

International retrospective cohort study of neural tube defects in relation to folic acid recommendations: are the recommendations working?

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Abstract

Objective To evaluate the effectiveness of policies and recommendations on folic acid aimed at reducing the occurrence of neural tube defects.

Design Retrospective cohort study of births monitored by birth defect registries.

Setting 13 birth defects registries monitoring rates of neural tube defects from 1988 to 1998 in Norway, Finland, Northern Netherlands, England and Wales, Ireland, France (Paris, Strasbourg, and Central East), Hungary, Italy (Emilia Romagna and Campania), Portugal, and Israel. Cases of neural tube defects were ascertained among liveborn infants, stillbirths, and pregnancy terminations (where legal). Policies and recommendations were ascertained by interview and literature review.

Main outcome measures Incidences and trends in rates of neural tube defects before and after 1992 (the year of the first recommendations) and before and after the year of local recommendations (when applicable).

Results The issuing of recommendations on folic acid was followed by no detectable improvement in the trends of incidence of neural tube defects.

Conclusions Recommendations alone did not seem to influence trends in neural tube defects up to six years after the confirmation of the effectiveness of folic acid in clinical trials. New cases of neural tube defects preventable by folic acid continue to accumulate. A reasonable strategy would be to quickly integrate food fortification with fuller implementation of recommendations on supplements.

Introduction

Supplements containing folic acid, when consumed from before conception, can reduce spina bifida and other neural tube defects by an estimated 80% or more. Neural tube defects annually affect at least 300 000 newborns worldwide. Because folic acid is inexpensive, safe, and easy to use, many professional organisations and some governmental agencies promote the use of folic acid supplements to prevent neural tube defects. Recommendations vary, but they typically include that women should eat a healthy diet and take folic acid supplements when planning a pregnancy or throughout childbearing age. In a few countries, including the United States, Canada, Chile, and South Africa, recommendations are integrated with a policy of widespread fortification of flour so the entire population receives at least a small additional amount of folic acid. This population-wide approach is effective.¹⁻³

A crucial question is how effective are recommendations alone, in the absence of fortification? We examined this by evaluating rates of neural tube defects and their temporal relation with recommendations on folic acid.

Methods

The study included selected registries from the International Clearinghouse for Birth Defects Monitoring Systems. Major criteria for inclusion were a structure for population based ascertainment; relatively large size; and ability to provide detailed case information for central clinical review, ascertain affected pregnancy terminations (where such a procedure was legal), and conduct an assessment of local folic acid policy. Funding sources were primarily from Europe, which led to the preferential inclusion of European registries. We gathered information on folic acid recommendations from interviews, publications listed on Medline, reports of workshops and committees, and documents issued by governmental agencies and professional bodies.

Thirteen registries provided listings of cases of anencephaly or spina bifida among liveborn infants, stillbirths, and pregnancy terminations that occurred between 1988 and 1998. Case information also included birth outcome, birth date, gestational age, and associated malformations. Registries also provided appropriate denominator information.

We assigned affected pregnancy terminations to the calendar year in which they would have been delivered had they reached the mean gestational age of liveborn cases in the database (adjusted by registry and birth year). We use the term "incidence" for the reported rates, although the true population at risk for neural tube defects (all conceptuses) cannot be ascertained. We plotted incidences by year, programme, and type of neural tube defect (anencephaly and spina bifida). We used Poisson regression to assess trends. From the Poisson regression, we derived for each programme an incidence rate ratio, which estimates the average relative change in rate per year.

We calculated incidence rate ratios for the entire study period as well as for before and after 1992 and before and after the year of introduction of national recommendations (where issued). We chose 1992 because of the timing of the publication of the

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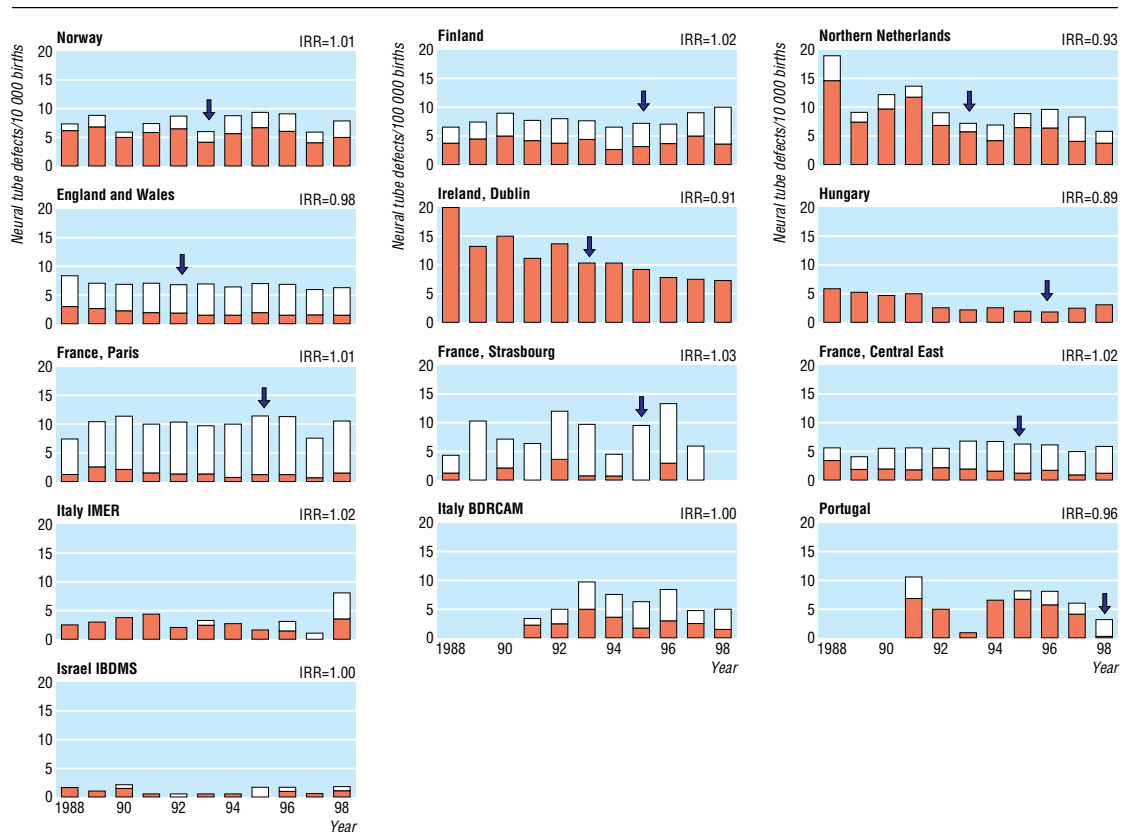


Fig 1 Rates of neural tube defects (anencephaly and spina bifida) per 10 000 births, 1988-98. Shaded top portion indicates terminated pregnancies. Arrow indicates time of recommendations in each country. IRR=average rate of change from one year to next

randomised trials (1991 and 1992) and of recommendations in the United States and the United Kingdom (in 1992), which were internationally known and readily available. We estimated the number of cases that might have been prevented in the study area since 1992 at different levels of folic acid effectiveness.

Results

The study included 8636 cases of anencephaly or spina bifida among over 13 million births in 13 areas in Europe and Israel (see *bmj.com*). Relative to other study areas, rates of neural tube defects tended to be higher in Ireland, Northern Netherlands, and France (Paris) (fig 1). Pregnancy terminations contributed considerably to reported rates in some registries.

Folic acid policies varied from no recommendations (Italy and Israel) or dietary recommendations only (Norway until 1998) to dietary recommendations plus use of supplements among selected women (Finland) or use of supplements for women planning pregnancy or all women of childbearing age (see *bmj.com*). The timing of recommendations also varied.

In most areas rates were stable. Four areas showed an overall decreasing trend (fig 1). Trends after 1992 were similar to trends before 1992. Organisational changes in the reporting system in Hungary in the mid-1990s caused under-ascertainment of affected pregnancy terminations, so we did not include pregnancy terminations in the subsequent analyses. We saw no material change in trends after the issuing of local recommendations. Findings were similar for anencephaly and spina

bifida separately and combined. Figure 2 shows the number of cases that might have been prevented in the study area beginning in 1993.

Discussion

In this study covering more than 13 million births, rates of neural tube defects showed no detectable change associated with recommendations to consume more folic acid. Either rates were unchanged or the decline was similar to that observed during the period before the recommendations. We estimate that

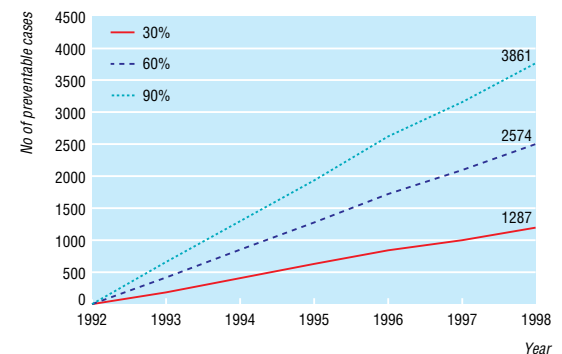


Fig 2 Estimated number of pregnancies with neural tube defects preventable by folic acid in study area, 1993-8. Estimates assume three scenarios of effectiveness (30%, 60%, 90%), which encompass a reasonable range from low dose fortification to highly effective supplementation

thousands of pregnancies that would otherwise have been healthy were affected by neural tube defects in the study area alone since 1992. These findings, which expand those from an earlier study,⁴ underscore the ongoing missed opportunities for prevention.

Limitations and strengths

Case ascertainment may have varied by registry and thus probably contributed to the geographical variation in reported rates. This does not necessarily invalidate monitoring if it remains constant over time. Constant ascertainment is difficult to prove, and variations may have occurred, particularly among pregnancy terminations. A second limitation is that the use of ecological data may have led to real effects going undetected. Rates may have decreased locally, for example, in areas in the Netherlands, United Kingdom, and Ireland that conducted extensive educational campaigns, but we may have been unable to observe them. A third limitation is the study's limited geographical scope. However, the study findings in Europe, where birth defects are a major contributor to infant death, are likely to be relevant to a more global discussion on missed opportunities for prevention of neural tube defects. Finally, we had incomplete information on the extent of implementation of recommendations. Such information is crucial if we are to understand why recommendations did not reduce the incidence of disease.

The study also had several strengths. We included areas with a range of reported rates and recommendations, from none at all (Italy) to early adoption of recommendations in association with educational campaigns (for example, Ireland). The registries used multiple sources of ascertainment, including pregnancy terminations. Finally, the findings were not confounded by fortification of flour.

Possible explanations and implications

Why did recommendations have no detectable effect on rates, despite the proved effectiveness of folic acid? Folic acid use increased in the Netherlands and the United Kingdom in conjunction with government sponsored education campaigns,^{5,6} but the long term persistence and effects are unknown. Otherwise, folic acid use in Europe is generally low—approximately 10% in Norway in 1998,^{7,8} and 6% in Italy in 2002 (Botto and Bianchi, unpublished data).

Intensive educational efforts and a very high proportion of planned pregnancies seem to have been crucial factors in the high effectiveness of a public health campaign to promote use of folic acid supplements in areas of China.⁹ In general, use of supplements tends to follow economic and educational lines,^{5,7,8} so targeting the entire population through recommendations on supplementation alone may not be practical.

Fortification of flour represents an additional opportunity to deliver some folic acid to nearly the entire population, across social and economic barriers. In countries that have fortified flour, blood folate concentrations have risen quickly,^{3,10,11} and although the reductions in incidence were not as large as that achievable through supplementation, such reduction occurred soon after fortification was implemented.¹⁻³

The estimated number of preventable cases of neural tube defect that have occurred since 1992 could be in the thousands. A reasonable and urgent strategy to reduce this growing burden is to quickly integrate for-

What is already known on this topic

Randomised trials showed, more than a decade ago, that folic acid can reduce the occurrence of neural tube defects by half or more

Professional organisations and public health agencies in many countries have tried to promote use of folic acid, either by fortifying foods with folic acid or, more often, by recommending the use of supplements

Studies have shown that fortification of flour can be quickly effective, but the effect of recommendations has not been clearly documented

What this study adds

Recommendations on use of folic acid have had no detectable impact on incidence of neural tube defects, regardless of the recommendations' form, timing, and intended target

In addition to actively promoting the use of supplements, public health agencies and medical professionals should strongly consider implementing food fortification programmes

tification with a fuller implementation of recommendations on folic acid.

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