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Low compliance with recommendations on folic acid use in relation to pregnancy: is there a need for fortification?

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Abstract

Objective: As a means to prevent neural tube defects (NTDs), women planning pregnancy in Denmark are recommended to take a dietary supplement of 400 μg folic acid daily during the periconceptional period. We examined compliance with this recommendation in a national survey.

Design: Cohort study on pregnant women in Denmark.

Setting: The Danish National Birth Cohort (DNBC).

Subjects: From November 2000 to February 2002, 22 000 pregnant women were recruited for DNBC. Use of dietary supplements was recorded at enrolment. Compliance with the recommendation was related to an information campaign that took place during the second half of 2001, and to lifestyle factors provided in a telephone interview by the end of the first trimester of pregnancy.

Results: An increase was seen in the proportion of women complying with the recommendation in the study period and this coincided with the information campaign events. However, even at the end of the period, only 22.3% of the women who had planned their pregnancy fully complied with the recommendation. No increase at all was seen in periconceptional folic acid use among women with unplanned pregnancies. Young age, low education and smoking were identified as factors that determined non-compliance.

Conclusions: Alternative and more effective strategies are needed if the Danish population is to benefit fully from the knowledge that folic acid prevents NTDs. Future strategies should not only target vulnerable groups, such as the less educated and the young, but also women who get pregnant without planning this. The only possible way to reach the last group may be through fortification of foods with folic acid.

Keywords
Folic acid
Neural tube defects
Compliance with recommendation
Fortification

It is well documented that periconceptional folic acid intake reduces the risk that a woman will have a pregnancy affected by neural tube defects (NTDs). It is generally accepted that prevention can be obtained at a dose corresponding to 0.4 mg folic acid per day, although the dose needed to obtain maximal or full effect is still debated[1–6].

Three different strategies are available to reach the above-mentioned daily dose: women may consume a diet rich in folate, they may take supplements with folic acid, or foods may be fortified with folic acid.

Strategies to increase the use of folic acid supplements have been applied in other countries, with varying results (UK[7], Ireland[8], Scotland[9], the USA[10], The Netherlands[11] and Australia[12]). Most countries have had campaigns to increase knowledge and use of folic acid supplements periconceptionally among women planning pregnancy. These campaigns, which have been evaluated, all detected an increase in folic acid use but only up to a limited level; the maximal effect was seen in the UK, where the proportion of women who took folic acid when planning a baby increased from 24 to 38%[7].

Some countries (e.g. USA, Canada and Chile) have implemented compulsory folate fortification of selected food items in addition to the supplement strategy to ensure a proper folate status.

Until 1997, the only general official recommendation in Denmark was that women should consume a prudent diet rich in folate. In 1997, a committee recommended that all women planning pregnancy should take 0.4 mg folic acid daily as a supplement until the 12th week of pregnancy[13]. In 1999, the official health authorities launched a series of activities to increase awareness of the benefit of periconceptional folic acid use. However, the impression

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has been that too few women adhere to the recommendation, but so far this has not been documented.

The Danish National Nutritional Council initiated an investigation of the use of periconceptional folic acid among Danish women. This could be achieved by means of The Danish National Birth Cohort (DNBC)[14]. It was possible to gather information regarding compliance with the folic acid recommendation for around 22 000 women recruited in the period from November 2000 to February 2002.

The aim of the present study was threefold: (1) to assess the size of the problem with non-compliance in Denmark; (2) to relate the development over time of the proportion of compliers to the points in time when various information activities were launched; and (3) to identify risk factors for non-compliance.

Methods

The Danish National Birth Cohort

This is a nation-wide study in which about 100 000 pregnant women and their subsequent offspring were recruited for long-term follow-up from early pregnancy and onwards[14]. Recruitment was performed primarily by general practitioners and to some extent midwives. Information derives from self-administered questionnaires, computer-assisted telephone interviews and national health registries; blood samples were also collected from the mother and child. Recruitment commenced in 1997 and was completed by September 2002, with 101 047 pregnancies. The study is described in detail elsewhere[14].

Data used in the present study

Recruitment took place during the first antenatal visit to the general practitioner. The visit typically takes place in gestation week 5–10, when the woman realises her pregnancy. The women recruited for DNBC received written information about the survey, together with an enrolment form and a stamped envelope to fill in and return if she wanted to participate. The enrolment form, typically completed in gestation week 10–12, provided the date of the last menstrual period and detailed information on the use of medication and dietary supplements. This included dosage and period of intake, which spanned from 4 weeks prior to the last menstrual period until the date of completing the form. Data from the first telephone interview, undertaken in gestation week 12–15, included information on smoking, height, pre-pregnant weight, parity, marital status, occupation, and whether the pregnancy was planned or not.

Study population and study period

Data cover the period from 1 November 2000 to 28 February 2002, which corresponds to a total of 22 291 enrolments. We chose this study period because a new enrolment form was implemented in April 2000, which improved the way of recording dosage and period of use of dietary supplements; by November 2000 and onwards nearly all women were recruited with this new form. Women who completed the registration form before they reached the 6th week of gestation were not eligible for these analyses, and were excluded (291, 1.3%). Of the remaining, 532 pregnancies (2.4% of 22 000) ended as abortions before the first telephone interview, and 3173 (14%) did not take part in the interview for other reasons (signed out of the study, lost contact, etc.). For the women who were not interviewed no information on confounders was available. In total, 18 294 women completed the first telephone interview.

Dietary supplements

Information on the content of nutrients in dietary supplements derived from the Danish Veterinary and Food Administration, the Danish Medicines Agency, from producers of dietary supplements and from the Internet. All pieces of information were entered into a database; information on more than 1200 supplements was collected. Information from the enrolment form on dietary supplement use was merged with the database containing all the supplements to obtain information on nutrient content. Folic acid in dietary supplements is derived from single folic acid tablets, multivitamin tablets, and vitamin preparations specially made for pregnant and lactating women. Contributions from all kinds of supplements were summed.

Definition of compliance with the recommendation

For the purposes of the present analysis, a full complier with the recommendation was defined as an individual who had taken a supplement of at least 80% of the recommended daily dose, i.e. 320 μg folic acid per day, from 4 weeks prior to the date of the last menstrual period until gestation week 6. This time window is referred to as the 'compliance period' in the text.

Potential risk factors for non-compliance

The association between use of folic acid supplements and the following variables was studied: parity (primiparous vs. multiparous), age of woman (<19 years, 20–24 years, ≥ 25 years), body mass index (BMI; <30 vs. ≥ 30 kg m^{-2}), smoking during pregnancy (never vs. ever), having a husband/partner (yes vs. no) and job description (manager, self-employed, long education, medium education, office/sales and services, craftsman/gardener, unskilled worker, student and unemployed/leave).

Information events

A series of information events was held in 2001, consisting of articles published in newspapers, on home pages and in leaflets by the Danish Veterinary and Food Administration. The events are listed in Table 1.

Statistics

Investigating which factors were involved in determining use of folic acid was done by means of logistic regression analysis. The dependent variable was use of folic acid according to the described criterion (yes/no). Several confounders were included in the models. The independent factors were parity (primiparous vs. multiparous), BMI (<30 vs. $\geq 30\,kg\,m^{-2}$), mother's age (<19, 20–24 and ≥ 25 years), smoking during pregnancy (ever/never), husband/partner and job description. By including the background variables in the models, any potential confounding of the results is also adjusted for. All analyses were done separately on women with planned, partly planned and unplanned pregnancies; only results for the group of women with planned pregnancies are shown. The results are shown as odds ratios and 95% confidence intervals. Analyses were carried out in SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

Time trend analyses

To study the time evolution, we monitored the weekly proportion between the number of full compliers and all registrations:

Full compliers = [(number of full compliers)/(number of all registrations)] per week.

To identify changes over time we employed, besides standard tests, the CUSUM (cumulative sum) plot. The CUSUM plot is a type of control chart used to monitor small, sustained shifts in the mean of a process over time[15,16]. This chart plots the cumulative sum of the deviation of the ith observation from the process mean value over time, μ:

$$C_i = \sum (X_k - \mu) \quad (k = 1, 2, \ldots, i; \;\; i = 1, 2, \ldots, n).$$

As long as the process remains centred at μ (i.e. X_k varies around the mean), the CUSUM plot will be around zero. If the observations shift downward (i.e. X_k is smaller than μ over a given time interval), the plot will also drift downwards and vice versa.

Table 1 List of the information events that took place during the study period to improve knowledge of folic acid (from the Danish Food Directory)

Date	Event
18/07/2001	Article on home page concerning children and pregnancy (www.voresborn.dk)
22/07/2001	Article in weekly national newspaper. Distributed to all households free of charge
23/07/2001	Article in the major Danish daily newspaper
24/07/2001	Information on folic acid on health-related home page
24/07/2001	Leaflet available to all pharmacies
16/09/2001	Recommendation on use of folic acid on front page of advertisement from the major health drugstore ('Matas') including free samples of folic acid supplements. Distributed to all households
01/10/2001	Leaflets available at doctors' surgeries, gynaecologists and hospitals in Denmark
01/11/2001	Issue discussed on a health programme on national television

Results

For the whole period, 14% of the women complied with the recommendations as defined above, while 40% did not take any folic acid at all; the remaining 46% used folic acid at some stage periconceptionally, but were not full compliers according to the applied definition.

Folic acid use increased with increasing gestation week (Table 2); an increase was seen particularly around the point in time when pregnancy can be established with pregnancy tests, i.e. from gestation weeks 5–7, but also to some extent around the time of conception.

The proportion of women who stated that their pregnancy had been planned, not planned or partially planned was 76.3, 12.1 and 11.6%, respectively. There was a substantially higher proportion that followed the recommendation among planners (16.4%) than among women whose pregnancy was not planned (3.3%, Table 3).

Time trend analyses

Figures 1–3 refer to women who planned their pregnancies. There was a general impression that the proportion of compliers increased over time, and this was confirmed when a simple linear regression for the time trend was applied (Fig. 1); the regression coefficient was 1.2% per week, which differed from 0 at $P < 0.001$. By the end of the period, 22.6% of the women fully complied with the recommendation.

When the period was divided simply according to the date of the first information event (22 July 2001), the weekly proportion of compliers was substantially higher in the second than in the first period (19% vs. 14%, $P < 0.0001$ for chi-square test). Figure 2 represents the change in time of the weekly proportion of full compliers (planned pregnancies). The vertical bars on the x-axis mark the timing of the information events (given in Table 1), while the mean proportion of compliers for the

Table 2 Use of folic acid from 4 weeks before to 6 weeks after the last menstrual period: the whole study period

Gestational week	0 μg day^{-1}		1–319 μg day^{-1}		320 μg day^{-1} or more	
	n	%	*n*	%	*n*	%
Week −4	15 169	69.0	3109	14.1	3722	16.9
Week −3	15 625	71.0	2913	13.2	3462	15.7
Week −2	15 311	69.6	3011	13.7	3678	16.7
Week −1	15 180	69.0	3044	13.8	3776	17.2
Week 1	14 087	64.0	3327	15.1	4586	20.8
Week 2	13 893	63.2	3364	15.3	4743	21.6
Week 3	13 477	61.3	3410	15.5	5113	23.2
Week 4	12 493	56.8	3523	16.0	5984	27.2
Week 5	10 946	49.8	3701	16.8	7353	33.4
Week 6	9738	44.3	3763	17.1	8499	38.6

Table 3 Number and percentage of women complying with the recommendations

		320 μg day^{-1}		0 μg day^{-1}		Other users	
Pregnancies	*n*	*n*	%	*n*	%	*n*	%
All	22 000	2962	13.6	8850	40.2	10 188	46.3
Planned	13 952	2291	16.4	4885	35.0	6776	48.6
Partly planned	2221	125	5.6	1095	49.3	1001	45.1
Not planned	2116	69	3.3	1302	61.5	745	35.2

whole period (November 2000–February 2002) is plotted as a horizontal line. There is an increase in compliers during the last part of the period, but it is difficult to assess when the increase started. It is interesting to note that after August 2001 the majority of the points lie above the average, while before that date most of the points are below the average.

Figure 3 represents the CUSUM plot. The plot is much smoother than that in Fig. 2 and in July–August 2001 there is a remarkable inversion in the slope of the curve (it is worth mentioning that the first event of the information strategy took place in late July 2001, see Table 1). The downward drift in the plot prior to July 2001 is due to the fact that, until then, the weekly ratio of full compliers was systematically smaller than the mean value. The inversion and the following upward drift of the CUSUM plot can be explained by the fact that, after that date, the weekly proportion of full compliers was consistently above the average (see Fig. 2). The upward drift of the CUSUM plot starting in mid-summer 2001 gives further indication for an increase in the proportion of compliers following the beginning of the information campaign.

Among non-planners (Figs 4–6), no increase could be detected at all in the weekly proportion of women using folic acid supplements. The linear regression (Fig. 4) resulted in a regression coefficient of -9.68×10^{-5}% per week ($P = 0.591$), and both the full compliers ratio and the CUSUM chart did not reveal any systematic changes in the proportion during the study period (Figs 5 and 6). It can be speculated that some changes occurred in the period July–November 2001, but both Fig. 5 and Fig. 6 indicate rather unstable behaviour and the association between the peaks of the graphs to any systematic change in time is not clear.

Individual factors determining compliance

Among women who had planned their pregnancy, compliance with the recommendation was positively associated with being primiparous, older than 25 years, having BMI < 30 kg m^{-2} and non-smoking. Having a husband or a partner was not associated with compliance in this group of women. After adjustment, all the factors mentioned, except for BMI, were still significantly associated with use of folic acid (Table 4). Job description was also associated with compliance. Compared with unskilled workers, all other groups except for self-employed and craftsmen/gardener had a significantly increased probability of complying; the highest odds ratio was seen in the group of women with long education,

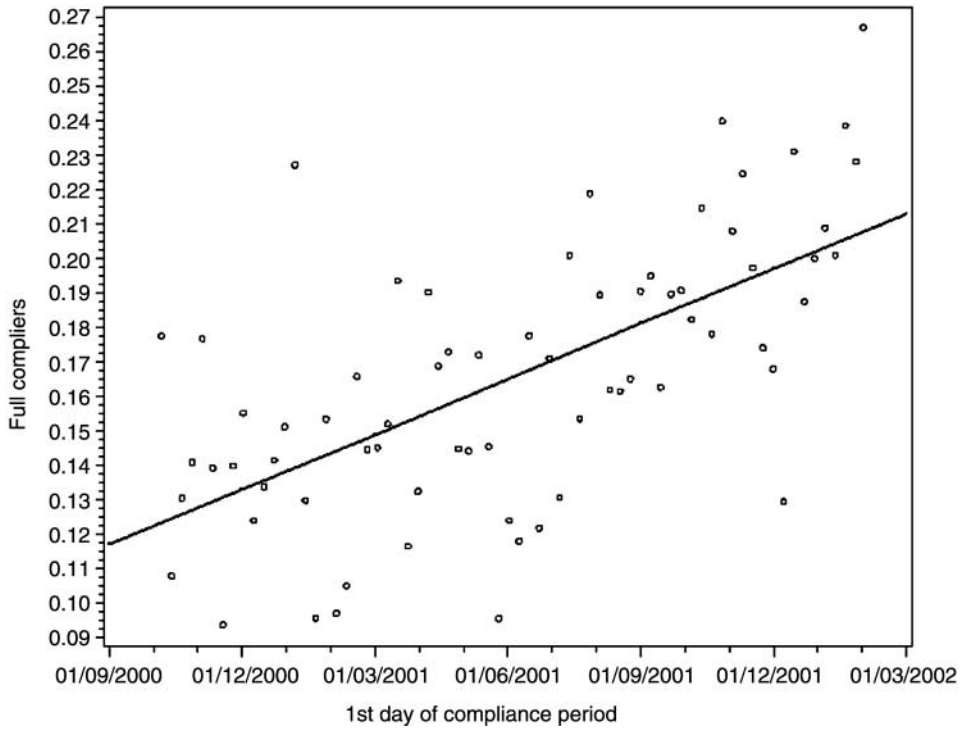

Fig. 1 Linear regression of the weekly proportion of full compliers versus the first day of the 'compliance period' (i.e. 4 weeks before the first date of the last menstrual period until gestation week 6, see Methods section) for planned pregnancies. The line indicates the linear fit

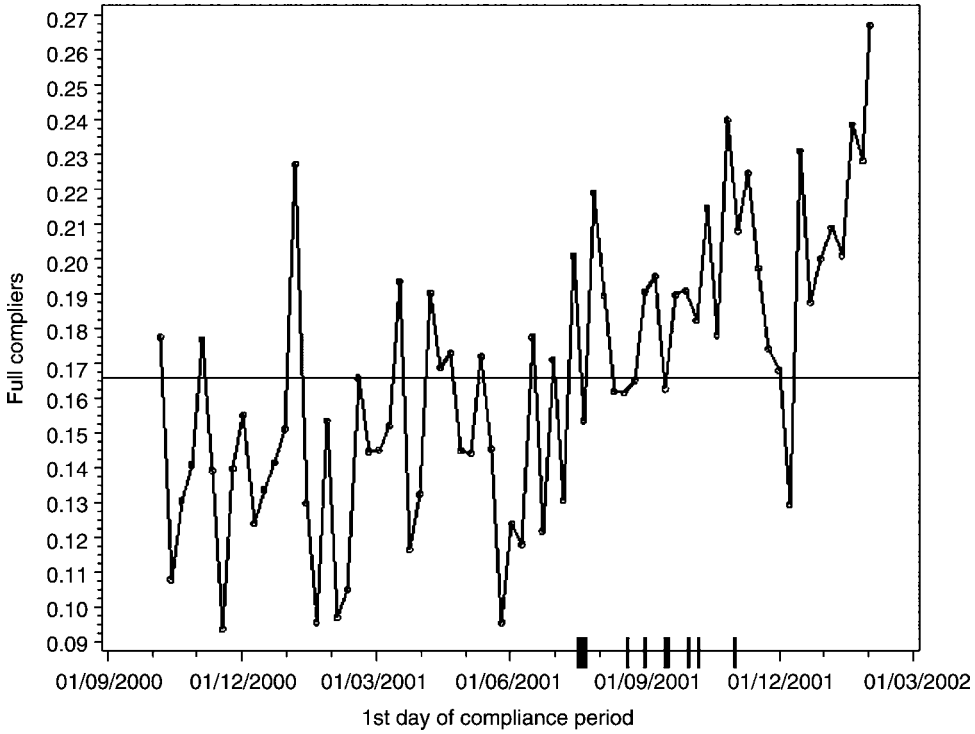

Fig. 2 Weekly proportion of full compliers plotted against the first day of the 'compliance period' (i.e. 4 weeks before the first date of the last menstrual period until gestation week 6, see Methods section) for planned pregnancies. The horizontal line indicates the mean over the study time period, the vertical bars on the *x*-axis mark the dates of the information events (Table 1)

Fig. 3 Cumulative sum (CUSUM) plotted against the first day of the 'compliance period' (i.e. 4 weeks before the first date of the last menstrual period until gestation week 6, see Methods section) for planned pregnancies. The vertical bars on the *x*-axis mark the dates of the information events (Table 1)

followed by women with medium education. The associations were somewhat weakened after adjustment; except for managers, however, they were all still significant (Table 4).

Among non-planners, smoking was the only characteristic that was associated with compliance in the univariate model; the association was weakened but still significant in the multivariate analyses. A higher proportion of compliers was seen among self-employed, before and after correction for confounders. No other statistically significant association between job description and compliance was seen (results not shown).

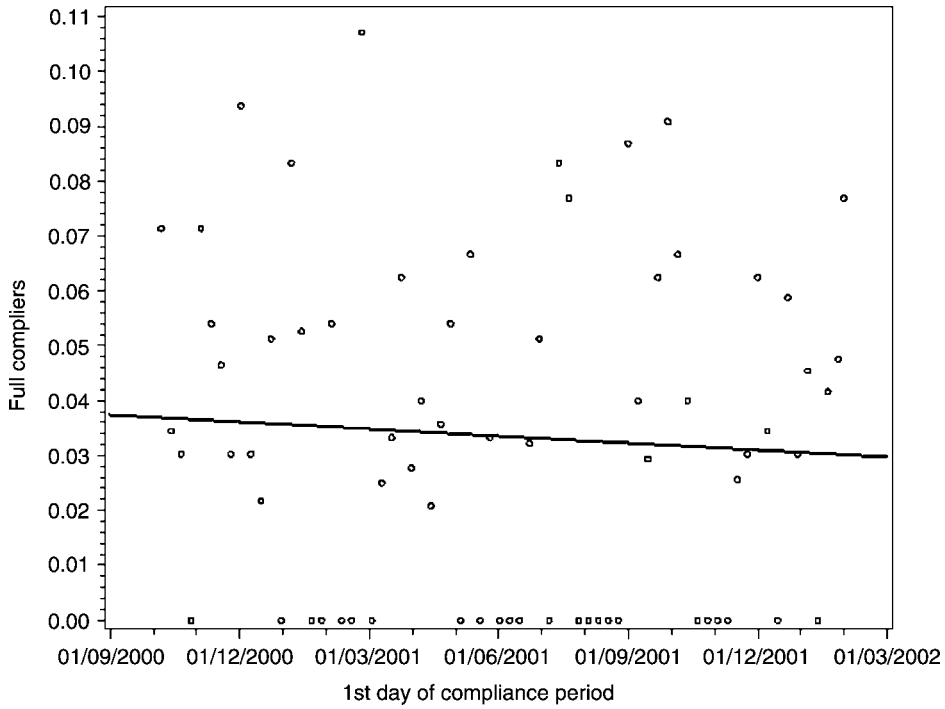

Fig. 4 Linear regression of the weekly proportion of full compliers versus the first day of the 'compliance period' (i.e. 4 weeks before the first date of the last menstrual period until gestation week 6, see Methods section) for unplanned pregnancies. The line indicates the linear fit

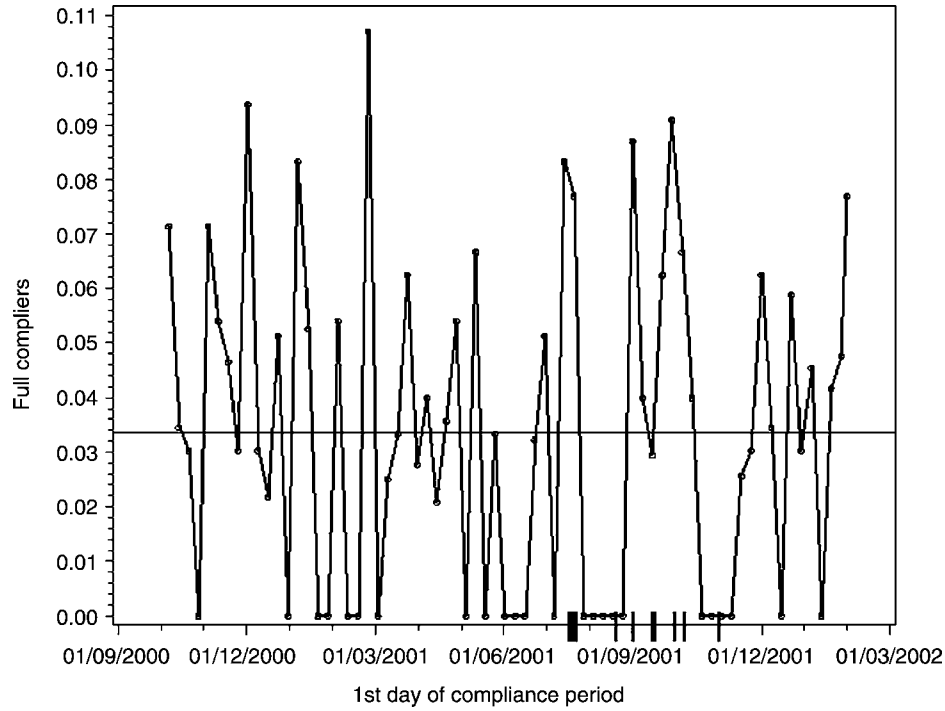

Fig. 5 Weekly proportion of full compliers plotted against the first day of the 'compliance period' (i.e. 4 weeks before the first date of the last menstrual period until gestation week 6, see Methods section) for unplanned pregnancies. The horizontal line indicates the mean over the study time period, the vertical bars on the *x*-axis mark the dates of the information events (Table 1)

Discussion and conclusion

The present study shows that the information activities of the Danish Veterinary and Food Administration launched during 2001 had an effect on the use of folic acid in relation to pregnancy. The data also suggest, however, that this kind of campaign only has an effect on a very limited proportion of women who are planning pregnancy and no

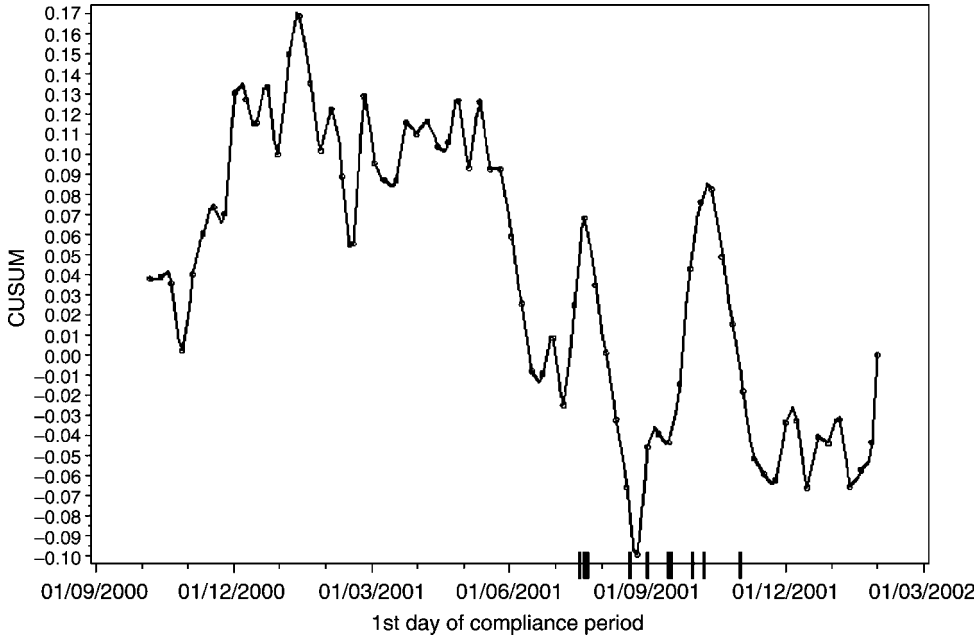

Fig. 6 Cumulative sum (CUSUM) plotted against the first day of the 'compliance period' (i.e. 4 weeks before the first date of the last menstrual period until gestation week 6, see Methods section) for unplanned pregnancies. The vertical bars on the *x*-axis mark the dates of the information events (Table 1)

Table 4 Univariate and multivariate analyses: odds ratio (OR), 95% confidence interval (CI) and *P*-value for the probability of taking folic acid as a function of a number of gestational and lifestyle factors, for women with a planned pregnancy ($n = 13\,680$)

		Univariate			Multivariate		
	n	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Parity							
Primiparous (reference group)	6968	1.00					
Multiparous	6712	0.80	0.73–0.88	<0.001	0.76	0.69–0.84	<0.001
Body mass index (kg m^{-2})							
< 30 (reference group)	12 430	1.00					
≥ 30	1250	0.87	0.74–1.03	0.090	0.93	0.79–1.10	0.389
Age (years)							
< 19	55						
20–24	1324	0.18	0.05–0.75	0.018	0.20	0.048–0.812	0.025
≥ 25 (reference group)	12 301	0.58	0.48–0.69	0.000	0.594	0.492–0.716	<0.001
Smoking during pregnancy							
Ever (reference group)	2922	1.00					
Never	10 758	1.65	1.46–1.87	<0.001	1.52	1.34–1.72	<0.001
Husband/partner							
Yes (reference group)	13 592	1.00					
No	88	1.13	0.66–1.95	0.656	1.26	0.73–2.19	0.413
Job description							
Manager	344	1.50	1.00–2.25	0.050	1.25	0.83–1.88	0.291
Self-employed	86	1.18	0.58–2.40	0.654	1.02	0.50–2.08	0.962
Long education	2139	2.37	1.77–3.17	<0.001	1.89	1.40–2.54	<0.001
Medium education	3859	2.00	1.50–2.65	<0.001	1.63	1.22–2.18	0.001
Offices, sales and services	4163	1.46	1.10–1.95	0.010	1.31	0.98–1.76	0.063
Craftsman, gardener	289	1.17	0.75–1.84	0.494	1.11	0.70–1.74	0.658
Student	1085	1.87	1.37–2.57	<0.001	1.68	1.22–2.31	0.001
Unemployed/leave	1159	1.63	1.19–2.23	0.003	1.59	1.15–2.19	0.004
Unskilled (reference group)		1.00					

effect at all on use of folic acid among women not planning to get pregnant. Furthermore, the data suggest that women of young age, with poor education and smokers (who may represent a group with general risk behaviours) were less prone to comply with the recommendation; similar patterns have been observed elsewhere[17]. These results may have important implications for future policies for the prevention of NTDs in Denmark.

The main strengths of this study are its size and data quality. To our knowledge, the study is the largest survey of periconceptional use of folic acid supplements conducted

in any country so far. The fact that women at around weeks 8–10 of gestation were asked to report their use of food supplements in the periconceptional period, means that they are likely to have had good recall of which supplements they had taken and of when they had taken them.

During the study period, 30–40% of all pregnant women in Denmark were recruited for the DNBC[14]. Of these, 14% did not complete the first telephone interview. It is therefore possible that the study sample is not representative for all pregnant women in Denmark. However, it seems unlikely that this could have affected the conclusions substantially. The participants in the DNBC are probably biased towards a more health-conscious group of women than the background population and the proportion of non-compliers is therefore likely to be lower than in the general population. In addition, the time pattern identified in the proportion of compliers does most likely reflect true changes occurring in the general population, since the recruitment rate was stable during the whole study period. Finally, although a selective recruitment may have resulted in biased estimates of the strength of the associations between compliance and individual factors in the women, it would seem unlikely that this could influence the direction of the estimates of association.

It can be concluded that alternative and more effective strategies are necessary if the majority of the Danish population is to benefit fully from the knowledge that folic acid can prevent NTDs. It should be taken into account that, for at lot of women planning to get pregnant, it is difficult to follow a recommendation of taking folic acid from the beginning, as that point in time may not be well defined. Future strategies should not only target vulnerable groups, such as the less educated and the young, but also women who get pregnant without planning this. The only possible way to reach the last group may be through fortification of foods with folic acid.

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V.K.K., I.O.-B., T.B.M. and S.F.O. were all involved in generating the data for the study. S.F.O. initiated the present analyses. V.K.K. was responsible for the interpretation of data on dietary supplements and for the logistic regression analyses. I.O.-B. was responsible for the time trend analyses and the figures. V.K.K., I.O.-B and S.F.O. together wrote the first draft of the paper. L.B.R., T.B.M. and K.F.M. contributed to the statistical analyses, the interpretation of the results and in the writing of the paper.

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