediately before pregnancy and in early pregnancy, are more health conscious than those who do not.

(b) Women who are more likely to report respiratory problems in their children to their doctor are more health conscious than those who do not.

If one accepts (a) and (b) as true, it follows that women who take folic acid in pregnancy will tend to be the same women who are more likely to report illness in their children to a doctor. In other words (a) is associated with (b) through each being associated with health conscious behaviour. Such an indirect association is called "confounding".

This confounding explanation is strengthened by the observation that the association is stronger for women who take folic acid supplements early in pregnancy (before 12 weeks) which will identify particularly health conscious

women (because women who start to take folic acid supplements before pregnancy and before being registered for antenatal care need to be more health conscious than women offered folic acid as part of their antenatal care). The effect of confounding will be stronger in this group than in women who start taking folic acid after 12 weeks of pregnancy. Only a relatively small such tendency would explain the reported results. This is illustrated by the following observation:

**If women who took folic acid in the first trimester are 6% more likely to report respiratory illness in their children, then this alone would explain the reported association.**

The authors state that confounding may have explained their results, but acknowledging the possibility does not dismiss it. Stating, as they do, that “folic acid supplements were not associated with an increased risk of colic before six months of age” does not exclude the confounding bias arising from this kind of study as an explanation because it may not have been common or worrying enough to seek medical attention.

(ii) Second possible explanation: Causal

Folic acid taken in pregnancy causes respiratory ill health in children. The association between taking folic acid immediately before a pregnancy and reporting childhood respiratory illness is not because health conscious women are more likely to do both.

The “confounding” explanation is so much more likely than the causal explanation that the causal explanation can be excluded.

#### 4. Conclusion

The slightly increased reporting of respiratory illness in children born to women who took folic acid supplements in early pregnancy was probably due to confounding and does not provide evidence of a causal association.

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