Prevention

Prevention of neural tube defects:

Periconceptional folic acid supplementation

defects

Folic acid

ntation

Karin M. van der Pal - de Bruin

PREVENTION OF NEURAL TUBE DEFECTS:
Periconceptional folic acid supplementation.

Stellingen

behorend bij het proefschrift

Prevention of neural tube defects:
periconceptional folic acid supplementation

1. Eén enkele voorlichtingscampagne is niet voldoende om het gewenste niveau van foliumzuurgebruik te bereiken.
   Dit proefschrift

2. Gehoord hebben van foliumzuur wil nog niet zeggen dat foliumzuur ook wordt gebruikt. Laat staan gedurende de aanbevolen periode.
   Dit proefschrift

3. Op populatieniveau is de verhoogde inname van foliumzuur door vrouwen met zwangerschapswens nog niet bewezen effectief, maar naar het lijkt zijn we op de goede weg.
   Dit proefschrift

4. Bij het vergelijken van perinatale sterfte tussen landen dient rekening gehouden te worden met zwangerschapsafbrekingen vanwege aangeboren afwijkingen.
   Dit proefschrift

5. Periconceptional intake of 400 μg of folic acid daily can reduce the risk of neural tube defects in areas with high rates of these defects and in areas with low rates.
   N Engl J Med 1999;341:1485-1490

6. Medicalisering van de zwangerschap door het gebruik van foliumzuur rond de conceptie staat in geen verhouding tot het medicaliserend effect van systematische prenatale diagnostiek.

7. Het niet financieren van adequate monitoring is een gemiste kans om het gevoerde gezondheidsbeleid ten aanzien van de preventie van neuralebuisdefecten te evalueren.

8. Bij kinderwens zou, voorafgaand aan de zwangerschap, advisering over leefstijlgewoonten tijdens de zwangerschap net zo vanzelfsprekend moeten zijn als het bezoek aan het consultatiebureau met een pasgeborene.

9. Het bevorderen van gezond gedrag bij specifieke groepen vereist tijd en continuïteit.
   Tijd voor gezond gedrag, RIVM 2002

10. Health is such an important issue. It deserves the hard sell – to be marketed with the verve and commitment usually applied to encouraging people to spend money on fizzy drinks.
    Lancet 1998;351:687.

11. Hoe treurig kennis te hebben als je er niets mee kunt.
    Sophocles (496 voor Chr), uit Oedipus Rex, regel 316.

Leiden, 30 oktober 2002

Karin M. van der Pal-de Bruin

PREVENTION OF NEURAL TUBE DEFECTS:
Periconceptional folic acid supplementation.

PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van de Rector Magnificus Dr. D.D. Breimer,
hoogleraar in de faculteit der Wiskunde en
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volgens besluit van het College voor Promoties
te verdedigen op woensdag 30 oktober 2002
te klokke 15.15 uur

door

Karin Maria van der Pal – de Bruin

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PROMOTIECOMMISSIE

Promotor	:	Prof. dr. S.P. Verloove-Vanhorick
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		Dr. A.L. den Ouden
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Overige leden	:	Prof. dr. M.H. Breuning
		Prof. dr. M.P. Springer
		Prof. dr. J.M. Wit

'All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action it appears to demand at a given time'.

Bradford Hill, 1965.

Voor Jack, Femke en Manouk

Cover design: Jaap van der Plas

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CONTENTS

Chapter 1

Introduction

Background

In the Netherlands, approximately 2.5% of newborns – about 5,000 babies per year – are born with a congenital anomaly.[1] Nowadays, due to the declining incidence of infectious diseases and malnutrition, congenital anomalies are an important cause of perinatal death, constituting a large proportion of the perinatal mortality rate.[2] The impact of congenital anomalies in terms of total foetal and neonatal mortality is even larger than visible in the perinatal mortality rate only. As antenatal screening can lead to pregnancy termination before a pregnant woman reaches the lower registration threshold of perinatal death, a number of deaths are never included in national statistics. In many cases continuation of the pregnancy would have led to the birth of a non-viable infant and thereby have led to an increase of perinatal mortality.

Neural tube defects

Neural tube defects are among the most common birth defects contributing to infant mortality and serious disability. This term refers to all disorders caused by insufficient closing of the neural tube, the origin of the neural system, which closes in the fourth week after conception. Most common are spina bifida, a defect of the spinal cord that has two forms, i.e. open or closed, and anencephaly, an absence of brain. Neither anencephaly nor severe cases of spina bifida are compatible with life. At least 27% of children registered with spina bifida die within the first month of life.[3] Morbidity is generally severe, and varies from limited handicaps through paralysis of the lower part of the body to anatomical deformation, hydrocephalus and incontinence.[3] Individuals with neural tube defects often need extensive surgical treatment and care during their whole life. This usually entails severe lifelong consequences for both child and family.

While the etiology of neural tube defects is still not fully understood, it is assumed to be multifactorial, with genetic and environmental factors (such as ethnicity, nutritional intake and use of medication) both playing a role.[4,5] However, the underlying mechanism is not sufficiently clear. One of those hypothesised is hyperhomocysteinuria, for which a mutation

in the methylenetetrahydrofolate reductase (MTHFR) gene is seen as one of the causal factors [6-8]. Research into such mechanisms is ongoing.

The birth prevalence of infants with a neural tube defect varies from one geographical region to another. Certain European countries and regions, such as the UK and Ireland, report a relatively high birth prevalence; in others, such as France and Belgium, it is much lower. In the Netherlands, the birth prevalence of neural tube defects lies roughly in the intermediate. [9] In many countries the prevalence of these defects has slowly decreased over recent decades, apparently because of changes in nutritional intake, and also partly thanks to the implementation of antenatal screening. [10]

The Netherlands have no national database on neural tube defects. Newborns with these defects are registered in several national and regional databases, none of which is complete. On the basis of regional data collected for EUROCAT, a programme for the epidemiological surveillance of congenital anomalies in Europe, it is estimated that approximately 260 children are born annually with such a defect, a figure that includes 125 live births with spina bifida.[9]

Folic acid and the prevention of neural tube defects

The first suggestion of a possible correlation between the prevention of neural tube defects and the intake of folic acid (vitamin B11) was made in 1965. [11] Several case-control studies of multivitamin use (including folic acid) and neural tube defects were carried out in the 1980s and 1990s.[12-17] Most of these studies showed that, if taken during the periconceptional period, multivitamins containing folic acid had a strong preventive effect. In a large prospective cohort study, Milunsky demonstrated a 64% reduced risk of a neural tube defect in the offspring of women who used a multivitamin containing folic acid during the first six weeks of pregnancy (compared to those who did not).[14] More importantly, the risk reduction was 73% in women who used multivitamins containing folic acid, and only 7% in women who used multivitamins that did not include folic acid. This study strongly suggests that folic acid use reduces the risk of a neural tube defect in offspring.

Recently these findings were enhanced by a large non-randomised controlled trial in China.[19]. All women in one northern and two southern provinces in China who were registered with a pregnancy-monitoring system and who were either pregnant or preparing for marriage were invited to take supplements containing 400 μg of folic acid. The trial involved their taking such supplements every day throughout the first trimester of pregnancy; controls were women who refused to take supplements, or who were already pregnant at the time of registration. In the northern region, where there was a high baseline rate of neural tube defects, a 79% reduction in the risk of neural tube defect was associated with folic acid use during the periconceptional period. In the south, which had much lower baseline rates of neural tube defects, there was a 41% reduction in risk. For women who were compliant with folic acid, the geographically-based difference between north and south in the occurrence of neural tube defects disappeared completely. In addition, the study resulted in an overall reduction in neural tube defects from 5.5/1,000 pregnancies at baseline to 3.3/1,000 during the intervention period in the north, and from 1.0/1,000 at baseline to 0.8/1,000 during the folic acid intervention in the south.

The preventive effect of multivitamins containing folic acid with regard to the risk of neural tube defects was also demonstrated in several intervention studies. [20-25] In 1991, the MRC Vitamin study, which is a randomised controlled trial, convincingly demonstrated that daily use of 4 mg folic acid around the time of conception reduces by 72% the recurrence risk of a child with such a defect.[20] The possibility that new occurrence of neural tube defects is also reduced by folic acid was shown in the Hungarian study of Czeizel, which reported a 75% reduction in the occurrence risk. [21]

Despite some criticism on points of methodology and on the interpretation of outcomes [26,27], there appears to be general agreement that folic acid is effective in preventing neural tube defects, both in high and low risk populations. [28] From the point of view of the primary prevention of such defects, this is important, since most cases of neural tube defects occur in the general population. [5]

Nonetheless, some questions remain. One is that the minimum effective dose required for the prevention of first occurrence and recurrence is unknown. Second, studies of the possible adverse effects of high-dose folic acid are needed. It is known that high-dose folic acid can mask vitamin B12 deficiency, a condition that is most common in the elderly and may result in severe neurological damage. The masking of vitamin B12 deficiency is important if fortification of food with folic acid is under consideration, and if there is thus a chance that the general population will be exposed to a higher folic acid intake. Fortification of food with folic acid may be considered in the prevention of neural tube defects but will be of more importance if folic acid is proved to reduce the risk of cardiovascular disease in adults. At present, the safe upper intake level is set at 1,000 μg for adults. In addition to the unresolved issues associated with vitamin B12 deficiency, it is not known whether high intake of folic acid may have teratogenic effect in the foetus, or lead to other adverse foetal or maternal outcomes. Similarly, high folic acid intake may stimulate seizure activity.[29] Increased folic acid intake during pregnancy has also been associated with an increase in twin births [30] and a higher rate of miscarriages [31], although the latter has not been confirmed.[32]

Prevention strategies

Since the early 1990s, many countries have started to focus on the prevention of neural tube defects in the general population, and many national Public Health Authorities have recommended periconceptional folic acid use.[33] Because it has generally been assumed that it is insufficient to increase intake of folates through dietary sources alone, two strategies for the primary prevention of neural tube defects in the general population have been developed, namely supplementation and fortification.

The first strategy, supplementation, involves taking folic acid daily in tablets during the period leading up to conception and into the first months of pregnancy. The recommended dose can be targeted, and tablets need to be taken only for a limited time. The tablets are relatively cheap, and are generally available in pharmacies and drugstores, with or without prescription. The common recommendation to women in the general population is to take a

daily 400-microgram supplement from four weeks before conception until eight weeks afterwards. In many countries, supplementation strategies focus on women planning pregnancy, whereas, in the US and UK, all women of reproductive age are recommended to take extra folic acid because of the high number of unplanned pregnancies. The reduction expected for neural tube defects is 50-70%, which can be achieved only if all women planning pregnancy use folic acid throughout the entire recommended period.[5]

The second strategy, fortification, consists of adding essential nutrients to food for the purpose of preventing or correcting a demonstrated deficiency in the population or specific population, irrespective of whether it is normally contained in the food. This can take place either on an obligatory basis, or voluntarily. With the exception of the Netherlands, Sweden, Finland and Norway, most countries allow the fortification of breakfast cereals, flour or special products for women planning pregnancy.
Compulsory folic-acid fortification of staple food occurs in Bolivia, Columbia, Venezuela, South Africa, New Zealand, Chile and the USA.[34] In the USA, the addition of folic acid to flour, rice, pasta and cereals became compulsory in 1998. The estimated increase (about 100 μg) was less than the recommended daily dose, but considered safe enough to avoid side effects. In addition, supplementation with tablets is still recommended, and the addition of vitamin B12 to prevent vitamin B12 deficiency is being debated.[35] The reduction in neural tube defects cases is expected to be about 20%. [36]
The UK has considered the recommendation that grain should be fortified to a level of 240 microgram per 100g [37,38], which is expected to reduce neural tube defects by 41%. Recently the UK Board of the Food Standards Agency decided against mandatory folic acid fortification. [39]

The Dutch situation

In November 1993, a Joint Committee of the Health Council and Food Council of the Netherlands recommended folic acid supplementation for all women planning pregnancy as legislation did not yet allow folic acid fortification. [5] To reduce the risk of a neural tube defect, a supplementary dose of 400 μg folic acid per day was advised. This advice was

adopted by the Chief Inspector of Health and all health-care professionals were informed by letter.[40]

To stimulate the implementation of the recommendation, a national health promotion campaign was initiated by the Ministry of Health and carried out by the Nutrition Bureau and the Dutch Alliance of Parent and Patient Organisations of genetic and non-genetic congenital disorders.[41] The national Folic Acid Campaign involved a two-part strategy, one aiming at health-care professionals, and the other at women planning pregnancy.
Initially, the campaign focused on the health-care professionals, e.g. general practitioners, midwives, obstetricians and pharmacists, who were informed about folic acid through their professional associations, through publications in national medical journals, and in personal correspondence before the campaign was implemented. In this way they were provided with educational materials on advising women about the use of folic acid.

Following the first phase of the campaign, the extension of the campaign to include women planning pregnancy came in the autumn of 1995. As such women are 'indistinguishable' from the general population, a mass media approach was chosen to inform them. The slogan of the campaign was 'Folic acid – already before you're pregnant'. A variety of sources were used to draw the attention of women planning pregnancy to a brochure about folic acid: they comprised advertisements in newspapers and women's magazines, plus TV and radio commercials, and posters in the waiting room of GPs, midwives and obstetricians. The brochure in question was available free at pharmacies, and gave full information about neural tube defects and recommendations on the perinatal use of folic acid. The aim was to inform at least 70% of women planning pregnancy, and to achieve proper folic acid use in 65% of women who had heard of it.[42]

An additional local campaign was conducted in two regions in the south of the Netherlands to inform women with a low socio-economic status about folic acid. Such women appear to be at greater risk of giving birth to a child with a neural tube defect, and are generally more difficult to reach than women with a high socio-economic status. [43] In two regions, local

health-care professionals were provided with additional information on the promotion of folic acid use; this information was disseminated by letter and at general meetings of the local professional association. The local media were also used to provide information about folic acid to women who wished to conceive. Furthermore, a poster about folic acid use was used as an advertisement at bus stops, and information was provided at a special stand during a regional pregnancy information market.

Aim and research questions

The aim of this thesis is to investigate the effect of the recommendation concerning periconceptional folic acid use and the Folic Acid Campaign on the prevention of neural tube defects. Outcome measures are awareness and use of folic acid, and the prevalence of neural tube defects in the Netherlands. The thesis discusses the following research questions:

1 Does antenatal screening for congenital anomalies in general have an impact on perinatal mortality?

2 Was public health education on folic acid in the Netherlands effective in increasing both knowledge and use of folic acid, and was this the same for women of all educational levels?

3 Does increased folic acid intake result in a lower prevalence of neural tube defects in the Netherlands?

Outline of the thesis

The aim of this thesis is to investigate the implementation and effectiveness of periconceptional folic acid use on the primary prevention of neural tube defects in the Netherlands. **Chapter 2** argues that, due to antenatal screening and the subsequent termination of pregnancy, the impact of congenital malformations in terms of foetal and neonatal mortality is underestimated.

The results of the Dutch Folic Acid Campaign are described in **chapters 3-6**. **Chapter 3** describes the attitudes of general practitioners and midwives to folic acid use. To aid understanding of folic acid use by Dutch women, **Chapter 4** presents the developed behaviour model, which compares to the central constructs of the Theory of Reasoned Action of Fishbein and Ajzen. This is followed in **chapter 5** by the main results of the evaluation of the national and local Folic Acid Campaign. **Chapter 6** focuses on differences in awareness and folic acid use by women of different levels of education.

In **chapters 7 and 8**, the national prevalence of neural tube defects in the 1989-1998 period is estimated, and the relationship between this and increased folic acid use in the same period is examined. **Chapter 7** presents the methodology used to estimate the national prevalence of neural tube defects; **chapter 8** presents the prevalence from 1989 to 1998, and discusses the effect of folic acid use.

In **chapter 9** the results of this thesis are discussed in relationship to potential avenues for the continuation of primary prevention of neural tube defects.

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Chapter 2

The influence of antenatal screening and termination of pregnancy on perinatal mortality rates.

K.M. van der Pal-de Bruin, W. Graafmans, M.C.J. Biermans, J.H. Richardus, A.G. Zijlstra, J. Reefhuis, J.P. Mackenbach, S.P. Verloove-Vanhorick

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Abstract

Objectives This study concerns the possible effect of practice of antenatal screening of congenital anomalies followed by termination of pregnancy on the perinatal mortality between European countries.

Methods Data of 9 region-specific EUROCAT-registries from 5 European countries were used to compare the pregnancy termination rate and perinatal mortality due to congenital anomalies between the registries. The impact of pregnancy terminations on the perinatal mortality rate was estimated using a calculated lethality for each congenital anomaly in the hypothetical case that no pregnancy terminations had been performed and was expressed in the 'natural' perinatal mortality rate.

Results There are large differences between the EUROCAT-registries in the number of pregnancy terminations for congenital anomalies. The difference between the 'natural' and regular perinatal mortality rate vary between 3.7 and 14.1 per 10.000 live births and stillbirths. The difference is greater in regions where antenatal screening is more common than in regions where this is not common.

Conclusion Differences in practice of antenatal screening and termination of pregnancy of congenital anomalies contribute to the variations in overall perinatal mortality rate between European regions and countries.

Introduction

Over the last decades advances in medical technology, positive changes in socio economic conditions, and improvements in maternal health status have made significant contributions to the reduction in perinatal mortality rates worldwide. Nowadays, due to the decrease in infectious diseases and malnutrition, congenital anomalies are an important cause of perinatal death. The rate of infant deaths due to lethal congenital anomalies has remained more or less stable and the percentage of infant deaths attributable to lethal congenital anomalies has been increasing over time. [1,2] Recently, Wen et al. reported that in Canada the infant mortality due to lethal congenital anomalies decreased from 3.11 per 1,000 live births in 1981 to 1.89 per 1,000 live births in 1995. [3,4] Thus suggesting that patterns of lethal congenital anomaly-attributed infant mortality may have changed in recent years, mainly because of advances in perinatal care like antenatal diagnosis. [3,4] Also in the Netherlands a decline in mortality due to congenital anomalies was reported which was explained by better detection, diagnostics, treatment and prevention of congenital anomalies. [5]

In many countries antenatal screening for congenital anomalies has increased and as a result the number of pregnancy terminations following antenatal screening has risen. Pregnancy termination following prenatal diagnosis of trisomy 21 and anencephaly are estimated 92% and 82% respectively based on a systematic review including studies from different countries in the US, UK and Europe. [6] Pregnancy terminations conducted before the lower limit of registration thresholds for perinatal death are not included in national statistics. Because these pregnancy terminations are performed for such reasons as serious illness in the foetus, it is reasonable to assume that many of these foetuses would have died perinatally if the pregnancy had continued. Therefore, the perinatal mortality due to congenital anomalies will be lower in a country with a high proportion of pregnancy terminations following antenatal screening. In consequence, differences between countries in standard practice of antenatal screening and termination of pregnancy can result in differences in perinatal mortality rates.

The EuroNatal study was started in 1997 to study the background of differences in perinatal mortality in various European countries and to determine the validity of national perinatal

mortality as an outcome indicator for the quality of antenal and perinatal care. [7] The present paper is related to the second objective of the EuroNatal study that investigates different types of risk factors of perinatal mortality amongst European countries. This study concerns the possible effect of practice of antenatal screening of congenital anomalies followed by termination of pregnancy on the perinatal mortality rate between European countries.

Material and methods

Data from the European Registration of Congenital Anomalies (EUROCAT) were used to calculate the pregnancy termination rate of congenital anomalies and analyse the possible effect of standard practice of antenatal screening for congenital anomalies with termination of pregnancy on perinatal mortality. EUROCAT is a programme for the epidemiologic surveillance of congenital anomalies in Europe. The EUROCAT registries are population or hospital (Paris) based and cover live births, stillbirths and pregnancy termination following prenatal diagnosis of congenital anomalies. Multiple sources of information and active case finding are used to achieve more complete case ascertainment and more accurate case description than is possible in systems dependent entirely on voluntary notification of the cases.

We obtained a file from EUROCAT Central Registry with data of live births, stillbirths and pregnancy terminations from all EUROCAT registries. Data for the denominator (births) were obtained from the EUROCAT Report 7 and 7 Update. [8,9] Only the registries from countries participating in the Euronatal study were included. Furthermore reliable data should be available for the period 1991-1996 with the exception of data from the Basque Country which were only available for the period 1991-1995. The following registries met these criteria: Antwerpen (n=51,082), and Hainaut-Namur (n=76,128) (Belgium), Northern Netherlands (n=115,992) (The Netherlands), Paris (n=219,868), and Strasbourg (n=79,982) (France), Saxony-Anhalt (n=47,858), and Mainz (n=23,259)(Germany) and Basque Country (n=79,252), and Asturias (n=41,865) (Spain).

For the coding of congenital anomalies the common nomenclature and coding system of the British Paediatric Association Classification of Diseases [10] was used, which is a five-digit code being an extension of the 9th revision of the International Classification of Diseases [11].

Up to eight congenital anomalies may be coded for each baby and in addition a syndrome can be coded. The anomalies were ordered by degree of lethality within the first week after birth in consultation with EUROCAT Northern Netherlands and are presented in appendix A. The first eight anomalies were selected to analyse separately because of the high lethality of the anomaly within the first week after birth and/or the possibility of antenatal screening. These anomalies are anencephaly (ICD 740), bilateral renal agenesis and hypoplasia (ICD 753.00), trisomy 13 (ICD 758.1), trisomy 18 (ICD 758.2), hypoplastic left heart syndrome (ICD 746.7), spina bifida (ICD 741), cystic kidney disease (ICD 753.1), and trisomy 21 (ICD 758.0). The remaining categories were combined in the analysis because of their relative small numbers of termination of pregnancy. If more than one anomaly was coded, the anomaly highest in rank was chosen.

Data were available of live births, foetal deaths and pregnancy terminations. Pregnancy terminations were divided in abortions before and from 24 weeks of gestation. For the purposes of this study, it was assumed that pregnancy terminations from 24 weeks of gestation are included in perinatal mortality registers. Thus to study the impact of pregnancy termination on perinatal mortality, pregnancy terminations from 24 weeks of gestation were handled as foetal deaths in the calculation of the regular perinatal mortality and 'natural perinatal mortality' i.e. the perinatal mortality that would occur if no medical interventions would take place.

The pregnancy termination rate for a congenital anomaly is calculated as the number of pregnancy terminations <24 weeks of gestation divided by the total number of live and stillbirths in the regions. The denominator includes live and stillbirths according to the stillbirth definition in each region for the period 1991-1996.

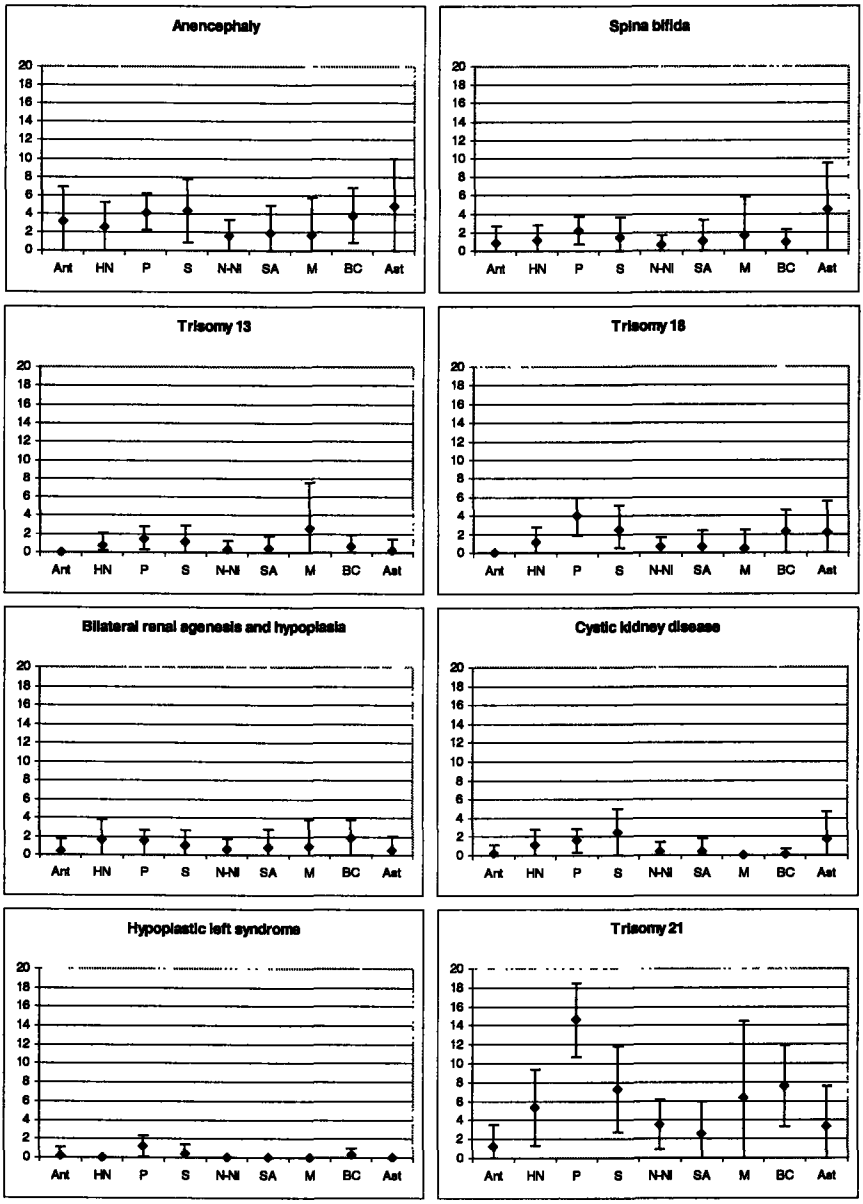
Survival of the infant in the first week after birth was used to calculate the number of deceased live-births in this time period. The percentage of missing was 0% for Northern-Netherlands, 0.1% for Strasbourg and the Basque Country, 0.2% for Paris, 2.3% for Mainz, 2.6% for Asturias, 5.8% for Antwerp, 19.7% for Hainaut-Namur and 20.9% for Saxony-Anhalt. Data about the moment of diagnosis was used to fill in the survival status in case it was unknown whether the infant had survived the first week. If the diagnosis was more than one week after birth the infant was considered to be alive one week after birth. This resulted in only a couple more cases of known survival. The number of missings about

survival of the first week is rather high in Hainaut-Namur and Saxony-Anhalt but it appeared that for the selected congenital anomalies with high lethality and/or the possibility of antenatal screening the percentage of missings was much lower and was comparable with the other registries. Therefore, it was decided to exclude live-births with unknown survival in the first week after birth as the impact on the results for the congenital anomalies of interest was considered to be marginal.

To be able to estimate the effect of pregnancy termination on perinatal mortality rates the lethality of a congenital anomaly had to be determined. If no pregnancy termination would have taken place, the pregnancy might have ended in a stillbirth, a live birth followed by neonatal death, or a survivor. The lethality was calculated by dividing the number of known live-births deceased in the first week after birth and the number of stillbirths ≥24 weeks by the total number of live and stillbirths. Live-births were included only if information on survival in the first week was available. Pregnancy terminations regardless of gestation were excluded in this calculation. The following lethality was calculated: anencephaly: 100%; spina bifida: 31.1%; trisomy 13: 61.5%; trisomy 18: 63.5%; bilateral renal agenesis and hypoplasia: 80.0%; cystic kidney disease: 16.7%; hypoplastic left heart syndrome: 64.3; trisomy 21: 8.0%.

The regular perinatal mortality rate for a congenital anomaly was calculated dividing the number of live births deceased within one week after birth and the foetal deaths affected in a EUROCAT region by the total number of live and stillbirths in that EUROCAT region. [8,9] The 'natural' perinatal mortality is defined as the perinatal mortality that would occur if no medical interventions would take place. The 'natural' perinatal mortality rate includes the number of pregnancy terminations <24 weeks of gestation for a congenital anomaly multiplied with the calculated lethality for that anomaly.

Figure 1: Pregnancy termination rate[1] before 24 weeks of gestation of congenital anomalies with 95% confidence interval by participating EUROCAT registry, 1991-1996.



Ant = Antwerp, HN = Hainaut-Namur, P = Paris, S = Strasbourg, N-Nl= Northern Nederlands, SA = Saxony-Anhalt, M = Mainz, BC = Basqque Country, Ast = Asturias

[1] Pregnancy termination rate before 24 weeks of gestation per 10.000 live births and stillbirths

Results

Figure 1 presents the pregnancy termination rate of the eight selected congenital anomalies (data are available on request). Figure 1 shows that the pregnancy termination rate varies between the registries. The Paris-registry reported the highest pregnancy termination rate for all congenital anomalies (48.4 per 10,000 live and stillbirths; 95% confidence interval: 41.3-55.5); the Antwerp registry the lowest pregnancy termination rate (9.2 per 10,000 live and stillbirths; 95% confidence interval: 2.8-15.6). Pregnancy termination for anencephaly, spina bifida and trisomy 21 are reported most frequently.

Table 1: Influence of pregnancy termination for spina bifida on perinatal mortality due to spina bifida

Registries	Deceased LB and FD [1] with spina bifida	PT [1]	New perinatal death because of spina bifida if no PT[2] had taken place	Regular PMR [3] from spina bifida	'natural' PMR [4] from spina bifida
	n	n	n		
Antwerp (B)	6	4	1.2	1.2	1.4
Hainaut-Namur (B)	20	8	2.5	2.6	3.0
Paris (F)	50	48	14.9	2.3	3.0
Strasbourg (F)	11	12	3.7	1.4	1.8
Northern Netherlands (NL)	30	7	2.2	2.6	2.8
Saxony-Anhalt (D)	2	5	1.6	0.4	0.7
Mainz (D)	1	4	1.2	0.4	1.0
Basque Country (Es)	5	7	2.2	0.6	0.9
Asturias (Es)	2	19	5.9	0.5	1.9

[1] LB = Live births; FD = foetal deaths and pregnancy terminations from 24 weeks; PT = pregnancy terminations before 24 weeks

[2] Deceased within the first week after birth assuming that if no pregnancy termination had taken place the lethality of spina bifida is 31.1%

[3] Regular PMR (perinatal mortality rate): LB and FD with spina bifida per 10,000 LB and SB in EUROCAT region

[4] 'Natural' PMR (perinatal mortality rate): perinatal mortality that would occur if no medical interventions would take place. LB, FD and PT <24 weeks of gestation with spina bifida per 10,000 live birth and stillbirths in EUROCAT region assuming that if no PT had taken place the lethality of spina bifida is 31.1%.

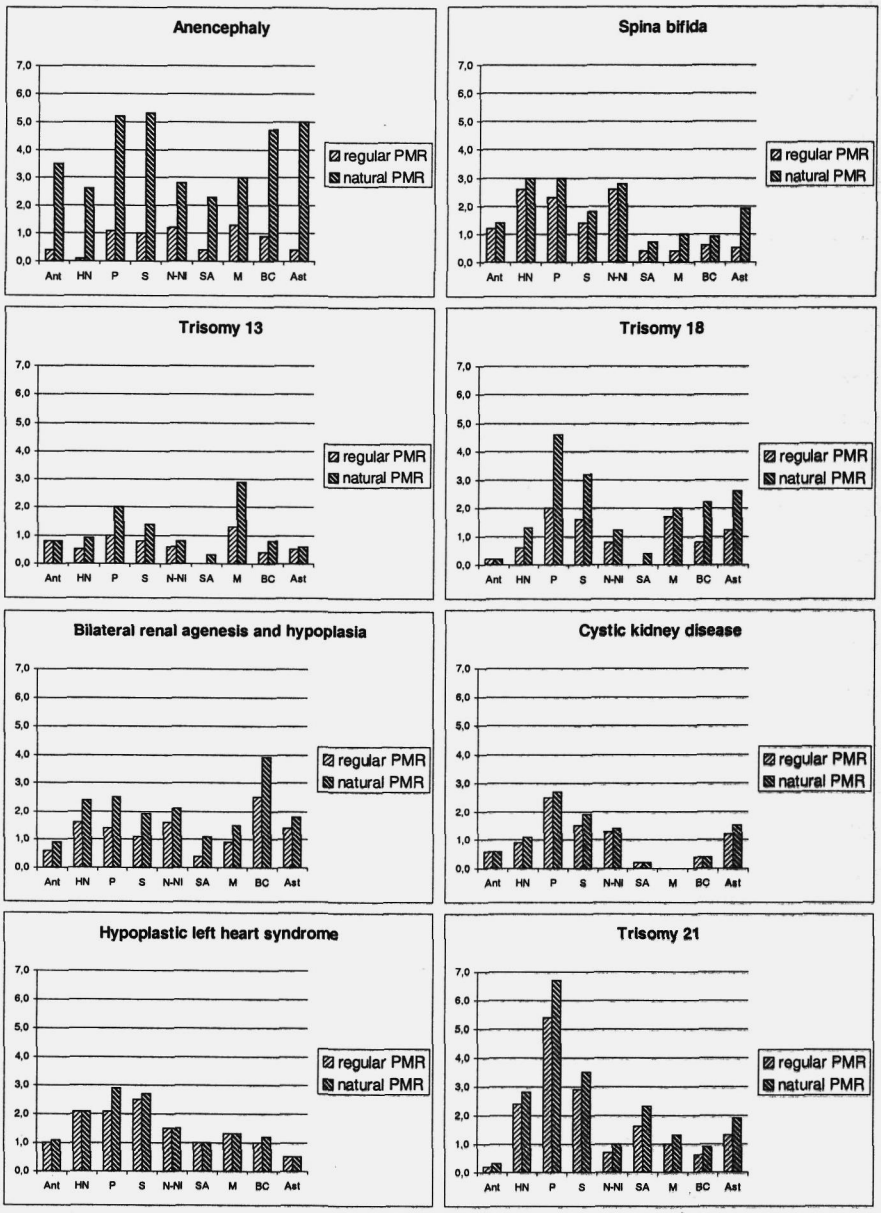
Table 1 shows the regular and 'natural' perinatal mortality rate for spina bifida only as an illustration. In the registry of the Northern Netherlands for instance, 30 cases of spina bifida died before birth or within one week after birth (2.6 per 10.000 total still born and live born infants). The 7 cases of pregnancy termination could hypothetically have led to 2.2 extra cases of perinatal mortality assuming a lethality of spina bifida of 31.1%, and thus increasing the perinatal mortality due to spina bifida from 2.6 to 2.8 per 10.000 total stillborn and live born infants.

The regular perinatal mortality rate due to spina bifida differs greatly between the registries. In Saxony-Anhalt and Mainz (Germany), and the Basque Country and Asturias (Spain) the regular perinatal mortality rate for spina bifida is very low (0.4, 0.4, 0.6 and 0.5 per 10,000 live and stillbirths respectively). Correcting for the influence of pregnancy termination, the 'natural' perinatal mortality is substantially higher than the regular perinatal mortality. The 'natural' perinatal mortality for spina bifida in Mainz (Germany) and Asturias (Spain) (1.0 and 1.9 per 10,000 live and stillbirths respectively), for instance, is more than twice the regular perinatal mortality. Due to the small number of pregnancy terminations for spina bifida there is only a small difference between the 'natural' perinatal mortality and the regular perinatal mortality for the registry of the Northern Netherlands and the registries in Belgium (Antwerp en Hainaut-Namur).

The influence of pregnancy termination on the perinatal mortality rate due to congenital anomalies is presented in figure 2 (data are available on request). For a congenital anomaly with a high lethality and the possibility of antenatal screening such as anencephaly, the difference between the regular and 'natural' perinatal mortality rate for that disease is rather big. For every registry the 'natural' perinatal mortality rate for anencephaly is at least more than twice the regular perinatal mortality rate. Although the calculated lethality of trisomy 21 during pregnancy until the first week after birth is low (8.9%), the 'natural' perinatal mortality rate does increase because of the high frequency of pregnancy termination due to trisomy 21.

Overall, the difference between regular and 'natural' perinatal mortality rate varies between 3.7 and 14.4 per 10.000 live and stillbirths. Differences between the regional perinatal mortality rates from congenital anomalies tend to diminish slightly but remain considerable in the calculated 'natural' perinatal mortality rates.

Figure 2: Regular and natural perinatal mortality rate for congenital anomalies by participating EUROCAT-registry, 1991-1996.



Ant = Antwerp, HN = Hainaut-Namur, P = Paris, S = Strasbourg, N-Nl= Northern Nederlands, SA = Saxony-Anhalt, M = Mainz, BC = Basqque Country, Ast = Asturias

Regular PMR: Perinatal mortality rate (LB and FD with congenital anomaly per 10,000 LB and SB in EUROCAT region). Natural PMR: 'natural' perinatal mortality (LB, FD and PT <24 weeks of gestation with congenital anomaly per 10,000 live birth and stillbirths in EUROCAT region, assuming that if no PT had taken place lethality as specified in method-section).

Discussion

In this article we described the effect of pregnancy terminations due to serious congenital anomalies on the perinatal mortality rate by assuming that some of the cases would have ended in perinatal death if no pregnancy termination had been performed. Assuming that no pregnancy terminations were performed was a practical decision made by the researchers and does not imply that pregnancy terminations should or should not be performed. Pregnancy terminations are not performed to decrease the perinatal mortality rate but to give pregnant women the opportunity to discontinue their pregnancy in case of a serious, life threatening congenital anomaly or to allow appropriate early interventions to be planned when a congenital anomaly is discovered at antenatal screening. The number of pregnancy terminations is very much influenced by the perinatal care policy concerning antenatal screening in each country. In some countries antenatal screening is more common than in other countries, as well as the acceptance of pregnancy terminations. We have shown that the pregnancy termination rate of congenital anomalies vary between the registries. As pregnancy terminations are performed for serious congenital anomalies with a high proportion of perinatal mortality if the pregnancy had been continued, the influence on the perinatal mortality rate due to congenital anomalies is substantial.

Our analysis is based on data from the EUROCAT programme for the period 1991-1996. [8,9] The frequency of late terminations from 24 weeks gestational age varies between the participating registries. In the registries of Paris and Strasbourg more late terminations were found than in the other registries. These late terminations were handled as foetal deaths and thus included in the regular perinatal mortality, which as a result have been overestimated. This overestimation will be larger for regions were the number of late termination is high. Furthermore the difference between the presented regular and 'natural' perinatal mortality will be smaller. Despite existing differences between EUROCAT registries, the data-collection and registration criteria are comparable for all registries and therefore allow for comparisons between the EUROCAT registries. It should be noticed that the reported pregnancy termination rate and perinatal mortality rate might not be extrapolated for the

country as a whole because the representativeness of the registries for the country may be questioned.

The effect of pregnancy termination on perinatal mortality was studied by estimating how many foetuses would have died, had the pregnancy termination not been performed. Although the lethality for a congenital anomaly may differ between countries and thus between the registries, a mean lethality combining the data of all registries was calculated. Using only information of live births with known survival may have resulted in an overestimation of the lethality since it is less likely for perinatal death to be mistakenly unregistered, than is for a live birth. But this does not seem to be a problem as the calculated lethality for most categories of congenital anomaly tends to be lower than expected compared to the literature. This is especially true for the calculated lethality of trisomy 13 being 61.5%, whereas the median survival for children with trisomy 13 is 2.5 days and 82% of these babies die within the first month. [12] Using a lower estimated lethality for a congenital anomaly will result in an underestimation of the effect. As a result the influence of pregnancy termination on the perinatal mortality rate for a congenital anomaly may be even higher than shown is this paper.

Large differences in the pregnancy termination rate until 24 weeks of gestation were found between the registries. These pregnancy terminations are not included in the regular perinatal mortality rate. For the comparison of perinatal mortality rate between countries the practice of antenatal screening and pregnancy termination should be taken into account because of the reported differences in frequency of pregnancy termination. This study shows that for regions where pregnancy terminations are less frequent, the increase to 'natural' in perinatal mortality due to congenital anomalies is lower than in regions with a high number of pregnancy terminations. Not including the cases of pregnancy termination in the perinatal mortality rate will lead to lower perinatal mortality for congenital anomalies in regions with a high rate of pregnancy terminations compared to regions with a low rate of pregnancy terminations.

Pregnancy terminations not only influence the perinatal mortality rate due to congenital anomalies but will also influence the overall perinatal mortality rate. In Finland it has been estimated that an increase in pregnancy terminations for medical reasons in the period 1985-1990 caused up to one-third of the decline in perinatal mortality. [13] We found a

decline in perinatal mortality rate due to congenital anomalies which will likely result in a decline of the overall perinatal mortality rate.

Reported perinatal mortality rates differ between countries. Graafmans et al. reported a perinatal mortality rate of 8.1 per 1,000 total births for the Netherlands. For Belgium, Germany, France and Spain the reported national statistics are 7.3, 6.4, 7.4 and 6.6 per 1,000 total births respectively. [14] The differences in overall perinatal mortality rate could partly be explained by criteria for registration and publication of perinatal deaths. Part of these differences may also be explained by differences in antenatal screening and pregnancy termination if the assumption is made that the EUROCAT registries reflect the differences in practice of antenatal screening and pregnancy termination between countries. Pregnancy terminations will result in a lower overall perinatal mortality rate and the decrease in overall perinatal mortality rate depends on the number of pregnancy terminations for medical reasons in the different countries. Differences in practice of antenatal screening and termination of pregnancy of congenital anomalies contributes to the variations in perinatal mortality rate and should be taken into account in comparisons of perinatal mortality rates between countries.

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APPENDIX A: Congenital anomalies registered by EUROCAT registries ordered by degree of lethality within the first week after birth.

1) Anencephaly (icd 740)
2) Bilateral renal agenesis en hypoplasia (icd 753.0)
3) Patau syndrome (icd 758.1)
4) Edwards syndrome (icd 758.2)
5) Hypoplastic left heart syndrome (icd 746.7)
6) Spina bifida (icd 741)
7) Cystic kidney disease (icd 753.1)
8) Down syndrome (icd 758.0)
9) Other chromosomal anomalies (icd 758)
10) Anomalies of diaphragm (icd 756.6)
11) Other congenital anomalies of nervous system (icd 742)
12) Other heart disorders (icd 745, 746 en 747)
13) Chondrodystrophy and osteodystrophies (icd 756.4 en 756.5)
14) Amniotic bands (icd 762.8)
15) Idiopatic hydrops fetalis (icd 778.01)
16) Anomalies of abdominal wall (icd 756.7)
17) Multiple congenital anomalies (icd 759.700)
18) Certain congenital musculoskeletal deformities, other congenital anomalies of limbs, and anomalies of skull and face bones (icd 754, 755 en 756.0)
19) Cleft palate and cleft lip (icd 749)
20) Congenital anomalies of eye (icd 743)
21) Congenital anomalies of ear, face and neck (icd 744)
22) Congenital anomalies of respiratory system (icd 748)
23) Other congenital anomalies of upper alimentary tract (icd 750)
24) Other congenital anomalies of digestive system (icd 751)
25) Congenital anomalies of genital organs (icd 752)
26) Congenital anomalies of urinary system (icd 753)
27) Other congenital musculoskeletal anomalies (icd 756)
28) Congenital anomalies of the integument (icd 757)
29) Other and unspecified congenital anomalies (icd 759)

Chapter 3a

The use of folic acid in women wishing to conceive: the view from General Practice

E. Brugman, K.M. van der Pal-de Bruin, A.L. den Ouden, A.J.M. Drenthen, S.E. Buitendijk

Translated from Dutch

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Introduction

In the Netherlands, approximately 300 children with a neural tube defect (NTD) are born every year (1.4 per 1,000 births).[1,2] Daily intake of folic acid in the periconceptional period reduces the recurrence risk in women who have already had one child with a neural tube defect will have another affected child by 72%.[3] In women who have not had a child with NTD, the risk is lowered by 60%. [4,5]

In November 1993 a joint committee of the Health Council and the Food Council of the Netherlands produced recommendations concerning the use of folic acid by women who could conceive or who wished to conceive.[6] The recommendation made to the health professionals was that all women wishing to conceive should take a dialy oral dosage of 0.4 mg folic acid, from at least four weeks prior to conception until eight weeks after conception.

In September 1995, the Nutrition Bureau, working in collaboration with the Dutch Alliance of Parent and Patient Organisations genetic and non-genetic congenital disorders and the National Association of Health Services, began a national campaign which advised all women considering pregnancy to take folic acid tablets. Prior to the campaign, the Nutrition Bureau contacted those groups of healthcare professionals (known as intermediaries) involved in the care of pregnant women and women wishing to become pregnant, to explain the pros and cons of folic acid use. The aim was to inform the intermediaries about a possible reduction in the risk of NTD associated with the preventive use of folic acid (during the recommended period) by women considering pregnancy. They also wished to create amongst healthcare professionals, a positive attitude towards folic acid use, and to encourage them, wherever appropriate, to draw women's attention to its use.

TNO Prevention and Health (TNO-PG) are evaluating the effect the national campaign has had on women. This has been done in collaboration with both the University of Groningen (EUROCAT registration and the departments of Social Pharmacy and Pharmaco-epidemiology) and with the health services in the 'Midden-Brabant' and 'Achterhoek' regions. The effect of the campaign depends to a considerable extent on the attitude of intermediaries towards folic acid. [7] General practitioners (GPs) fulfil an important role in

providing information on folic acid to potential parents before pregnancy. Even though women often visit the GP only when they are pregnant (or when they think they are), research has shown that the majority of women considering pregnancy prefer information from the GP on the prevention of congenital abnormalities. [8] It has also been shown that GPs are the most frequently consulted source of information concerning pregnancy, and that the information they provide is regarded as being absolutely trustworthy. [9]
In order to measure the effects of the folic acid campaign, TNO-PG conducted a study among GPs to assess their familiarity with the campaign, their opinions on the advisability of folic acid use, and the actual amount of information they passed on about folic acid. The results of this study are described here.

Method

Respondents and procedure

A random sample of 300 GPs from four regions of the Netherlands ('Midden-Brabant', 'Achterhoek', the Randstad area and the northern Netherlands) were selected from the register of Dutch College of General Practitioners (NHG). In the spring of 1996, TNO-PG and the NHG jointly sent out a questionnaire to the group. This was based partly on a questionnaire developed by the Nutrition Bureau. Non-responders were first contacted by letter, and then by telephone, to enquire why they had not taken part. Those GPs who promised to fill in and return the questionnaire but failed to do so were sent a second written reminder.

Questionnaire

The instructions accompanying the questionnaire stressed that it concerned GPs' experience with and approach towards women with no increased risk of having a child with NTD. The questionnaire included questions about the GPs' knowledge of the campaign, their attitude towards folic acid use, and the approach they actually adopted.

Data analysis

Differences in outcome were tested for statistical significance with the χ^2 test, and, in the case of small numbers, with the Fisher exact test; p-values < 0.05 were regarded as statistically significant.

Results

Response

Three hundred GPs contacted of which 12 were no longer in practice. Of the remaining 288 doctors, 233 (81%) returned a completed questionnaire. In the group of 55 non-responders, 20 (36%) reported that they generally refused to take part in any research projects, and 9 said they were too busy to take part; a further 26 (47%) consented in a telephone interview to fill in the questionnaire, but, for unknown reasons, subsequently failed to do so. One GP had a negative attitude toward folic acid and did not wish to participate.

Knowledge

Table 1 shows that the majority of GPs (87%) were familiar with the national folic acid campaign organised by the Nutrition Bureau. More than 1 in 6 GPs (18%) thought they had been insufficiently informed about the campaign itself or about the advice pertaining to folic acid. Answers to an additional open question showed that respondents especially felt that there was a lack of information about food high in folic acid.

Attitude

Table 2 shows that more than half of the respondents thought that the use of folic acid tablets by women wishing to conceive was important or very important. Almost two-thirds (64%) of the respondents thought that the use of folic acid contributed to the medicalisation of normal pregnancy; 82% thought it possible that women who did not take folic acid in pregnancy could develop feelings of guilt. There was no relation between the GPs' attitude and their knowledge of the campaign and the folic acid recommendations.

The GPs were asked if the effort put into the campaign was proportionate to the desired result, i.e. preventing 84 NTD births a year. Half the GPs answered this question in the affirmative, 37% had no opinion, and 14% saw the relationship as disproportionate.

Table 1: Results of a questionnaire concerning the familiarity of 233 GPs with the use of folic acid in the periconceptional period and with the national folic acid campaign run by the Nutrition Bureau.*

	n (%)
The GP is familiar with the national folic acid campaign	
Yes	202 (87)
No	31 (13)
The GP feels he/she has been provided with enough information about the campaign and the recommendations.	
Yes, about both campaign and recommendations	190 (82)
Yes, but only about recommendations	22 (9)
Yes, but only about campaign	13 (6)
No, neither about campaign nor recommendations	7 (3)

* Incomplete answers have not been included

Behaviour

When women inquired about the benefits of folic acid, two-thirds of the GPs advised them to take it within the recommended period; one-third took a neutral position and let the women decide for themselves. One GP (0.4%) advised against the use of folic acid. GPs familiar with the campaign (69%) advised patients more often to use folic acid more often than GPs who were unfamiliar with it (36%) ($p<0.01$).

Of the GPs who thought taking folic acid to be important or very important, 93% advised women to take it. Of those who remained neutral about its's use, 36% advised to use folic acid. Of the GPs who did not find folic acid important nonetheless 11% prescribed folic acid. Those GPs who thought that prescribing folic acid medicalised normal pregnancy, advised its use less often (51%) than those who did not (87%) ($p<0.0001$).

Table 2: Results of a questionnaire concerning the attitude of 233 GPs towards the use of folic acid in the periconceptional period by women not at risk of having a child with a neural tube defect*

	n (%)
I find the use of folic acid tablets by women who wish to conceive	
Unimportant	20 (9)
Neutral	86 (37)
Important	105 (45)
Very important	20 (9)
The use of folic acid serves to medicalise pregnancy	
Agree	147 (64)
Disagree	75 (32)
No opinion	9 (4)
Women who have not taken folic acid tablets may develop guilt feelings	
Yes, absolutely	26 (11)
Yes, it is possible	163 (71)
No	42 (18)

* Incomplete answers have not been included

If a woman requested folic acid, most GPs (63%) wrote out a prescription: 22% referred the woman to a pharmacy, but were willing to write out a prescription if necessary. The remaining 15% did not write out prescriptions for folic acid.

Table 3 shows that 75% of the GPs introduced the subject of folic acid to women who were considering pregnancy, although most said they sometimes forgot to do so (58%). Almost a quarter (23%) of the GPs said they discussed it only if specifically asked; 2% reported that they never advised folic acid, as they did not support its use. The subject of folic acid use was brought up more often by GPs who thought it was important or very important (94%), than by those who took a neutral position (58%) or by those who found it unimportant (35%) ($p < 0.0001$). The subject of folic acid was brought up less frequently by GPs who thought that folic acid tablets medicalised normal pregnancy (68%) than by GPs who did not share this opinion (88%) ($p < 0.01$). The subject was raised by 79% of GPs who

expected to encounter feelings of guilt in women who did not use the tablets in pregnancy, compared to 56% of GPs who did not expect to encounter such feelings ($p < 0.01$).

Table 3: Methods of approach taken by 233 GPs to the use of folic acid in the periconceptional period by women not at risk of having a child with a neural tube defect.*

	Yes, always n (%)	Yes, but not always n (%)	No n (%)
The GP always introduces the subject of the use of folic acid if a woman indicates she wishes to conceive.	40 (17)	134 (58)	57 (25)
At a family planning consultation following the birth of a baby, the GP mentions the use of folic acid prior to any subsequent pregnancy.	5 (2)	61 (27)	163 (67)
The GP advises a woman who wishes to conceive to choose a folic acid rich diet.	12 (5)	72 (32)	140 (63)

* 4% of respondents said they never gave contraceptive advice following the birth of a baby

When women received for contraceptive advice following the birth of a child, 2% of the doctors introduced the subject of using folic acid before any subsequent pregnancy (see Table 3). Thirty-seven percent of GPs advised a diet rich in folic acid, and 42% did so only if the patient brought up the subject; 21% did not find it useful. The majority of doctors (83%) estimated that they reached less than half of the women eligible for this advice. According to their own estimation, nearly half the doctors (46%) gave information on folic acid to between 10% and 30% of the women in their practice who were eligible for it.
No statistically significant differences were found between the knowledge, attitudes and behaviour of the GPs from the four different regions.

Discussion

There was a high level of response from the GPs to the study. The level of non-response did not appear to be related to a negative attitude towards folic acid, although account should be taken of the possibility that respondents may give answers that were socially acceptable rather than ones they actually believed. As no differences were found between GPs from different regions, we might cautiously assume that these results reflect national opinions.

The Nutrition Bureau was particularly diligent in its efforts to provide information to the intermediaries, a task in which it seems to have succeeded. The results of this study show that almost 90% of GPs were aware of the national campaign, and that most of them thought they had received adequate information.

There is some debate in the medical world between supporters and opponents of supplementary folic acid recommendation.[7 10-13] One point put forward by critics of these recommendations is that it could lead to the medicalisation of pregnancy. Critics also point out that it is possible that women who hear too late about these recommendations, or who have forgotten to take their tablets, may develop feelings of fear or guilt. The study shows that most of the GPs share this opinion. A study examining the willingness of 188 women to take folic acid shows that they thought they should do everything they possibly could to ensure having a healthy baby; 86% of whom had no objections to taking folic acid over a long period of time.

Despite the mentioned objections, the vast majority of GPs indicated that they would actively participate in encouraging women to use, although this was not yet part of their routine practice. Only one third included advice about the use of folic acid tablets in any subsequent pregnancy during a consultation following the birth of a baby.

As long as the fortification of food with folic acid is not permitted by law, the use of folic acid tablets in the periconceptional period remains an important preventative measure against NTDs. Research carried out by Klok et al shows that the majority of women of childbearing age are willing to use folic acid.[14] Research conducted by TNO-PG into the effectiveness of the campaign will show if women are indeed using extra folic acid in the periconceptional period. Then it will be determined if the folic acid campaign has led to a

decrease in the number of children born with NTD. The ultimate goal of the folic acid campaign is after all, the prevention of NTD's.

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Chapter 3b

Folic Acid: Awareness and attitudes of midwives

M.M.P.A. van Riemsdijk, K.M. van der Pal-de Bruin,
E. Brugman, S.E. Buitendijk

Translated from Dutch

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Introduction

Approximately 300 children with a neural tube defect (NTD) are born in the Netherlands each year. This most commonly manifests itself as spina bifida and anencephaly. [1,2] Neural tube defects occur when the neural tube fails to close sufficiently in the third or fourth week after conception. Daily use of folic acid in the periconceptional period reduces the risk of having an NTD baby. In a woman who has already had a child with NTD, the recurrence risk is reduced by 72%. [3] In women who have not had a child with NTD, periconceptional use of folic acid reduces the risk by 60%. [4,5]

In November 1993, a commission on folic acid and neural tube defects formed jointly by the Health Council and the Food Council of the Netherlands produced recommendations on the use of folic acid by women considering pregnancy. [6] They advised all women who wished to conceive to take 0.4 mg folic acid in tablet form daily for a minimum of four weeks prior to conception until eight weeks afterwards.

The Nutrition Bureau, the Dutch Alliance of Parent and Patient organisations of genetic and non-genetic congenital disorders and the National Association of Health Services (LvGGD) organised a national information campaign to publicise these recommendations. The campaign had two main aims: to provide healthcare intermediaries with information on the pros and cons of folic acid supplementation, and to get the message across to women who wished to become pregnant.

The information given to intermediaries, including midwives, was aimed at making them aware of the chances of NTD being reduced by the use of folic acid in the periconceptional period. It was also intended to positively influence the attitude of the intermediaries towards folic acid so they would pass on the advice to their clients.

In the spring of 1996, the knowledge and attitudes of general practitioners towards folic acid were tested in the form of a questionnaire. [7] At the end of 1997 a similar survey among midwives was conducted.

Method

For this survey we chose candidates by means of a non-selected random sample of 155 independently practising midwives from the register of members of the Dutch Midwivery Association. In the autumn of 1997 they received a questionnaire from the School of Midwifery in Amsterdam working in collaboration with TNO Prevention and Health (TNO-PG). Non-responders were initially contacted by letter, then by telephone to enquire why they had not taken part; they were asked to fill in the questionnaire and return it. If they did not wish to take part in the survey they were asked to indicate their reasons for refusal.
The questionnaire contained questions concerning the midwives' knowledge of folic acid and the ways in which they passed on information about it. Questions also covered the midwives attitudes towards periconceptional supplementation of folic acid. The questionnaire was based on one sent out to GPs. [7] This in turn, was based on the one developed by the Nutrition Bureau.
The introduction to the questionnaire emphasised that it was related to women having no increased risk of having a child with NTD.
Differences were tested for statistical significance by the χ^2 test, and, in the case of small numbers, by the Fisher exact test; p-values < 0.05 were regarded as statistically significant.

Results

Response

Two of the 150 midwives contacted were no longer in practice. Five questionnaires were addressed incorrectly, and therefore not completed. Of the remaining 143 midwives, 126 returned the completed questionnaire (response 88%). Of the 17 non-respondents, six (35%) said they never took part in surveys, three (18%) said they were too busy, one (6%) was away on an extended holiday, and two (12%) were unable to take part due to illness. The remaining five midwives (29%) failed to return the questionnaire despite agreeing to do so during a telephone interview.

Awareness

Most of the midwives were aware of the national folic acid campaign held by the Nutrition Bureau (94%) (Table 1). The majority felt they had received sufficient information about the campaign. The midwives were asked if they had been asked more questions about using folic acid by their clients since the start of the campaign in September 1995 than previously. Four-fifths of them (81%) confirmed that this was the case; these questions concerned the usefulness of folic acid, the period during which it should be taken, the safety of the tablets, and any harmful consequences that might follow if the tablets were not taken.

Table 1: Midwives' familiarity with the national folic acid campaign and with the folic acid recommendations (n=126).

	n [1] (%)
Midwife is familiar with the national folic acid campaign	
Yes	108 (94)
No	8 (6)
Midwife feels he/she has been provided with enough information about the campaign and the recommendations.	
Yes, about both campaign and recommendations	107 (86)
Yes, but only about recommendations	7 (5)
Yes, but only about campaign	9 (7)
No, neither about campaign nor recommendations	2 (2)

[1] n does not always add up to 126 due to incomplete answers

Attitude

Table 2 shows that almost two-thirds of the midwives thought that the use of folic acid tablets by women wishing to become pregnant was important or very important. More than half did not think it resulted in the medicalisation of normal pregnancy. Thirty-three percent thought that the women who do not use folic acid might experience feelings of guilt.

The midwives were asked if the effort put into the campaign was proportionate to the desired result, i.e. to avoid 84 NTD births each year. Sixty-five percent of the midwives

answered this question in affirmatively, 25% had no opinion and 10% saw the relationship as disproportionate.

Table 2: Attitude of midwives towards the use of oflic acid by women not at risk of having a child with NTD (n=126).

	n [1] (%)
I find the use of folic acid tablets by women who wish to conceive	
Not important	3 (2)
Neutral	44 (35)
Important	63 (50)
Very important	16 (13)
The use of folic acid serves to medicalise pregnancy	
Agree	48 (38)
Disagree	71 (56)
No opinion	7 (6)
Women who have not taken folic acid tablets may develop guilt feelings	
Yes, absolutely	21 (17)
Yes, it is possible	95 (76)
No	9 (7)

[1] n does not always add up to 126 due to incomplete answers

Behaviour

The midwives were questioned about what their advice would be to women asking if they should take folic acid or not. Nearly two-thirds (64%) reported that they would advise these women to take it during the critical period. More than a third said they took a neutral position and left it up to the woman to decide for herself. No-one advised against its use.

When asked about family planning advice following the birth of a baby, almost half the midwives said they would recommend the use of folic acid prior to any subsequent pregnancy (Table 3). Thirty-five percent said they sometimes forgot to do this, and 51%

said that they only discussed it at this time if a woman specifically asked about it. Only one midwife (1%) never gave family planning advice.

Of the midwives who thought taking folic acid to be important or very important 61% advised women at the post-natal visit about folic acid use. Thirty percent who took a neutral position on folic acid nevertheless said that they gave advice on folic acid during a post-natal visit ($p<0.01$). Midwives who thought that folic acid use contributed to the medicalisation of normal pregnancy recommended the use of the tablets less often (48%) than those who were of the opposite opinion (79%) ($p<0.01$).

More than a third of the midwives (38%) advised women wishing to conceive to eat a diet rich in folic acid, although 29% reported that they sometimes forget to do so. Forty percent advised this diet only if the client herself brought up the subject. Twenty-two percent did not find the advice useful.

Table 3: Methods of approach taken by midwives towards women not at risk of having a child with a NTD (n=126) [1].

	Yes, Always n (%)	Yes, but not always n (%)	No n (%)
At a family planning consultation following the birth of a baby, the midwife mentions the use of folic acid prior to any subsequent pregnancy.	16 (13)	44 (35)	64 (51)
The midwife advises women who wish to conceive to choose a diet rich in folic acid.	11 (9)	34 (32)	74 (62)

[1] n does not always add up to 126 due to incomplete answers

Discussion

The response from the midwives was high. The non-respondents indicated that their lack of participation had nothing to do with their attitude towards folic acid. A negative attitude towards folic acid is therefore unlikely to have influenced the outcome.

Prior to the campaign the Nutrition Bureau contacted all groups of healthcare professionals concerned with pregnant women and with women wishing to become pregnant. The aim was to inform them about the relationship between the reduction in the incidence of NTD and the daily use of folic acid in the periconceptional period. It was also intended to create a positive attitude towards folic acid within these groups, and to encourage them to provide information on the subject to their clients.

Almost all midwives (94%) were familiar with the national campaign, and 86% considered themselves to be adequately informed about the campaign and its recommendations. The information from the Nutrition Bureau had therefore reached its target.

A discussion arose between supporters and opponents of the recommended use of supplementary folic acid. [8,9] Opponents believed that a daily dose of folic acid could lead to the medicalisation of normal pregnancy. More than a third of the midwives (38%) voiced this opinion, while over the half disagreed. Another argument voiced by the opponents was the possibility that women who do not take folic acid may develop feelings of guilt. Almost all of the midwives (93%) shared this objection. Despite the problem of feelings of guilt in pregnant women who have not taken folic acid, midwives are generally positive about the use of folic acid. Nearly two-thirds of respondents thought its use was important or very important.

The right time

Midwives regarded the family planning consultation following the birth of a baby as the right time to give information about folic acid. While 48% said that this was the moment when they brought up this subject, it also was reported that they quite often forgot to do so. It is difficult for midwives to give advice to women wishing to become pregnant, as they rarely encountered them in practices. As a rule, midwives only encounter these women during routine post-natal visits, or occasionally during check-up after a miscarriage.

However, there are also other times at which a midwife might be able to recommend folic acid. One example i when making an appointment for a first antenatal visit. At this time, many women are not yet ten weeks pregnant and the midwife can draw folic acid to their attention. A family planning consultation following the birth of a baby is also an ideal opportunity to do this.

The most important contribution a midwife can make at this time is to recommend the use of folic acid in any subsequent pregnancy.

General Practitioners

TNO-PG investigated the knowledge and attitude of GPs towards the use of folic acid.[7] General practitioners also appeared to be well informed about the national campaign, although, generally speaking, midwives seemed to be more positive about it. Fifty-three percent of midwives and 45% of GPs thought the use of folic acid was important to very important. Fewer midwives (56%) than GPs (64%) thought that it medicalised normal pregnancy.

Research into the effect of folic acid on the mechanism of neural tube closure has shown that a woman with a metabolic disorder has, in the most unfavourable circumstances, six times a higher risk of having a child with a neural tube defect. [10] Where a metabolic disorder is present, the closing of the neural tube is influenced by unknown factors. For this reason, it is not possible to screen women who are at high risk of having a child with a neural tube defect. To reduce the number of children born with this defect, all women wishing to conceive should take folic acid in the periconceptional period.

Consumers

In 1997, TNO Prevention and Health (TNO-PG), working in collaboration with the University of Groningen (EUROCAT registration and the departments of Social Pharmacy and Pharmaco-epidemiology), and with the local health services in the 'Midden-Brabant' and 'Achterhoek' regions, evaluated of the effect the national campaign on pregnant women. Results showed that most pregnant women were aware of the folic acid recommendations. The actual increase in its use was lower than expected, however. More than half of the

respondents (54%) took folic acid at some point in time in 1996, and 21% of respondents took it during the recommended period.

As long as the use of folic acid by women wishing to conceive has not reached the desired level and it is not yet possible to screen women who are at risk, the folic acid campaign must be continued. Reducing the number of children born with a neural tube defect can be achieved by incorperating information about folic acid into daily midwifery practice.

Acknowledgements

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Chapter 4

Understanding folic acid use in Dutch women

K.M. van der Pal-de Bruin, T.G.W.M. Paulussen

Submitted

Abstract

Periconceptional folic acid use reduces the occurrence and recurrence risk of a child with a neural tube defect considerably. A framework, comparable to the central constructs of the Theory of Reasoned Action, was developed to improve our understanding of determinants that influence folic acid use in the Netherlands. Data were used of the base-line study of 1995. Data of 1996 were used in order to confirm the behaviour model based on the 1995 data. Subjective norm (OR_{1995}=2.0; 95%CI=1.5-2.6), perceived safety (OR_{1995}=5.1; 95%CI=3.1-8.3) and attitude (OR_{1995}=2.0; 95%CI=1.5-2.8) appear to have a direct relation with folic acid use. Awareness knowledge was mediated through the above mentioned determinants. The model was confirmed by the data of 1996. Furthermore, the relation between the determinants and folic acid use appeared to be independent of level of education. Overall we find that the developed behavioural model appears to be useful in understanding (part of) the pathway that leads to folic acid use. The model can be used for explaining folic acid use by women planning pregnancy and for studying the effectiveness of interventions promoting the use of folic acid.

Introduction

Neural tube defects are among the most common birth defects contributing to infant mortality and serious disability. Neural tube defects refer to all disorders due to insufficient closing of the neural tube, the origin of the neural system, which closes in the fourth week after conception. The most common are spina bifida (defect of the spinal cord that can be open or closed) and anencephaly (no brain development). Anencephaly is not compatible with life as holds for severe cases of spina bifida. At least 27% of the registered children with a neural tube defect die within the first month after birth. [1] Every year, about 260 children with a neural tube defect are born in the Netherlands. Periconceptional use of folic acid reduces the recurrence and occurrence risk of a child with a neural tube defect with 60-70%. [2-4] This has led to recommendations concerning periconceptional folic acid use which mostly describe the use of folic acid enriched food or use of folic acid supplements. [5, 6] In the Netherlands, foods fortified with folic acid are not available because of legal constraints, and so women planning pregnancy have been advised to daily take tablets containing of 0.4-0.5 mg folic acid starting at least four weeks before conception and continuing the use until eight weeks after conception. [7] In the autumn of 1995 a Folic Acid Campaign was conducted to promote folic acid use in women planning pregnancy.

The content of the Folic Acid Campaign was used to design a behaviour model that can best be compared with the theory of reasoned action. [8,9] This theory is widely used for explaining health behaviour. According to this theory, behaviour results from one's intention, which in turn is affected by attitudinal beliefs and subjective norms.

The purpose of this study was to improve our understanding of determinants of periconceptional folic acid use in the prevention of neural tube defects. The content of the Folic Acid Campaign was the basis of the development of a framework for outcome criteria. The framework is comparable to the central constructs of the Theory of Reasoned Action. Data were used from the base-line study (survey 1995) to monitor the effect of the Folic Acid Campaign. The data of the effect study (survey 1996) were used to study whether the developed model remained valid. Besides the presentation of the developed behaviour model, we present the results of the difference in mean score on the behavioural determinants for non-users and users.

Methods

Surveys

Two cross-sectional surveys were carried out to assess the effectiveness of the national and local Folic Acid Campaign. The first survey was carried out just before the start of the Folic Acid Campaign (September through November 1995; 1995 survey), and the second was carried out one year after the completion of the Folic Acid Campaign (September through November 1996; 1996 survey). Data were collected in four regions in the Netherlands: Randstad (West), Noord-Nederland (North), Midden-Brabant (South) and the Achterhoek (East). In the Randstad and Noord-Nederland regions, only the national Folic Acid Campaign was conducted. These regions were combined in the analysis and are referred here to as the region with the national campaign. In the Midden-Brabant and Achterhoek regions, the national and the additional local campaigns were both implemented. These two regions were also combined for the analysis, and are referred to here as the region with the additional local campaign.

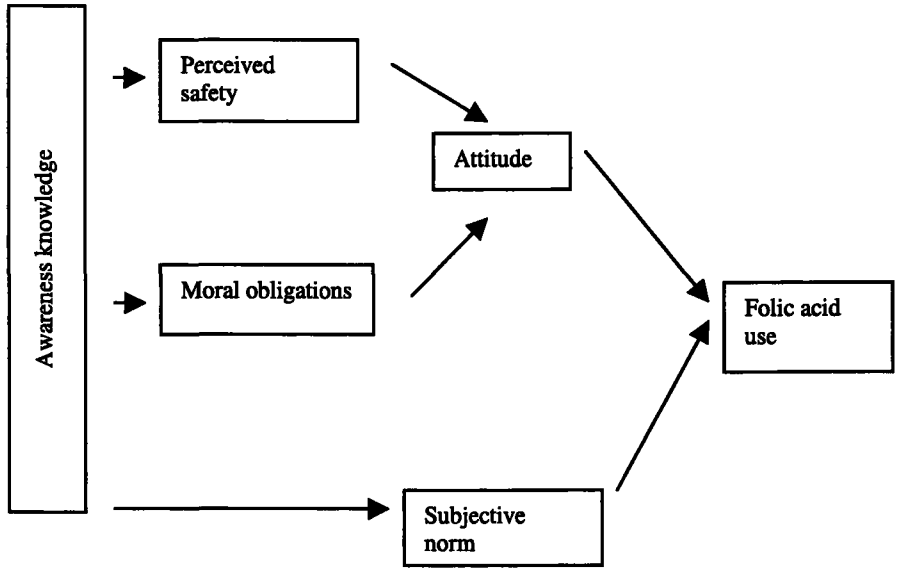
The study design of the two surveys was identical. Data were gathered by means of a structured questionnaire. The questionnaire was based on the questionnaire developed from a study about channels to be used for folic acid education, attitude, and social influence. The study was carried out among women planning pregnancy in the region Midden-Brabant and Achterhoek in the Netherlands. [10] It was handed to pregnant women visiting a midwife, obstetrician or general practitioner for the first or second prenatal visit (around 12 or 16 weeks of pregnancy, respectively) and was filled out in the waiting room directly after the consult. The identity of the participant was unknown to increase honest description of the participant's behaviour. Details about the characteristics of the participants of both surveys are described elsewhere. [11] No data are available of women who refused to participate.

Behaviour model

The theory of reasoned action of Fishbein and Ajzen was the basis of our hypothesised behaviour model to study behavioural determinants of folic acid use. [8,9] According to this theory, intention is assumed to be the immediate antecedent of behaviour, in this case folic acid use. In turn, the formation of a behavioural intention is a combined effect of one's attitude

toward the behaviour (which results from beliefs about the likely advantages and disadvantages of the behaviour) and a subjective norm (which results from beliefs about the normative expectations of others). The impact of other correlates on intention or behaviour – for example knowledge, SES or personality traits – is expected to be mediated by the proximal behavioural determinants, attitude and subjective norm. The hypothesised behaviour model is presented in figure 1a and was the starting point of the analysis. The hypothesised behaviour model consists of five behavioural determinants: 1) awareness knowledge, 2) perceived safety, 3) moral obligation, 4) attitude, and 5) subjective norm. Perceived safety and moral obligation are part of attitude. All variables were measured by self-report.

Figure 1a: Hypothesized model of behavioural determinants of folic acid use.



Awareness knowledge was assessed by two questions. The first question determined when the respondent had first heard of folic acid use (i.e. before the last menstrual period, after the last menstrual period, or that they had never heard of folic acid). Those who had heard of folic acid before the last menstrual period were eligible for this study, since only these women were able to use folic acid during the entire recommended period. The second question was an

open question concerning the period in which one should use it. The answer of women that folic acid should be started before conception and continued after conception was considered right. All other answers were considered wrong.

Perceived safety and moral obligation are part of attitude towards folic acid. Attitude was measured using a 5-point scaled item 'What do you think of the use of folic acid supplements by women planning pregnancy?' The answer was scored on a five point Likert scale(strongly agree = -2 through strongly disagree = 2). Perceived safety is a multi-item scale and was assessed by twelve 5-point scaled items, such as 'Using folic acid will have negative side effects on the health of my baby'. Factor analysis was used to select the items for the construct. The internal consistency of the multi-item scale was assessed by Cronbach's coefficient alpha and was 0.88 for the construct perceived safety. The total score was calculated by dividing the sum score of all items of perceived safety by the number of items resulting in a range from –2 to 2. Records with missing responses were excluded.

Moral obligation, which is part of attitude, was measured with the answer to the statement 'I feel obliged to take every action necessary protecting the health of the baby I am expecting'. The answer was scored on a five point Likert scale(strongly agree = -2 through strongly disagree = 2) .

Subjective norm was assessed by four 5-point scaled items concerning the normative expectations of the respondent's partner, plus her family members, friends and her own general practitioner. Again factor analysis was used to select the items. The Cronbach's coefficient alpha for internal consistency was 0.89. The total score was calculated by dividing the sum score of all four items by the number of items resulting in a range from –2 to 2. Records with missing responses were excluded.

The criterion variable of the conceptual model was folic acid use (yes/no). Women were asked if they had used folic acid and if so the name of the used product and the period in which they used it. All women that used folic acid (some part of) the recommended period (four weeks before until eight weeks after conception) were defined as users; all other women are non-users.

Statistical method

Data of the 1995 survey were initially used to test the behaviour model. Only respondents who had heard of folic acid before the last menstrual period were included in the analysis. Pearson correlation was calculated for the five behavioural determinants and folic acid use. Behavioural determinants were only considered in the logistic regression analysis if the Pearson correlation with folic acid use was significant at the 0.01 level (2-tailed).

Logistic regression was used to explore the relative impact of the selected determinants on folic acid use, the dependent variable being folic acid use (yes/no). The determinants were entered in the regression equation according to the theoretically expected order in three steps: (step 1) the determinants attitude and subjective norm were entered to confirm the direct relation with folic acid use; (step 2) perceived safety was entered in the model. This was done to determine whether perceived safety also has a direct relation with folic acid use and if the direct relation of attitude with folic acid use remained; (step 3) the determinant awareness knowledge was entered into the model.

The data of the survey of 1996 were used to determine whether the behaviour model tested on the 1995 data could be confirmed. Multivariate analysis was used to study whether the relation between the determinants and folic acid use was independent of level of education.

Mean scores were calculated for users and non-users for the determinants attitude, perceived safety and subjective norm. Differences in mean scores between users and non-users for these determinants were tested with the T-test. Differences between users and non-users were tested with the chi-square test.

Results

Behaviour model

In 1995, 1,636 pregnant women participated in the survey of which 604 (36,9%) had heard of folic acid use before the last menstrual period. The data of these women was used to explore the hypothesised behaviour model. The correlation of the model variables with folic acid use is shown in table 1. The correlation coefficients show that the relationships of perceived safety (r=0.51), attitude (r=0.50) and subjective norm (r=0.39) with folic acid use are fair to moderate. There is also a moderate relationship between perceived safety and

attitude (r=0.63). The Pearson correlation of moral obligation with folic acid use was not significant at the 0.01 level and was therefore not included in the logistic regression analysis.

Table 1: Pearson correlation and odds ratio between behavioural determinants and folic acid use based on 1995 survey.

	Pearson correlation						OR	95% CI
	Awareness knowledge	Moral obligation	Perceived safety	Attitude	subjective norm	Folic acid use		
Awareness knowledge	1.00	0.03	0.22 **	0.20 **	0.09 *	0.11 *	n.a.	n.a.
Moral obligation		1.00	0.24 **	0.15 **	-0.14	0.04	n.a.	n.a.
Perceived safety			1.00	0.63 **	0.28 **	0.51 **	5.1	3.1-8.3
Attitude				1.00	0.41 **	0.50 **	2.0	1.5-2.8
Subjective norm					1.00	0.39 **	2.0	1.5-2.6

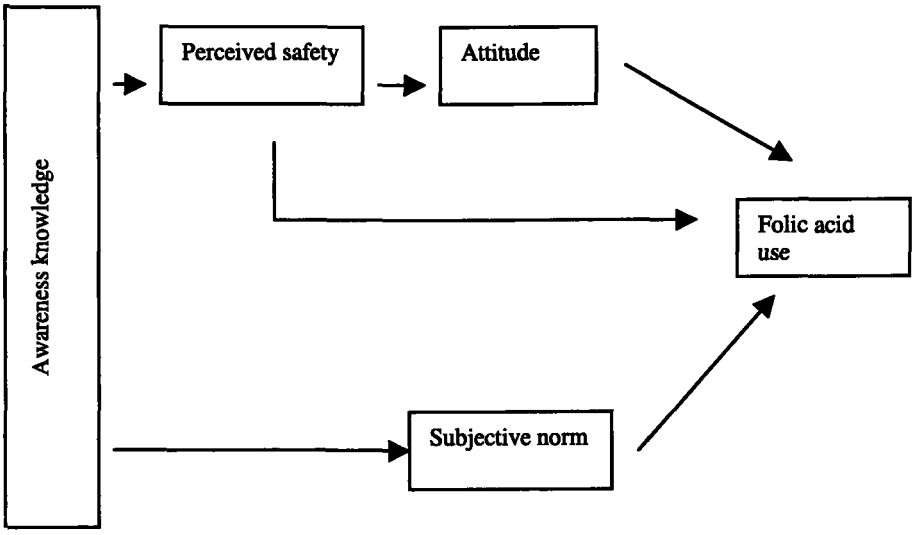
* Correlation is significant at the 0.05 level (2-tailed)
** Correlation is significant at the 0.01 level (2-tailed)

First, attitude and subjective norm were included simultaneously in the logistic regression analysis to explore the impact of the selective determinants of the behaviour model. Both criteria were significant at the 0.05 level ($OR_{attitude}$=3.3; 95% CI: 2.5-4.3, ($OR_{subjective\ norm}$=1.8; 95%CI: 1.5-2.3)). Inclusion of perceived safety in the second step resulted in a minor change in odds ratio for subjective norm (OR=2.0; 95%CI: 1.5-2.6) but had a greater impact on the odds ratio of attitude (OR=2.0; 95% CI: 1.5-2.8). The odds ratio of perceived safety is 5.1 (95% CI: 3.1-8.3) and seems to be the most important determinant in the prediction of folic acid use (table 1). In the third step of the analysis awareness knowledge was included but appeared not to be significant at the 0.05 level. This means that the influence of knowledge awareness on folic acid use is mediated by subjective norms and attitudinal beliefs. The final model is presented in figure 1b and was confirmed by the data of the 1996 survey. The odds ratio for subjective norm (OR=2.0; 95% CI: 1.6-2.4) and general attitude (OR=2.0; 95% CI: 1.6-2.6) from the 1996 survey were comparable with the

1995 survey. The impact of perceived safety on folic acid use (OR=8.9; 95%CI: 5.8-13.7) was even larger than in 1995.

The relation between the determinants and folic acid use appeared to be independent of level of education. In the multivariate analysis, no interaction was found between folic acid use and level of education for either one of the determinants.

Figure 1b: Model of behavioural determinants of folic acid use based on the 1995-data.



Determinants

Awareness knowledge

In 1995, 94.7% (n=522) of the women who had heard of folic acid before the last menstrual period wrote down that folic acid should be used before and during the first weeks of pregnancy. Users more often knew in which period folic acid is recommended to be used (97.4% (n=263) in users versus 92.8% (n=259) in non-users, p=0.01).

Perceived safety

The construct perceived safety is formed by 12 items. Table 2 presents the mean score for each of the 12 items for non-users and users, the difference between these scores and the

total mean score for each item. Overall users were found to have a higher mean score on this construct than non-users (1.07 and 0.44 respectively, $p<0.001$). Users also scored higher on each item of the construct than non-users. The difference in mean score between users and non-users was highest for the item 'folic acid is not sufficiently available by daily food intake'. The mean score for users for this item was 1.04 and for non users -0.03 (differenc=1.08, $p<0.001$) indicating that non-users more often thought folic acid to be sufficiently available by daily food intake. For most of the other items the difference in mean scores varied between 0.53 and 0.80, users having a higher mean score than non-users. For instance, users scored higher than non-users on the item 'there is sufficient evidence that periconceptional folic acid use is good' (mean score 0.75 and –0.05 respectively, $p<0.001$) and on the item 'folic acid use will reduce the risk of an NTD affected child' (mean score 1.64 and 0.85 respectively, $p<0.001$). The mean score of users and non-users did not differ for the items 'There is still a change of having a NTD affected child despite periconceptional folic acid use' (means score 0.90 and 0.78 respectively) and 'By using folic acid periconceptionally I will not give birth to an NTD affected child' (mean score 1.12 and 1.02 respectively).

Attitude

The attitude towards folic acid use differed between users and non-users (table 2). As expected, users were more positive towards folic acid use. The mean score for users was 1.53 compared to 0.65 for non-users ($p<0.001$) indicating that a positive attitude precedes folic acid use.

Subjective norm

The construct subjective norm consists of 4 items. Users were found to have a higher mean score on this construct than non-users (0.05 versus –0.71, $p<0.001$). Users were also found to have a higher mean score on each of the four items of the construct (table 3). The difference in mean score between users and non-users was highest for the item 'I do not think that my partner finds I should use folic acid' (difference 1.02, $p<0.001$). For the other items the difference in mean score between users and non-users was at least 0.60 and was statistically significant.

Table 2: Mean score on behavioural determinants for non-users and users.

	Non-users	Users	Difference	Total
Perceived safety *				
Folic acid use enables me to reduce the risk of a NTD affected child	0.85	1.64	0.79 **	1.23
Folic acid use is not harmful for my baby	0.40	1.10	0.71 **	0.74
Folic acid use is not harmful for myself	0.49	1.15	0.66 **	0.80
Folic acid use effects the normal course of pregnancy	0.20	0.93	0.73 **	0.55
Folic acid use is related to medication use in pregnancy	0.31	0.91	0.60 **	0.60
Folic acid use may result in a harmful blood level of folic acid	0.34	1.01	0.67 **	0.66
Folic acid use guarantees me not to give birth to a NTD affected child	1.02	1.12	0.09	1.06
There are no long term harmful side effects of folic acid use	0.36	0.90	0.53 **	0.62
Tablets containing folic acid are too expensive	0.56	1.12	0.56 **	0.83
It is not well known that the use of folic acid use before and during pregnancy is good	-0.05	0.75	0.80 **	0.34
It is not necessary to use tablets containing folic acid because folic acid is sufficiently available in daily food intake	-0.03	1.04	1.08 **	0.48
Even if I use folic acid I still have a chance of giving birth to a NTD affected child	0.78	0.90	0.12	0.84
Total	0.44	1.07	0.63 **	0.74
Attitude *	0.65	1.53	0.88 **	1.08
Subjective norm *				
I suppose my ... expect(s) me to use folic acid				
Partner	-0.82	0.20	1.02 **	-0.33
Family	-0.78	-0.18	0.60 **	-0.50
Friends	-0.79	-0.13	0.65 **	-0.47
general practitioner	-0.43	0.36	0.80 **	-0.04
Total	-0.71	0.05	0.76 **	-0.35

* scale –2,2
** $p<0.001$

Discussion

This study describes a behaviour model to understand periconceptional folic acid use for the prevention of neural tube defects. Four determinants were included in the model. Perceived safety showed to be the most predictive determinant for folic acid use. Perceived safety not only has a direct effect on folic acid use but also has an indirect effect through attitude. Users were found to have better awareness knowledge and had a higher mean score on perceived safety, attitude and subjective norm than non-users.

The determinants that could be included in the behaviour model appeared to be strong determinants for folic acid use. This was especially the case for perceived safety. Users were found to have a significantly higher mean score on perceived safety than non-users. The beliefs that contributed to perceived safety indicate that public health education concerning folic acid use should contain clear information on several aspects of folic acid use. First of all the proven preventive effect of folic acid use on neural tube defects should be covered. It should be stressed that folic acid is a vitamin and should not be associated with medication. It should be discussed that because folic acid is not sufficiently available in our food women planning pregnancy are advised to take a supplement of folic acid in the form of tablets. Attention should be paid to the fact that folic acid use, even for a longer period of time, will not result in adverse effects for mother and child.

The behaviour model was confirmed with data of the survey of 1996 and showed to be consistent for women with a different level of education. The model can therefore be used for evaluation of the effect of the Folic Acid Campaign and can be useful in explaining differences in folic acid use between women of different level of education.

Using public health theories and models helps us to understand and describe folic acid use in a structured way. Kloeben and Batish used the Health Belief model to understand and predict the intention of permanently following a high folate diet among low-income pregnant women.[12] The content of the Folic Acid Campaign was the basis of the development of the framework for outcome criteria. This framework is comparable to the central constructs of the Theory of Reasoned Action but is a less complete model than the model introduced by Fishbein and Ajzen. Data concerning intention to use folic acid periconceptionally were only available for non-users. One may assume that once a woman uses folic acid during pregnancy she will use it again in a subsequent pregnancy, although it may very well be that there are reasons not to use folic acid. Complete information about intention to use may have improved the model as well as our understanding of periconceptional folic acid use considerably and should be included in further studies. Furthermore there may be perceived barriers as suggested by Bandourra's self-efficacy theory that were not measured in this study. Information about these barriers may help us to understand why many women do not start folic acid use four weeks before conception and thus to improve future public health efforts in this area.

In the Netherlands folic acid is available without prescription. This also means that women have to pay for it. It appeared that non-users more often indicated they found use of folic acid expensive than users did. We also know that women with a low level of education are less likely to use folic acid than women with a high level of education. One of the existing barriers may be that tablets containing folic acid are found to be too expensive. These kind of barriers should be avoided if the government advises periconceptional folic acid use for women planning pregnancy.

This study was carried out to increase our understanding of determinants of folic acid use. Women who had heard of folic acid before the last menstrual period were included in the analysis. Nevertheless, we should bear in mind that the first step to periconceptional folic acid use is to hear of the recommendations in time, i.e. before they wish to become pregnant. In 1996, 77.3% of the respondents had heard of folic acid before the last menstrual period. Although this result is higher than the target of 70%, continuous health education is necessary to maintain and, preferably, to increase the percentage of women that has knowledge of periconceptional folic acid use.

The tested behaviour model appears to be useful in understanding the pathway leading to folic acid use. The model may offer health educators an opportunity to promote folic acid use effectively. It also provides us with a tool to systematically evaluate interventions to promote folic acid use for the prevention of neural tube defects.

Acknowledgement

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Chapter 5

The Dutch 'Folic Acid Campaign'-have the goals been achieved?

K.M. van der Pal-de Bruin, H.E.K. de Walle, W. Jeeninga, C. de Rover, M.C. Cornel, L.T.W. de Jong- van den Berg, J. Schouten, R. Brand and S.E. Buitendijk

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Summary

Periconceptional folic acid use considerably reduces the risk of neural tube defects. The aim of this study was to measure the effect of the national and the local Folic Acid Campaign on periconceptional folic acid use. Before (1995 survey) and 1 year after the campaign (1996 survey), the awareness and use of folic acid was measured among pregnant women in four regions of the Netherlands. To this end, pregnant women who visited the midwife, general practitioner or obstetrician for the first or second prenatal visit were asked to complete a questionnaire. The results showed that use of folic acid for any period around conception increased from 25.1% in 1995 to 53.5% in 1996. Appropriate use (4 weeks before until 8 weeks after conception) increased from 4.8% in 1995 to 21.0% in 1996. No additional effect of the local Folic Acid Campaign was found (adjusted odds ratio=1.0; 95% confidence interval=0.7, 1.4). It was possible to conclude that folic acid use at the recommended time increased considerably as a result of the national and the local Folic Acid Campaign, but the target (use in 46% of women wishing to conceive) was not achieved. New health education programmes are needed to increase further its use at the appropriate times.

Introduction

In the Netherlands, ≈ 260 children annually are born with a neural tube defect, including 125 live births with spina bifida. [1] Periconceptional folic acid use considerably reduces the recurrence as well as the occurrence risk of neural tube defects, [2-4] and since the early nineties many national Public Health Authorities have recommended its use. [5,6] In several of these countries, health education programmes have subsequently been set up to provide information to women wishing to conceive.[7-9] In accordance with the published advice, these programmes focused primarily on use of folic acid-enriched food or of folic acid supplements. In the Netherlands, foods fortified with folic acid are not available because of legal constraints, and so women wishing to conceive have been advised to take orally a supplementary daily dosage of 0.4-0.5 mg folic acid.[10]

Two years after the recommendations were issued, a national Folic Acid Campaign was conducted to provide information about the effects of folic acid to women wishing to conceive and to their health-care professionals. Thus, midwives, obstetricians, general practitioners, pharmacists and drug store personnel, for example, were targeted and given information about folic acid through professional associations, publications in national medical journals and a personal letter. In this way, they were provided with educational materials to establish a positive attitude towards advising women to use folic acid. Additionally, women wishing to conceive were given information via a multimedia approach. The aim was to reach at least 70% of women wishing to conceive and that 65% of these women would use it appropriately.[11] These targets were based on results from other health education programmes such as non-smoking campaigns for pregnant women.

In two regions in the Netherlands (Midden-Brabant and Achterhoek), a local campaign was conducted to support the national campaign in providing information to the health-care professionals and women wishing to conceive. Further information was given to the local professionals by letter and at general meetings of the local professional association. The local media were specifically used to provide information about folic acid to women wishing to conceive. Special attention was given to reaching those of low socio-economic status.

In this article, the results of the national and local Folic Acid Campaign on folic acid use are presented. In addition, these two sets of results are compared in order to describe the additional effect of the local campaign.

Methods

Study population and data collection

To evaluate the effect of the national and local Folic Acid Campaigns, two surveys were carried out; the first, before the start of the campaigns (September-November 1995; survey 1995), and the second 1 year afterwards (September-November 1996; survey 1996). The study designs of the two surveys were identical.

Data were collected in four regions in the Netherlands: Randstad (West), Noord-Nederland (North), Midden-Brabant (South) and the Achterhoek (East). In the Randstad and Noord-Nederland regions, the results of only the national campaign were analysed, whereas in the Midden-Brabant and the Achterhoek regions the analysis also included the results of the additional local campaign.

The health services in the regions where the additional campaign was conducted had previously performed research into the factors that are important for women who want to become pregnant and that may increase the success of health education. As a result of this previously existing knowledge, these two regions were chosen for the additional campaign; these regions are somewhat more rural in character than those in which only the national campaign was conducted.

Pregnant women visiting a midwife, obstetrician or general practitioner for the first or second prenatal visit (around 12 or 16 weeks of pregnancy respectively) were asked to participate. Consent was only asked once. Women who were unable to read Dutch were excluded from, the two surveys. In the 1995 survey, women were included in the analysis only if their last menstrual period had occurred before the start of the national and local Folic Acid Campaign. In this way, it was possible to see who was taking it correctly before they had seen any of the publicity at the start of the campaign. The selected midwives and obstetricians involved were representative of the Dutch obstetric system.

Questionnaire

A self-administered questionnaire was designed to estimate whether pregnant women knew about folic acid and its use. The questionnaire was completed in the antenatal clinic waiting room by those participating and took ≈ 15 min to complete. It consisted of three parts. The first and third parts included questions concerning demographic variables (age, marital status, education, employment and nationality) and reproductive history (parity and history of previous children with neural tube defects or other congenital malformations).

In the second part of the questionnaire, information about knowledge of and use of folic acid was collected. Respondents were first asked if they had heard of folic acid and, if so, when they had heard of it (before or after they became pregnant). Respondents who reported that they were aware of it were asked to indicate whether they had taken it. If so, they were asked to say whether they had taken either folic acid tablets or multivitamins containing folic acid and to describe for which period they had used it. Correct folic acid use was defined as from 4 weeks before conception until 8 weeks after conception.

If the respondent reported having heard of folic acid but had not taken it, the reason for non-use was asked. The women in this group were asked if they felt they had been sufficiently informed about folic acid before the current pregnancy and whether they regretted not having taken it. Finally, the respondent was asked if she intended to use folic acid in a possible future pregnancy.

Data analysis

Univariate (descriptive) methods and logistic regression analysis were used to describe and to estimate the effect of the national Folic Acid Campaign. A logistic regression model was also used to estimate the additional effect of the local Folic Acid Campaign. The model evaluates the dichotomous outcome parameter 'correct folic acid use'.

The distribution of demographic and reproductive variables was compared between the 1995 and the 1996 surveys, and also between the regions where only the national Folic Acid Campaign was conducted and those where both the national and the local campaigns were conducted. Differences between groups were statistically analysed with the Student T-test if the variable was continuous. Otherwise, the chi-squared test was used. Differences between groups were considered to be statistically significant at $P < 0.05$.

Table 1. Distribution of demographic and reproductive variables in the regions of the national Folic Acid Campaign only and the regions of the national and local Folic Acid Campaign in 1995 and 1996

	National Folic Acid Campaign only		National and local Folic Acid Campaign		Dutch women of childbearing age
	1995	1996	1995	1996	1996
Variable	n (%)	n (%)	n (%)	n (%)	n (%)
Maternal age (yrs)					
15 – 19	18 (2.2)	7 0.9)	2 (0.2)	3 (0.4)	1,857 (1,0)
20 – 24	94 (11.6)	82 (11.6)	56 (6.8)	61 (7.3)	16,760 (8,8)
25 – 29	282 (34.9)	277 (35.9)	343 (41.7)	344 (41.3)	61,129 (32,2)
30 – 34	303 (37.5)	287 (37.2)	345 (42.0)	353 (42.4)	77,057 (40,7)
35 – 39	94 (11.6)	103 (13.4)	74 (9.0)	71 (8.5)	28,740 (15,2)
≥ 40	16 (2.0)	15 (1.9)	2 (0.2)	1 (0.1)	3,978 (2,1)
Respondent born in the Netherlands					
Yes	722 (89.5)	708 (91.6)	785 (95.3)	801 (96.2)	177,958 (94,8)
No	85 (10.5)	65 (8.4)	39 (4.7)	32 (3.8)	9,716 (5,2)
Education					
Basic	18 (2.2)	18 (2.3)	9 (1.1)	6 (0.7)	799,770 (15,4)
Low	288 (35.8)	275 (35.6)	286 (34.7)	251 (30.3)	1,018,350 (19,6)
Medium	305 (37.9)	298 (38.6)	381 (46.2)	398 (48.1)	2,479,950 (47,7)
High	181 (22.5)	171 (22.2)	140 (17.0)	156 (18.8)	901,380 (17,3)
Not specified	13 (1.6)	10 (1.3)	8 (1.0)	17 (2.1)	
Worksituation					
Employed	510 (63.7)	501 (65.3)	560 (68.7)	589 (71.1)	2,614,000 (53,3)
Unemployed	35 (4.4)	30 (3.9)	34 (4.2)	33 (4.0)	2,054,000 (41,9)
Disablement	10 (1.2)	16 (2.1)	10 (1.2)	11 (1.3)	
Housewife	225 (28.1)	207 (27.0)	209 (25.6)	186 (22.5)	
Student	21 (2.6)	13 (1.7)	2 (0.2)	9 (1.1)	231,000 (4,7)
Marital status					
Married	616 (77.1)	591 (77.0)	713 (86.7)	699 (84.1)	157,329 (83,0)
Unmarried	160 (20.0)	157 (20.4)	104 (12.7)	123 (14.8)	32,192 (17,0)
Divorced	22 (2.8)	19 (2.5)	5 (0.6)	8 (1.0)	
Widow	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	

	National Folic Acid Campaign only		National and local Folic Acid Campaign		Dutch women of childbearing age
	1995	1996	1995	1996	1996
Variable	n (%)	n (%)	n (%)	n (%)	n (%)
Parity					
0	344 (44.6)	333 (45.0)	354 (44.1)	388 (48.0)	85,030 (44,6)
1	287 (37.2)	271 (36.6)	302 (37.6)	304 (37.6)	69,611 (36,5)
2	102 (13.2)	96 (13.0)	121 (15.1)	92 (11.4)	24,861 (13,0)
3	25 (3.2)	27 (3.6)	19 (2.4)	24 (3.0)	11,011 (5,8)
≥4	14 (1.8)	13 (1.8)	7 (0.9)	1 (0.1)	
Pregnancy planned					
Yes	680 (84.9)	664 (86.9)	766 (92.7)	785 (94.1)	
No	121 (15.1)	100 (13.1)	60 (7.3)	49 (5.9)	
Previous child with a congenital deformation					
Yes	17 (3.5)	19 (4.1)	13 (2.7	19 (4.0)	
No	467 (96.5)	442 (95.9)	474 (97.3)	456 (96.0)	
Previous child with a neural tube effect					
Yes	4 (0.8)	3 (0.6)	0 (0.0)	4 (0.8)	
No	481 (99.2)	460 (99.4)	485 (100.0)	470 (99.2)	

[1] Based on figures from the Central Bureau of Statistics[8,9]

[2] P<0.05 between the regions where the national Folic Acid Campaign and the local Folic Acid Campaign was conducted

[3] p<0.05 within the regions where the Folic Acid Campaign was conducted between the survey of 1995 and 1996.

[4] Nulliparous women could not be included of this variable.

[5] The Fisher-extract test was used.

[6] Includes unemployment, disablement and housewives

[7] Infants born in married women and unmarried women.

[8] ≥3 children

The Spearman correlation was used to test for colinearity among candidate variables for the multivariable analyses. If a correlation > 0.95 had existed, only one of the correlated variables would have been used in the logistic regression model. However, the highest correlation found was 0.40.

To correct for differences in the distribution of demographic and reproductive variables, the logistic regression model included the following variables: age (continuous), education (low/medium/high), work situation (employed/unemployed), marital status (married/not married), parity 0/1/≥2), planned pregnancy (yes/no). The logistic regression model was evaluated for Dutch women only. Women of other nationalities were excluded from the study because of small numbers. The model also tested for interaction between the intervention (the Folic Acid Campaign) and demographic and reproductive variables. No interaction was found. The model was used to estimate the probability of appropriate folic acid use for various combinations of risk factors.

Results

A total of 1636 respondents participated in 1995 and 1612 in 1996. During the 1995 survey, 809 questionnaires (49.4%) were completed in the regions where only the national campaign was conducted and 827 (50.6%) in the regions where the additional local campaign was held. During the 1996 survey, this was 773 (48.0%) and 839 (52.0%) respectively. Table 1 shows similar distribution of demographic and reproductive variables during 1995 and 1996. Between the regions where only the national campaign and those where the local as well as the national campaigns were conducted, differences were seen in the distribution of age, nationality, education, work situation, marital status and proportion of planned pregnancies. No difference was found in the mean age between the two regions in 1995 and 1996. The distribution of the most important demographic variables such as age and education is similar to that of demographic variables in women of childbearing age in the Netherlands. [12,13]

Table 2 compares the women who used folic acid in 1995 and in 1996. In 1995, 41 % (n = 671) of all respondents reported that they knew about folic acid before the last menstrual period. In 1996, that awareness nearly doubled (77%, n = 1241). Correct use

increased from 4.8% in 1995 to 21.0% in 1996. Of those who took folic acid at any period around conception, 47.8% began before conception but after the recommended 4 weeks before and 23.7% stopped within 8 weeks after conception.

The increase in folic acid use between the regions where only the national campaign took place was compared with the increase in the regions with the additional local campaign. Compared with 1995, in 1996 the odds of correct periconceptional use increased threefold in both regions (adjusted odds ratio [aOR] $_{\text{national campaign}}$=3.0; 95% confidence interval [CI] = 2.1, 4.3; aOR $_{\text{national and local campaign}}$ = 3.1; 95% CI= 2.2, 4.3).

Table 2: Prevalence of awareness and use of folic acid in 1995 and 1996

	1995		1996	
	n	(%)	n	(%)
Heard of folic acid before last menstrual period	676	(41.7) *	1239	(77.3)
Folic acid use at some period around conception	411	(25.1)	862	(53.5)
Correct folic acid use [b]	78	(4.8)	339	(21.0)

* In total, 62.2% (n=536) of the women used only folic acid and 37.8% (n=326) of the women used a multivitamin containing folic acid.

b Correct folic acid use was lower than aimed for (21% versus 46% respectively): starting at least 4 weeks before conception and continued use until 8 weeks after conception.

For various combinations of the risk factors (covariates) used in the logistic regression model, the estimated probability of correct folic acid use is presented in Table 3. The logistic regression model is presented in the Appendix. The woman is 30 years old and planned her pregnancy in all presented combinations of the covariates. Table 3 shows that higher educated women, married women, women who are holding a job, and those who are expecting their first child are more likely to take folic acid at the recommended time. A combination of these factors especially increases the probability of its correct use. For example, if a woman is expecting her first child, is married, is holding a job and has a high education level, her probability of correct periconceptional folic acid use is 56% vs. 25% for an unmarried unemployed woman with a low educational level expecting her second child.

Table 3: Visualisation of the effect of variouscombinations of risk factors in the estimated probability of correct folic acid use.

Age (years)	Planned pregnancy (yes / no)	Parity (0/1> 1)	Married (yes / no)	Education level (low/medium/high)	Employed (yes/no)	Estimated probability of proper folic acid use (%)
30	Yes	>1	No	Low	No	25
30	Yes	Nulliparous	No	Low	No	35
30	Yes	Nulliparous	Yes	Low	No	47
30	Yes	Nulliparous	Yes	High	No	56
30	Yes	Nulliparous	Yes	High	No	56

Discussion

Our data show that the Dutch Folic Acid Campaign was indeed effective in reaching the target group. One year after the conclusion of the campaign, 77% of all respondents reported knowing about folic acid before the last menstrual period. Furthermore, a considerable increase occurred in the percentage of pregnant women who used it correctly. Shortly after the advice of the public health authorities in 1993, correct folic acid use in the Netherlands was only 1%.[14] This increased to 5% before the start of the campaign[15] and was 21% one year after conclusion of the campaign.

The aim of the Folic Acid Campaign has not been achieved entirely. The health education programme has been very intensive for a short period of time. Establishing changes in attitude of this magnitude probably needs health education programmes that run for a longer period. Although it may be easier for woman wishing to conceive to use folic acid than to quit a habit such as smoking, more time and additional health education programmes seem to be needed before the goals can be met. Most women who did not use folic acid expressed the intention to use it in a future pregnancy. Almost two-fifths of the women did not start in time, and the major reason for not taking it was that they were already pregnant. Future health education programmes should focus more on the period in which it should be used. Additional campaigns to reach subgroups such as multiparous women and the unemployed may increase its use.

Both the national and local campaigns resulted in an increased level of awareness and use. Although extra information was distributed through the local campaigns, this did not result in more women knowing about or using it. No decrease in the difference in use between lower- and higher-educated women was found. The general problem that higher-educated women benefit more from health education was not diminished by local action. Furthermore, lower-educated women appear to gain less from local mass media than expected. For instance, they did not notice the additional pamphlets more often.

Overall, correct periconceptional use of folic acid in the Netherlands appears to be lower than in other countries. [16] In reports from the United Kingdom, it increased to 31 % in 1997,[17-19] and in the United States Johnston and Staples [20] reported that 23% of the women had used folic acid before becoming pregnant. Use of multivitamins containing folic acid is much more common in the United States than in the Netherlands, which may explain the difference.

The ultimate goal of any public health education concerning folic acid use is a reduction in the prevalence of neural tube defects through primary prevention. Periconceptional use reduces the risk of a child with a neural tube defect by 60-70%.[2-4] In the 1996 Dutch survey, folic acid was used during a period around conception by 53.5% and was properly used by 21% of the target population. Assuming this percentage applies to all women wishing to conceive in the Netherlands, a reduction in the prevalence of neural tube defects of about 13% may be expected. As even suboptimal periconceptional folic acid use may cause a reduction in risk, this estimate may be conservative. Initiatives are presently being undertaken to study the trend in prevalence of neural tube defects in the Netherlands. Not only the prevalence of live births and perinatal deaths with a neural tube defect will be studied, but also that of termination of pregnancy because of neural tube defects. In the Netherlands, no antenatal screening programme for neural tube defects exists. It is conceivable that the increased attention has led to more antenatal screening and that that resulted in an increased rate of pregnancy terminations.

From this study, it appears that women are willing to take tablets containing folic acid that is necessary to improve their folate status more effectively than an increased intake of natural food containing folate. The advantage of this approach is that a small proportion of the general population increase their folic acid intake for a rather short period. The benefits

of more general use through food fortification may become evident if in the future other health benefits of increased folic acid intake, such as the prevention of cardiovascular diseases, can be shown. In that situation, the Dutch policy to increase folate status in pregnant women may change from recommending tablets containing folic acid to recommending consumption of fortified foods. If this measure is to be implemented, food products should not only be fortified with folic acid but with vitamins B6 and B12 as well for the prevention of hyperhomocysteinaemia. [22] Until that time, supplementation by tablets will remain the first choice approach in women wishing to conceive. The Dutch Folic Acid Campaign has reached 77% of the target population, but did not succeed in increasing appropriate folic acid use to 46%. A percentage of 21 % was established. In the near future, further health education programmes will be needed to ensure that more women wishing to conceive take folic acid-containing tablets.

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Appendix. Description of model used in the logistic regression analysis

Variable	OR	[95% CI]
Intervention		
Survey 1995	1.00	Reference
National campaign only	3.05	[2.14, 4.34]
Nation and local campaign	3.07	[2.20, 4.29]
Age (continuous; per year)	1.08	[1.04, 1.13]
Parity		
0	1.00	Reference
1	0.71	[0.52, 0.97]
1	0.59	[0.36, 0.95]
Working		
Yes	1.00	Reference
No	0.97	[0.7, 1.37]
Married		
Yes	1.00	Reference
No	0.62	[0.42, 0.92]
Pregnancy planned		
Yes	1.00	Reference
No	0.29	[0.13, 0.67]
Educational level		
Low	0.72	[0.50, 1.04]
Medium	0.76	[0.56, 1.05]
High	1.00	Reference

Chapter 6

Socio-economic differences in folic acid use in the Netherlands

K.M. van der Pal-de Bruin, H.E.K. de Walle, C.M. de Rover, W. Jeeninga, M.C. Cornel, L.T.W. de Jong-van den Berg, S.E. Buitendijk, T.G.W.M. Paulussen

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Abstract

In the Netherlands periconceptional folic acid use to prevent neural tube defects was promoted through a national Folic Acid Campaign. In two regions, a local campaign supplemented the national campaign to increase chances of reaching women with a low social economic status (SES). To evaluate the effectiveness of the two educational approaches (i.e. national campaign only versus national and additional local campaign) we developed a framework for outcome criteria, being awareness knowledge, perceived safety, attitudes, and subjective norms. Data were gathered by means of two cross-sectional studies conducted just before and one year after the campaigns were implemented.

Before the campaigns were conducted, there were already differences in all effect criteria, including folic acid use, between women of different educational level. These were mostly in favour of women with a high level of education. While both educational approaches appeared to have a positive impact on all outcome criteria, they failed to reduce the existing differences in these outcome criteria between women of different educational level.

Folic acid use can effectively be promoted by mass media campaigns, certainly in a large group of women with no prior knowledge of the health benefits associated with periconceptional folic acid use. However in order to achieve more equal health outcomes among women of low and high SES, it seems that more tailored interventions for women of low SES are needed.

Introduction

Periconceptional folic acid use considerably reduces both the recurrence and occurrence risk of neural tube defects. [1-3] For this reason, periconceptional folic acid use has often been recommended, usually in food enriched with folic acid, or in folic acid supplements. [4,5] In the Netherlands, legal constraints mean that foods fortified with folic acid are not available. Women wishing to conceive have therefore been advised to take tablets containing 0.4-0.5 mg folic acid daily, starting at least four weeks before conception and continuing until eight weeks after conception. [6]

This advice was implemented in the autumn of 1995 via a national Folic Acid Campaign. As women wishing to conceive are indistinguishable from the general population, a mass media approach was chosen to inform them. The slogan of the campaign was 'Folic acid – already before you are pregnant'. Via advertisements in newspapers and women's magazines, TV and radio commercials, and posters in the waiting rooms of GPs, midwives and gynaecologists, the attention of women wishing to conceive was drawn to a brochure about folic acid, which was available free at the pharmacist.

The brochure explained what folic acid is, and that it is not available in sufficient quantities in our daily food. It also described what neural tube defects are, and that by using folic acid it is possible to reduce the risk of having an affected child. Furthermore the brochure gave information on the period in which folic acid should be used, on the dosage, and on where folic acid can be obtained. The campaign was intended to be similar to other campaigns that alert women to health risks during pregnancy, for example from smoking. The aim was to reach at least 70% of women wanting to conceive, and to achieve appropriate folic acid use in 65% of women who had heard of folic acid.[7] Furthermore the campaign wanted to stimulate healthcare professionals to inform women about folic acid use; these professionals were informed about folic acid through their professional associations, publications in national medical journals and personal correspondence before the campaign was implemented to inform women wishing to conceive. In this way they were provided with educational materials aimed at establishing a positive attitude towards advising women in the use of folic acid.

Women with a low social economic status (SES) appear to be at greater risk of giving birth to a child with a neural tube defect than women with a high SES. [8] Therefore, in two regions a local campaign supplemented the national Folic Acid Campaign, specifically targeting women with a low SES. In these two regions local healthcare professionals were provided with additional information on the promotion of folic acid use; this information was disseminated by letter and in general meetings of the local professional association. The local media were used to provide information about folic acid to women wishing to conceive. Furthermore a poster about folic acid use was used as an advertisement in bus stops, and information was provided at a special stand during a pregnancy information market.

This article presents the differential effects of the two campaigns on folic acid use, i.e. the national campaign, and the national campaign plus the local campaign, and of the related social psychological determinants of folic acid use between women of different SES. The effect criteria were derived from a previously tested model of determinants of folic acid use among Dutch women wishing to conceive. We analysed the differences in folic acid use and related psychosocial determinants that existed before the two campaigns were implemented (i.e. the 1995 survey), and what had happened to these differences one year after the campaigns were conducted (i.e. the 1996 survey). Furthermore, we explored whether the local campaign had had an additional effect on the national campaign on folic acid use and related determinants, especially for women with a low educational level.

Methods

Study design

Two cross-sectional surveys were carried out to assess the effectiveness of the national and local Folic Acid Campaign. The first survey was carried out just before the start of the Folic Acid Campaign (September through November 1995; 1995 survey), and the second was carried out one year after the completion of the Folic Acid Campaign (September through November 1996; 1996 survey). Data were collected in four regions in the Netherlands: Randstad (West), Noord-Nederland (North), Midden-Brabant (South) and the Achterhoek (East). In the Randstad and Noord-Nederland regions, only the national Folic Acid

Campaign was conducted. These regions were combined in the analysis and are referred here to as the region with the national campaign. In the Midden-Brabant and Achterhoek regions, the national and the additional local campaigns were both implemented. These two regions were also combined for the analysis, and are referred to here as the region with the additional local campaign.

The study design of the two surveys was identical. Data were gathered by means of a structured questionnaire. The questionnaire was based on the questionnaire developed from a study about channels to be used for folic acid education, attitude, and social influence. The study was carried out among women planning pregnancy in the region Midden-Brabant and Achterhoek in the Netherlands. [9] It was handed to pregnant women visiting a midwife, obstetrician or general practitioner for the first or second prenatal visit (around 12 or 16 weeks of pregnancy, respectively) and was filled out in the waiting room directly after the consult. The identity of the participant was unknown, in order to increase honest description of the participant's behaviour. Details about the characteristics of the participants of both surveys are described elsewhere. [10] No data are available of women who refused to participate.

In the section about the effects on folic acid use, we will also refer to data collected in the spring of 1994. This was a few months after women had first been officially recommended to use folic acid before conception, but more than one year before the campaigns were started. These data were also collected among pregnant women who made a first or second prenatal visit to the midwife or obstetrician, but only in the Randstad, and Noord-Nederland regions. [11]

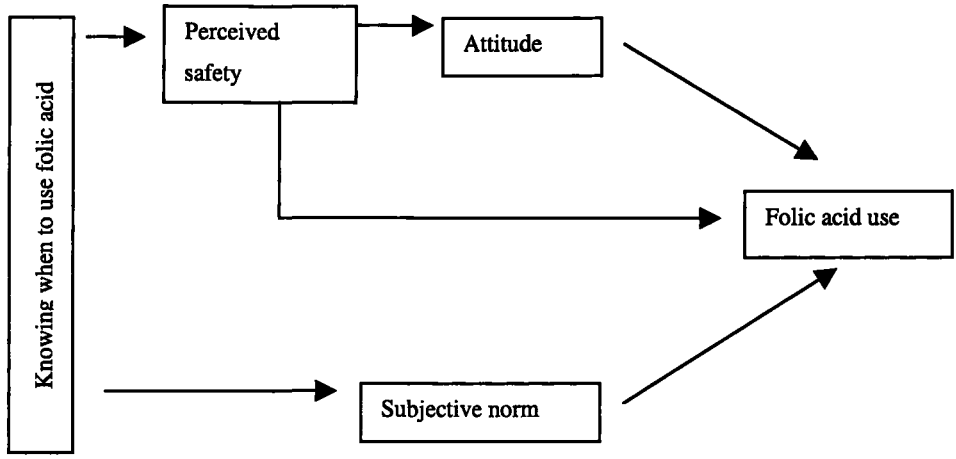
Selection of effect criteria

The content of the Folic Acid Campaign was the basis of the development of the frame work for outcome criteria. The framework is comparable to the central constructs of the Theory of Reasoned Action. [12-13] According to this theory, intention is assumed to be the immediate antecedent of behaviour, in this case folic acid use. In turn, the formation of a behavioural intention is a combined effect of one's attitude toward the behaviour (which results from beliefs about the likely consequences of the behaviour) and a subjective norm (which results from beliefs about the normative expectations of others). The impact of other correlates on

intention or behaviour – for example knowledge, SES or personality traits – is expected to be mediated by the proximal behavioural determinants, attitude and subjective norm.

The data of the 1995 survey were used to test our hypothetical model of determinants, which included estimates of women's awareness knowledge of folic acid use, plus their attitude towards it, their perceived moral obligation to take it, its perceived safety, and subjective norms (for details on the analyses the reader is referred to Van der Pal & Paulussen [14]. The behavioural model that resulted from the logistic regression analysis included attitude, subjective norm, and perceived safety, while awareness knowledge appeared to affect folic acid use through subjective norm and perceived safety (figure 1). This model was confirmed by analysing the data from the 1996 survey. The conceptual model also appeared to be consistent among women with a different level of education.

Figure 1: Effect criteria for the evaluation of folic acid use.



As a result, analysis of the effectiveness of the campaigns focused on awareness knowledge, attitude, perceived safety, subjective norm, and folic acid use. Awareness knowledge was assessed by the question on when the respondent had first heard of folic acid use (i.e. before the last menstrual period, after the last menstrual period, or that they had never heard of folic acid), and by the open question concerning the period in which one should use it. The second answer could be either right or wrong. Attitude towards folic acid was measured via a 5-point

scaled item 'What do you think of the use of folic acid supplements by women wishing to conceive?' Perceived safety was assessed by twelve 5-point scaled items (Cronbach's coefficient alpha for internal consistency=0.88), such as 'Using folic acid will have negative side effects on the health of my baby'. Attitude towards folic acid was measured via a 5-point scaled item 'What do you think of the use of folic acid supplements by women wishing to conceive?' The answer was scored on a five point Likert scale(strongly agree = -2 through strongly disagree = 2).

Subjective norm was assessed by four 5-point scaled items (Cronbach's coefficient alpha for internal consistency =0.89) concerning the normative expectations of the respondent's partner, plus her family members, friends and her own general practitioner. The criterion variable of the conceptual model was folic acid use during some period around conception.

Data analysis

The effect of the mass media campaigns was evaluated in three steps for each of the five components of the model. First the overall change in the five components between 1995 and 1996 was analysed. Then, a distinction was made with regard to exposure to the type of campaign, i.e. the national Folic Acid Campaign, or the combined national and local campaign. This makes it possible to detect the additional effect of the local campaign. Last, the study population was divided into three levels with regard to highest fulfilled education (i.e. low, moderate, and high), which was used as a proxy for social economic status, to study differential effects in use and related determinants. The results for women with a moderate education lay more or less between those of women with a low education and women with a high education. While (for purposes of clarity) only the results for women with either a low of a high level of education are discussed in the text, the results of the three groups are presented in the tables. Differences between 1995 and 1996 were analysed using descriptive univariate analysis. Statistical differences were tested by using chi square test or t-test where appropriate.

Results

Within each region the same distribution of educational level was found in both 1995 and 1996 (table 1). However, the distribution of this level was not equally distributed between the two regions (P-value<0.001). More respondents in the region with the national campaign reported a low level of education than in the region with the additional local campaign (1995: 38.0% versus 35.8%, respectively; 1996: 38.0% versus 31.0%, respectively).

Table 1: Distribution of level of education by type of intervention.

	National campaign		Additional local campaign		Total	
	1995	1996	1995	1996	1995	1996
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Respondents	809	773	827	839	1636	1612
Education						
Low	306 (38.0)	293 (38.0)	295 (35.8)	257 (31.0)	601 (37.4)	550 (35.0)
Moderate	318 (39.5)	308 (39.0)	389 (47.2)	415 (50.1)	686 (42.7)	696 (44.2)
High	181 (22.5)	171 (22.2)	140 (17.0)	156 (18.8)	321 (20.0)	327 (20.8)

Respondents reported that they obtained information on folic acid use from many different channels (table 2). These channels were divided into written materials, personal communication by caregivers, and information from social contacts, such as family and friends. The channels indicated with the greatest frequency were a brochure, the general practitioner and friends. After the campaigns had been conducted, most channels were mentioned more frequently. The increase in use of channels was greatest for the brochure and the general practitioner. Most channels were indicated more frequently by women with a high level of education than by women with a low level.

A feature of the additional local campaign was that it used complementary channels to inform women wishing to conceive; in particular, it was aimed at women with a low level

Table 2: Percentage increase in use of channels for women with a low and high level of education by type of intervention.

Level of education	National campaign				Additional local campaign			
	Low		High		Low		High	
	Δ^1('95-'96)		Δ^1('95-'96)		Δ^1('95-'96)		Δ^1('95-'96)	
Written materials								
Brochure	6.7	(25.3-32.0)	9.2	(26.0-35.2)	11.6	(16.7-28.3)	17.2	(18.8-36.0)
Billboards	-1.6	(3.8-2.2)	0.7	(4.2-4.9)	2.7	(9.0-6.3)	20.9	(6.3-27.2)
Local newspaper [2]	1.8	(3.8-5.6)	1.4	(6.3-7.7)	-3.5	(16.7-13.2)	-0.6	(21.9-21.3)
Advertisement	4.6	(3.8-8.4)	0	(4.2-4.2)	1.1	(11.5-12.6)	12.3	(3.1-15.4)
Poster in waiting room [1]	4.4	(11.3-15.7)	3.0	(12.5-15.5)	6.1	(9.0-15.1)	25.3	(6.3-31.6)
Advertisement in bus stops [1]	0.6	(0-0.6)	-4.2	(4.2-0)	3.1	(2.6-5.7)	6.7	(10.9-17.6)
Care givers								
General practitioner	9.1	(13.9-23.0)	12.2	(18.8-31.0)	10.9	(2.6-5.7)	3.8	(21.9-25.7)
Pharmacy	2.5	(7.6-10.1)	7.5	(11.5-19.0)	1.7	(11.5-13.2)	8.7	(3.1-11.8)
Gynaecologist	0.8	(7.6-8.4)	-0.9	(11.5-10.6)	-2.7	(7.7-5.0)	2.7	(4.7-7.4)
Midwife	-0.7	(1.3-0.6)	-0.3	(3.1-2.8)	0.6	(3.8-4.4)	1.3	(1.6-2.9)
Social contacts								
Partner	-2.1	(3.8-1.7)	-2.8	(6.3-3.5)	-1.3	(2.6-1.3)	-1.0	(4.7-3.7)
Friends	-0.6	(15.2-14.6)	0.2	(12.5-12.7)	12.3	(10.3-22.6)	2.8	(14.1-16.9)
Family	14.0	(6.3-20.3)	5.4	(7.3-12.7)	3.5	(10.3-13.8)	1.0	(7.8-8.8)

[1] Percentage of increase in use of channel

[2] Channels only used in the regions with the additional local campaign

of education. These complementary channels were the local newspapers, posters in waiting rooms, and advertisements in bus stops. The frequency with which respondents said they had seen advertisement about folic acid in local newspapers did not increase after the additional local campaign had been conducted. While sightings of the posters in the waiting room and the advertisements in bus stops were reported more frequently, they were not reported more often by women with a low level of education than by those with a high level. For example in 1996, 5.7% of the women with a low level of education and 17.6% of the women with a high level of education reported seeing the advertisement in the bus stops.

Awareness knowledge

The percentage of women who reported that they had heard of folic acid before the last menstrual period increased from 41.7% in 1995 to 77.3% in 1996. In 1995, the frequency with which women with a low educational level reported they had heard of folic acid was lower than that of women with a high level of education (28.1% versus 57.5%). In 1996, the figures had increased to 63.6% and 88.0% respectively. Only women who had heard of folic acid before the last menstrual period were included in the analysis of the effect criteria.

Table 3: Distribution of awareness knowledge by level of education and type of intervention.

	National campaign		Additional local campaign		Total	
	1995 n (%)	1996 n (%)	1995 n (%)	1996 n (%)	1995 n (%)	1996 n (%)
Heard of folic acid before last menstrual period						
Low	81 (26.7)	187 (63.8)	87 (29.5)	163 (63.4)	168 (28.1)	350 (63.6)
Moderate	123 (40.9)	237 (79.8)	189 (50.3)	342 (85.()	312 (46.1)	579(83.3)
High	108 (60.0)	146 (85.4)	75 (54.3)	141 (91.0)	183 (57.5)	287 (88.0)
Knowing when to use folic acid [1]	256 (94.8)	470 (93.3)	282 (94.6)	567 (94.0)	538 (94.7)	1037 (93.7)
Low	62 (87.3)	148 (91.9)	66 (93.0)	130 (93.5)	128 (90.1)	278 (92.7)
Moderate	97 (97.0)	199 (93.9)	156 (95.7)	296 (94.0)	253 (96.2)	495 (93.9)
High	93 (97.9)	121 (93.8)	56 (93.3)	123 (94.6)	149 (96.1)	244 (94.2)

[1] Percentage calculated on those who had heard of folic acid.

In 1995, 94.7% of the respondents who had heard of folic acid knew when to use it, compared to 93.7% in 1996. Neither did we find any difference in knowledge between the region with the national campaign and the region with the additional local campaign in 1995 and 1996 (see table 3). In the region with the additional local campaign, there were no

differences in knowledge about when to use folic acid with regard either to the women's educational levels, or to when the women were polled (i.e. before or after the implementation of the campaigns). Neither was there any noteworthy change in these knowledge levels between 1995 and 1996. In 1995, women with a low level of education in the region with the national campaign were slightly less likely to indicate an accurate knowledge of the matter than women with a high level of education in this region (87.3% versus 97.9%, respectively; P<0.01). In 1996, this difference had levelled (91.9% versus 93.8%, respectively).

Perceived safety

Overall, the mean score for perceived safety increased from 0.74 in 1995 to 0.81 in 1996 (P<0.05; table 4). The difference in mean score between 1995 and 1996 for women in the region with the national campaign was comparable with that for women in the region with the additional local campaign. Both in 1995 and 1996, women with a low level of education had a lower mean score on perceived safety than women with a high level (1995: 0.60 versus 0.87, respectively, p=0.001; 1996: 0.69 versus 0,95, respectively, P<0.001). Overall, the increase in perceived safety among women with a low educational level appeared comparable to that of women with a high level.

Attitude

The mean score for attitude towards folic acid use increased from 1.09 in 1995 to 1.29 in 1996 (P<0.001, table 4). In both regions, a similar increase in mean score for attitude was found after the implementation of the campaigns. In 1995, women with a low level of education were found to have a mean score for attitude that was similar to that of women with a high level, and both subgroups also had a comparable positive change in their attitude after the campaigns had been implemented.

Subjective norm

The mean score for subjective norm increased from –0.35 in 1995 to –0.09 in 1996 (P<0.001). The increase in mean score for subjective norm from 1995 to 1996 was not higher in the region with the additional campaign than in the region with the national

campaign. In 1995, the mean score for subjective norm in women with a low level of education was similar to that for women with a high level. In the region with the local campaign, the subgroups showed a comparable increase in mean score after the implementation of the campaigns. This was different in the region with the national campaign, where the increase in mean score was less for women with a low level of education than for women with a high level.

Table 4: Mean score on behavioural determinant by level of education and type of intervention.

	National campaign		Additional local campaign		Total		
Effect criteria [1]	1995	1996	1995	1996	1995	1996	
Perceived safety	0.76	0.85	0.72	0.77	0.74	0.81	*
Low	0.60	0.72	0.60	0.67	0.60 **	0.69	**
Moderate	0.74	0.86	0.74	0.76	0.74	0.80	
High	0.91	1.00	0.81	0.89	0.87	0.95	
Attitude	1.18	1.36	0.99	1.23	1.09	1.29	*
Low	1.22	1.44	1.00	1.27	1.11	1.36	
Moderate	1.22	1.33	0.99	1.21	1.08	1.26	
High	1.13	1.32	0.98	1.22	1.07	1.27	
Subjective norm	-0.30	-0.09	-0.38	-0.10	-0.35	-0.09	*
Low	-0.25	-0.09	-0.34	-0.11	-0.30	-0.10	
Moderate	-0.31	-0.17	-0.42	-0.06	-0.38	-0.11	
High	-0.33	-0.02	-0.29	-0.09	-0.31	-0.03	

[1] Mean score on a scale from –2 to 2

* $p<0.05$ for overall change between 1995 and 1996

** $p<0.05$ for difference between low and high level of education

Folic acid use

Folic acid use during the time around conception increased from 16.8% in 1995 to 48.6% in 1996. (table 5) Both in 1995 and 1996, use was higher in women with a high level of

education (1995: 27.4% versus 9.7%, P<0.001; 1996:61.5% versus 38.7%, P<0.001). The difference in folic acid use between women of different educational level increased. The difference in folic acid use between women with high and low educational levels was comparable across regions.

Table 5: Folic acid use[1] by level of education and type of intervention.

	National campaign				Additional local campaign				Total [1]			
	1995		1996		1995		1996		1995		1996	
	n	%[2]	n	%[2]	n	%[2]	n	%[2]	n	%[2]	n	%[2]
Level of education	140	17.3	355	45.9	135	16.3	428	51.0	275	16.8	783	48.6*
Low	28	9.2	116	39.6	30	10.2	97	37.7	58	9.7**	213	38.7**
Moderate	52	16.4	136	44.2	72	18.5	221	53.3	124	18.2	357	51.3
High	56	30.9	102	59.6	32	22.9	99	63.5	88	27.4	201	61.5

1 Odds ratio of additional effect of local Folic Acid Campaign on proper folic acid use = 0.8, 95% confidence interval 0.5-1.5. Odds ratio is adjusted for level of education.

2 Percentage calculated on all women of that level of education.

3 Number of women who heard of and used folic acid. Women who took folic acid by accident because it was included in the multivitamin supplement they took but had not heard of folic acid were excluded.

* p<0.05 for overall change between 1995 and 1996

** p<0.05 for difference between low and high level of education

This sharp increase in folic acid use between 1995 and 1996 was compared to the increase in folic acid use from 1994 to 1995, when no official campaign was conducted, to determine whether the increase between 1995 and 1996 had resulted mainly from the Folic Acid Campaign. As the data for 1994 are available only for the regions with the national campaign, the comparison was limited to these regions. Folic acid use in woman of all educational levels increased faster after the national Folic Acid Campaign was conducted. In 1994, 6.4% of women with a low level of education reported folic acid use; in 1995 and 1996, folic acid use in the same group had increased to 9.2% and 39.6% (Table 5). For

women with a high level of education, folic acid use was 12.0%% in 1994, 30.9% in 1995 and 59.6% in 1996.

Discussion

In the Netherlands, women wishing to conceive are advised to use tablets containing 0.4 or 0.5mg folic acid periconceptually to reduce the risk of having a child with a neural tube defect. To stimulate the use of folic acid, a national and additional local Folic Acid Campaign was conducted in the autumn of 1995. The additional local campaign was targeted at women with a low SES.

A mass media approach using many different channels was used to reach women wishing to conceive. The respondents reported on the channels in which their attention had been drawn to the campaign. In general, women with a high level of education indicated all channels more often. A brochure, the general practitioner and friends were mentioned most frequently both by women of both educational levels. Though both groups also reported seeing the complementary channels used during the additional local campaign – i.e. local newspapers, posters in waiting rooms, and advertisements in bus stops – women with a high level of education more often reported seeing these channels, even though the introduction of these complementary channels had been targeted at women of a low educational level. Overall, we find a mass media approach effective in bringing women information on folic acid use, certainly in a large population of women with no prior knowledge of health benefits associated with folic acid use. Unfortunately, even though complementary channels were introduced to reach women with a low educational level, these women were not reached to the same extent as women with a high level of education.

For the evaluation of the mass media campaigns a framework of outcome criteria was developed. [12,13] Empirical tests of the hypothetical framework indicated that folic acid use was best predicted by attitudes and subjective norm, and that women's attitudes were strongly grounded in beliefs about the health benefits and safety (i.e. perceived safety) of folic acid use. [12] As a consequence, awareness knowledge, attitude, subjective norm, perceived safety and folic acid use were selected as criteria for assessing the effectiveness of the mass media campaigns promoting the use of folic acid. It certainly is a weakness of this study that we

were not able to catch up with the newer and more extended version of the model, the Theory of planned behaviour. This would have given the opportunity to get insight in the importance of perceived behavioural control for the formation of one's intention to use folic acid. Our study agreed with the results of a Norwegian study in that we found that women with a low level of education had less often heard of folic acid than women with a high level. [15] This difference already existed before the onset of the campaigns, and persisted after the campaigns had been implemented. The results indicate that, once a woman was reached, the information on folic acid was equally well understood by woman of all groups, irrespective of their educational background: we found no difference with regard to knowledge about the period in which women are advised to use it.

The mean scores for three effect criteria (perceived safety, attitude, and subjective norm) had all increased considerably between 1995 and 1996. Before the campaigns were implemented no difference in mean score on subjective norm for low and high-educated women was found. It was only in the region with the additional local campaign that women with a low level of education had derived as much benefit from the campaigns as their better-educated counterparts. This indicates that in the region with the additional local campaign for women with a low educational level, the subjective norm changed more in a positive direction than in the region with only the national campaign. As women with a low level of education seems to be more sensitive for the social environment this could be the key to success in reducing differences in folic acid use between women of different educational level. This should be explored in new promotion health strategy.

The aim of the health education is that the proportion of women that use folic acid should be similar, regardless of educational level, especially for women in the region where the additional local campaign was conducted. Therefore, we chose to report the absolute difference in folic acid use between women of different level of education in stead of odds ratios. As shown the proportion of folic acid use is not similar is both groups of educational level, but at least the absolute differences did not increase. Despite the additional efforts of the local campaign, the uptake of folic acid intake was not greater in these regions compared to the regions with only the national campaign. Although, there is still considerable difference in folic acid use between women across educational groups, the impact of the rise in folic acid use on public health may be larger than expected at first

sight. More than one third of Dutch women have a low level of education, whereas approximately 17% have a high level. A small increase in folic acid use in the larger group will therefore have a greater effect on public health than a large increase in folic acid use by women in the smaller group. Furthermore women with a low level of education appear to be at greater risk of having a child with a neural tube defect. So, more children with a neural tube defect are born is this grroup and, therefore, more neural tube defects may be prevented in this group.

From this study it seems legitimate to conclude that a mass media approach is generally effective in increasing folic acid use. In this case the used approach was not effective in reducing the gap that exists between women of different educational levels with regard to proportion of women reached and folic acid use. Research is needed on how women with a low educational level can be reached, i.e. which communication channels lead to more exposure to the preventive measure. To maintain proper folic acid use (and, preferably, to increase it), there is a need for new health education and health promotion strategies that target both the general population and a specific target population. There is a wide diversity of information channels: if we intend to inform women who wish to conceive, many such channels should be used. Three channels appear to be particularly important in reaching women with low level of education: family, friends, and the general practitioner. The effectiveness of the use of these channels should be evaluated in future campaigns aimed at informing women with a low level of education.

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Chapter 7

The multiple records system estimator when registrations partly overlap in time and by region.

E.N. Zwane, K.M. van der Pal-de Bruin, P.G.M. van der Heijden

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Abstract

In multiple records systems estimation it is usually assumed that all registrations relate to the same population. In this paper we develop a method which can be used when the registrations relate to different populations, in the sense that they cover, for example, different time periods or regions. We show that under certain conditions ignoring that the registrations relate to different populations results in correct estimates of population size. The EM algorithm is presented as a method that can be used for more general problems. The parametric bootstrap is used to construct a confidence interval. The proposed method is then applied to a data set with five registrations of neural tube defects, that cover different time periods.

Introduction

Capture-recapture analysis was developed by ecologists for assessing the size of animal populations in the wild. [1] The population size is estimated from the degree of overlap between two or more samples obtained from the same population. In epidemiology capture-recapture methods are used to estimate or adjust for the extent of incomplete ascertainment using information from overlapping cases from distinct sources. [2,3]

For two overlapping samples (from the same population) the method is used to estimate the part of the population that is not observed (individuals in neither of the two samples). This estimation is accomplished under the assumption of independence of inclusion probabilities. [2,3] Another assumption is homogeneity of inclusion probabilities over individuals. Although it has been long thought that the inclusion probabilities for both lists should be homogeneous [2], it has recently been shown that only one of the lists has to have homogeneous inclusion probabilities [4,5]when the joint probability is positive.

Categorical covariates are frequently used to diminish heterogeneity of inclusion probabilities, and for this log-linear models are widely used, as it is possible to incorporate stratification variables and permit dependence between sources. [6-8]

In this paper we deal with a special case of heterogeneous inclusion probabilities, namely the case where populations from where the lists emanate partially overlap. This results in some individuals being systematically missed by one or more of the lists. Therefore the *joint* inclusion probabilities are zero for some individuals in the combined population. A first example is that lists do not cover the same region. For this example, a stratum is defined as a subregion, and not every list is observed in each subregion. A second example is when lists do not cover the same time periods. Here the strata are defined as the subperiods of time. We approach the absence of observations in certain strata for certain lists as an incomplete data problem.

The EM algorithm [9] is an iterative procedure for obtaining maximum likelihood estimates in incomplete data. In the standard capture-recapture problem the EM algorithm was can be used to estimate part of the population missed by all sources [10]. As we have partially overlapping populations there are more entries missing in the contingency table than in the standard capture-recapture problem. When some lists are not operating in some strata,

implying that there are several unobservable cells that are a result from non-operating lists, the EM algorithm can be used to estimate these missing entries, and thus the population size.

In Section 2 we present two simple capture-recapture models, one where one list is operating in a larger region than another list, and one where two lists operate in different but partially overlapping regions. We show under which conditions stratification by region can be ignored. We then present the EM algorithm in Section 3, and show how it can be used to estimate population size in partially overlapping populations, and further show that for simple models the results will be equivalent with using traditional methods. Finally, in Section 4 analyse a data set on neural tube defects which motivated this article.

Simple partially classified data

In this section we develop a method of estimating population size in dual record systems when the registrations relate to different but overlapping populations.

Simple capture-recapture model

The simplest multiple record system consists of two lists. Let Π_1 and Π_2 be the probability of capture by list 1 and 2 respectively. The joint probabilities are denoted by π_{ij} (i=0,1; j=0,1), where π_{10} is the probability to be in list 1 only, π_{01} is the probability to be in list 2 only and, π_{11} is the probability to be in both lists. The corresponding frequencies are shown in table 1. The probability π_{00} and frequency n_{00} are unknown and have to be estimated in order to compute an estimate of the unknown population size N. Furthermore $n_{ij}=N\pi_{ij}$.

Table 1: Simple capture-recapture problem

List 1	List 2	
	No	Yes
No	n_{00}	n_{01}
Yes	n_{10}	n_{11}

Assuming independence of inclusion probabilities Π_1 and Π_2 we can estimate Π_1, Π_2 and N by

$$\hat{\Pi}_1 = \frac{n_{11}}{n_{11}+n_{01}} \quad , \quad \hat{\Pi}_2 = \frac{n_{11}}{n_{11}+n_{10}} \tag{1}$$

$$\hat{N} = \frac{n_{11}}{\hat{\Pi}_1 \hat{\Pi}_2}$$

and this result forms the basis of our development.

Two lists and two strata

Assume now that we have two strata, for example, two regions. Region is a stratifying variable with two categories indexed by k, where k=1 denotes the "north region" and k=2 the "south region" (see table 2).

Table 2: Capture-recapture problem with 2 lists and 2 regions

Region	List 1	List 2	
		No	Yes
North	No	$n_{00\|1}$	$n_{01\|1}$
	Yes	$n_{10\|1}$	$n_{11\|1}$
South	No	$n_{00\|2}$	$n_{01\|2}$
	Yes	$n_{10\|2}$	$n_{11\|2}$

Let $\Pi_{1|1}$ and $\Pi_{2|1}$ be the probabilities to be in list 1 and 2 in the north region and $\Pi_{1|2}$ and $\Pi_{2|2}$ be the probabilities to be in list 1 and 2 in the south region. Let the joint probabilities for the north region be $\pi_{ij|1}$ and the joint probabilities for the south region be $\pi_{ij|2}$. Let the unknown population size for the north and south region be N_1 and N_2 respectively. By analysing the data from each stratum separately we can estimate $\Pi_{1|1}$, $\Pi_{2|1}$, and N_1 by

$$\hat{\Pi}_{1|1} = \frac{n_{11|1}}{n_{11|1} + n_{01|1}} \quad , \quad \hat{\Pi}_{2|1} = \frac{n_{11|1}}{n_{11|1} + n_{10|1}} \tag{2}$$

$$\hat{N}_1 = \frac{n_{11|1}}{\hat{\Pi}_{1|1}\hat{\Pi}_{2|1}}$$

and $\Pi_{1|2}$, $\Pi_{2|2}$, and N_2 by

$$\hat{\Pi}_{1|2} = \frac{n_{11|2}}{n_{11|2} + n_{01|2}} \quad , \quad \hat{\Pi}_{2|2} = \frac{n_{11|2}}{n_{11|2} + n_{10|2}} \tag{3}$$

$$\hat{N}_2 = \frac{n_{11|2}}{\hat{\Pi}_{1|2}\hat{\Pi}_{2|2}}$$

Now let list 2 be observed only in the north region. Further assume that we ignore the fact that the registrations refer to different populations, by ignoring the variable region. Let us denote the elements in the table where region is ignored by $n_{ij|+}$. These elements are related to the elements in table 2 by $n_{11|+}=n_{11|1}$, $n_{01|+}=n_{01|1}$, and $n_{10|+}=n_{10|1}+n_{10|2}+n_{11|2}$. The question is: can (1) be used to estimate N? and if so, under what assumptions? In other words, when would ignoring the fact that list 2 is observed only in one region lead to and unbiased estimate of the population size? The observations to be estimated are $n_{00|+}=n_{00|1}+n_{00|2}+n_{01|2}$. Using this we find that,

$$\hat{\Pi}_{1|+} = \frac{n_{11|1}}{n_{11|1} + n_{01|1}} \quad , \quad \hat{\Pi}_{2|+} = \frac{n_{11|1}}{n_{11|1} + n_{1011} + n_{11|2} + n_{10|2}},$$

$$\hat{N}_{+} = \left(\frac{n_{11|1}}{\hat{\Pi}_{1|1}}\right)\left(\frac{n_{11|1} + n_{10|1} + n_{11|2} + n_{10|2}}{n_{11|1}}\right) \tag{4a}$$

$$= \left(\frac{n_{11|1}}{\hat{\Pi}_{1|1}}\right)\left(\frac{1}{\hat{\Pi}_{2|1}} + \frac{n_{11|2} + n_{10|2}}{n_{11|1}}\right) \tag{4b}$$

$$= \hat{N}_{1} + \left(\frac{n_{11|2} + n_{10|2}}{\hat{\Pi}_{1|1}}\right) \tag{4c}$$

$$= \hat{N}_{1} + \left(\frac{n_{11|2}}{\hat{\Pi}_{1|1}\hat{\Pi}_{2|2}}\right) \tag{4d}$$

Equation (4d) shows that if $\hat{\Pi}_{1|1}=\hat{\Pi}_{1|2}$, then $\hat{N}_{+}=\hat{N}_{1}+\hat{N}_{2}$. Thus for two lists and two strata even if the joint inclusion probability of some individuals in the combined population is zero the dual record-systems estimator can still be used, as long as $\hat{\Pi}_{1|1}=\hat{\Pi}_{1|2}$, or alternatively, the list observed in both strata has to have homogeneous inclusion probabilities.

Two lists and three strata

Instead of two regions we now assume that we have two lists and three regions (north, south, and west). We denote the "west region" by k=3, and this scenario is shown in table 3.

Table 3: Multiple record system for 2 lists and 3 regions

Region	List 1	List 2	
		No	Yes
North	No	$n_{00\|1}$	$n_{01\|1}$
	Yes	$n_{10\|1}$	$n_{11\|1}$
South	No	$n_{00\|2}$	$n_{01\|2}$
	Yes	$n_{10\|2}$	$n_{11\|2}$
West	No	$n_{00\|3}$	$n_{01\|3}$
	Yes	$n_{10\|3}$	$n_{11\|3}$

Assume that list 1 operates in the north and south, and list 2 operates in the north and west, so the regions of list 1 and 2 partly overlap but the region of list 2 is not simply a subregion of the region of list 1. The cells actually observed in the north are $n_{10|1}$, $n_{11|1}$, $n_{01|1}$, in the south $n_{1+|2}$, and in the west $n_{+1|3}$. Only the observations in the north have non-zero joint 'capture' probabilities. Ignoring region, the elements of the resulting table are related to those in table 3 by $n_{11|+}=n_{11|1}$, $n_{10|+}=n_{10|1}+n_{10|2}+n_{11|2}$, and $n_{01|+}=n_{01|1}+n_{01|3}+n_{11|3}$. The estimates of $\Pi_{1|+}$, $\Pi_{2|+}$, N_+ from this table are

$$\hat{\Pi}_{1|+}=\frac{n_{11|1}}{n_{11|1}+n_{01|1}+n_{01|3}+n_{11|3}},\hat{\Pi}_{2|+}=\frac{n_{11|1}}{n_{11|1}+n_{1011}+n_{11|2}+n_{10|2}},$$

$$\hat{N}_+ = n_{11|1}\left(\frac{n_{11|1}+n_{01|1}+n_{01|3}+n_{11|3}}{n_{11|1}}\right)\left(\frac{n_{11|1}+n_{10|1}+n_{10|2}+n_{11|2}}{n_{11|1}}\right) \quad (5a)$$

$$= n_{11|1}\left(\frac{1}{\hat{\Pi}_{1|1}}+\frac{n_{01|3}+n_{11|3}}{n_{11|1}}\right)\left(\frac{1}{\hat{\Pi}_{2|1}}+\frac{n_{10|2}+n_{11|2}}{n_{11|1}}\right) \quad (5b)$$

$$= \hat{N}_1+\frac{n_{11|2}}{\hat{\Pi}_{1|1}\hat{\Pi}_{2|2}}+\frac{n_{11|3}}{\hat{\Pi}_{1|3}\hat{\Pi}_{2|1}}+\frac{(n_{10|2}+n_{11|2})(n_{01|3}+n_{11|3})}{n_{11|1}} \quad (5c)$$

This shows that, even if $\hat{\Pi}_{1|1}=\hat{\Pi}_{1|2}$ and $\hat{\Pi}_{2|1}=\hat{\Pi}_{2|3}$, collapsing the table over region results in a positively biased estimate of population size, the bias being $(n_{10|2}+n_{11|2})(n_{01|3}+n_{11|3})/n_{11|1}$. However, as this quantity has observable values it can be subtracted from $\hat{N}_{+}$ to get an unbiased estimate for the population size.

In conclusion, we note that in certain cases ignoring stratification is not a problem but in some cases it is. This shows that there is a need to develop a general approach which would work for the cases where stratification has to be incorporated in the models.

EM algorithm

A widely used method for analysis of partially classified counts is the EM algorithm. [9] This technique was developed for data that are 'missing at random' (MAR). Applying the EM algorithm to capture-recapture data with partially overlapping populations is valid, if the non-operating lists are missing by design (the missingness is ignorable). For epidemiological capture-recapture data populations might partially overlap, for example:

- by year due to development of registrations which are hoped to be better than active ones or the closing of obsolete existing registrations,
- and by region as some regions might have registrations that are not yet implemented in other regions.

These examples are all design based, implying that the use of the EM algorithm is valid.

As an illustration of how the EM algorithm works we use the example of Section 2.2 where we have two lists and two strata (regions), with only list 1 operating in the second region. In the E-step of the EM algorithm we distribute the observations of list 1 in the "south", $n_{1+|2}$ using the information obtained in the "north". The expectations for $n_{10|2}$ and $n_{11|2}$ (using conditional probabilities) are

$$\hat{n}_{10|2} = \frac{n_{10|1}}{n_{10|1}+n_{11|1}} \times \hat{n}_{1+|2}$$

$$\hat{n}_{11|2} = \frac{n_{11|1}}{n_{10|1} + n_{11|1}} \times \hat{n}_{1+|2}$$

For this example, in the M-step a saturated log-linear model with structural zero cells for the observations $n_{00|1}$, $n_{00|2}$ and $n_{01|2}$ is fitted. After convergence the parameter estimates can be used to estimate the number of observations in the structurally zero cells. The EM algorithm implicitly assumes $\hat{\Pi}_{1|1}=\hat{\Pi}_{1|2}$. It can be easily verified that the total number of observations missed by all lists $n_{00|1}+n_{00|2}+n_{01|2}$ will be equal to that obtained by collapsing the table as shown in Section 2.2. Thus the also EM is able to provide the solution to the problem.

For the example in Section 2.3, we have two lists and three strata, with the first region having both lists operating, region two having only list 1 operating and region three having only list 2 operating, the procedure for the EM algorithm is the same. In the E-step the numbers observed in region two ($n_{1+|2}$) and those in region three ($n_{+1|3}$) are distributed using the information from the complete region (region 1). In the M-step a saturated log-linear model with structurally zero cells for $n_{00|1}$, $n_{00|2}$, $n_{00|3}$, $n_{01|2}$, and $n_{10|3}$ is fitted. Afterwards the structural zero cells are estimated using the parameter estimates from the model. The EM algorithm in this case implicitly assumes $\hat{\Pi}_{1|1}=\hat{\Pi}_{1|2}$ and $\hat{\Pi}_{2|1}=\hat{\Pi}_{2|3}$. The estimate of population size obtained using the EM algorithm is unbiased, and thus it results in an estimate of population size from the collapsed table corrected for the bias $([n_{10|2}+n_{11|2}][n_{01|3}+n_{11|3}]/n_{11|1})$ found in (5c).

The above are simple cases, where the EM algorithm has one E-step and a saturated model holds for the M-step. These cases assume homogeneous ascertainment probabilities, that is, the ascertainment probabilities in the complete stratum are also assumed to hold in the incomplete strata. When there are multiple lists and multiple strata, lists effects as well as stratum effects can be entertained, implying that, instead of the saturated model, a wide array of restrictive (log-linear) models can be investigated.

The EM algorithm can be easily extended to situations where there are multiple lists and many strata. To illustrate the general procedure, assume that we have four lists. Denote n_{ijklr} to be the observed cell frequencies from a stratum where all lists are operating, with the indices for the lists being i, j, k, and l, (i=0,1; j=0,1; k=0,1; l=0,1) and the stratum index is r (r=1,2,...,R). Assume that in stratum 1 and 2 only the first two lists are operating, implying that for r=1,2 n_{ij++r} is observed. For stratum 3 up to R there is only one structurally zero cell, that is, the missing observation n_{0000r} (r=3,⋯,R). For stratum 1 and 2, there are 4 structurally zero cells, namely the observations n_{0000r}, n_{1000r}, n_{0100r} and, n_{1100r} (r=1,2). Let $\pi_{ijklr}^{(t)}$ be the current estimate of the joint probability for cell (i,j,k,l,r) at the t^{th} iteration of the EM algorithm. The E-step of the EM algorithm calculates the expectation of the cell frequencies for the partially classified frequencies (n_{ij++r}) in stratum 1 and 2 using

$$\hat{n}_{ijklr}^{(t)} = \frac{\sum_{r=3}^{R} \hat{\pi}_{ijklr}^{(t)}}{\sum_{r=3}^{R}\sum_{k,l} \hat{\pi}_{ijklr}^{(t)}} \times \hat{n}_{ij++r}$$

Here $\hat{n}_{ijklr}^{(t)}$ are the completed data at the t^{th} iteration. In the M step a log-linear model is fitted to the completed data, with the cells missing by design denoted as structurally zero. The fitted values from this model are used in the E step of the (t+1) iteration, to derive updates for the completed data. This procedure is repeated until the observed-data likelihood converges. After convergence the parameter estimates are used to find point estimates for the structural zero cells, and an estimate of population size.

As there might be several competing models that can be entertained, it is imperative to find a parsimonious model which best fits the data. The likelihood ratio test can be used to discriminate between two competing (log-linear) models. This test compares the difference in deviance of the two models with the chi-squared distribution for a given the number of degrees of freedom (difference in number of parameters). For this the observed-data

likelihood should be used. Rather than using the likelihood ratio test the researcher can also use the AIC or BIC statistics, which penalise the maximised likelihood for a model by number of parameters. Thus models with more parameters receive a high penalty. The model with the lowest AIC or BIC is preferred.

We propose to use the parametric bootstrap [11,12] to calculate confidence intervals for the point estimates. The advantage of the bootstrap method over asymptotic methods is that formulae for asymptotic standard errors are available only for the usual approach of multiple record systems estimation, but not for the situation where some of the registrations are not operating in some strata.

Application

We will use data on neural tube defects (NTD's) in the Netherlands to illustrate our procedure. In the Netherlands cases with NTD's are registered in several national databases. We will describe the five registrations briefly.

1. **Dutch Perinatal Database I (R1)**: This is an anonymous pregnancy and birth registry of low risk pregnancies and births, even if care only relates to a part pregnancy or delivery. Data over the period 1988 through 1998 are used.
2. **Dutch Perinatal Database II (R2)**: This list registers anonymous data concerning the birth of a child in secondary care. Data over the period 1988 through 1998 are used.
3. **National Neonate Database (R3)**: This list contains anonymous information about all admissions and re-admissions of newborns to paediatric departments within the first 28 days of life. Data was used for the period 1992-1998.
4. **Dutch Monitoring System of Child Health Care (R4)**: R4 registers live born infants with a NTD who visit a paediatrician for the first time. All paediatric departments participate. NTD's are registered since 1993.
5. **Dutch Association of Patients with a NTD (R5)**: A short questionnaire was sent to every member of R5 with a NTD affected child between 1986 and 1998.

It should be noted that abortions are possible in R1 and R2, whereas they cannot appear in the other registrations. Therefore we consider only children with pregnancy duration from 24 weeks.

None of these databases include all cases of neural tube defects because of, for instance, non-participation of Healthcare professionals. Thus multiple record estimation has to be used to estimate the size of babies born with NTD's. The usual approach is to fit log-linear models with a structural zero for the observations missed by all lists. [3] In our situation this usual approach could not be adopted as some of the registrations were not available for some years: for 1988-1991 only three registrations are available (R1,R2,R5) and in 1992 only four registrations are available (R1,R2,R3,R5). Thus the EM algorithm is a tool which can effectively analyse data of this form, by utilising information on relations between registrations while stratifying by year.

To apply the EM we note that for 1992 the observed array is 2×2×2×2, and in the E step it is spread out into a five dimensional array of 2×2×2×2×2 using the five dimensional arrays for years 1993-1998. In 1993-1998 we have one structural zero cell in a year, namely the cell corresponding to observations missed by all lists. For 1992 we have two structural zeros, one corresponding to the observations missed by all lists and one corresponding to the observations which are only contained in the registration not operating in 1992. For 1988-1991 there are four structural zero cells and the two registrations are completed using the procedure described above.

The main effects only model has a poor fit, see table 4. Year (Y_{cat}) is used as a stratifying variable in the table. In the second step, we use the approach to include heterogeneity terms in the model. [2] First order heterogeneity (H1) results in a big improvement of the fit, but second order heterogeneity (H2) does not significantly fit better than model 2. It turns out that the inclusion probabilities for R1 and R2 vary over time (model 7) but the other registrations do not (models 4-6). Model 11 shows that the registrations are pairwise related except for R3 and R4 (as the R4 and R5 interaction is set to zero in order to estimate H1). Models 12-14 allow the interactions to vary over time but none of these models lead to an improvement in the fit.

Table 4: Selected models with deviance and AIC

Model	Design matrix	Number of parameters	Deviance	AIC	Total $\hat{N}_y$
1	R1+R2+R3+R4+R5+Y_{cat}	16	409.42	441.42	3196
2	1 + H1	17	358.82	392.82	4786
3	2 + H2	18	358.67	394.67	4510
4	2 + (R1+ R2+R3+R4+R5) * Y_{cat}	67	190.75	324.75	4703
5	2 + (R1+ R2+R3+R5) * Y_{cat}	57	192.99	306.99	4710
6	2 + (R1+ R2+R3) * Y_{cat}	47	203.27	297.27	4685
7	2 + (R1+ R2) * Y_{cat}	37	212.74	286.74	4678
8	2 + R1 * Y_{cat}	27	280.46	334.46	4988
9	2 + R2 * Y_{cat}	27	255.95	309.95	4540
10	7 + R1*(R2+R3+R4+R5)+ R2* (R3+R4+R5)+ R3*(R4+R5)	46	156.29	248.29	3983
11	7 + R1*(R2+R3+R4+R5)+ R2* (R3+R4+R5)+ R3*R5	45	156.30	246.30	3983
12	11 + (R1*(R2+R3+R4+R5)+ R2* (R3+R4+R5)+ R3*R5)*Y_{cat}	135	101.88	371.88	4064
13	11 + (R1*(R2+R3+R5))*Y_{cat}	85	118.33	288.33	3960
14	11 + R1*R2*Y_{cat}	55	140.02	250.02	3979

The final model we chose is model 11. We used the parametric bootstrap with 500 replications to compute the confidence intervals for the yearly estimates of population size (see table 5). The confidence intervals show that, most often, the distribution of the estimates by year is skewed. Furthermore, years with a higher number of structurally zero cells (1988-1992) have somewhat wider confidence intervals.

Table 5: Estimates of population size and 95% quantile confidence interval by year for model 11

Year	Observed	Estimates for structural zero cells	Estimated population size	95 % C.I. lower	upper
1988	145	93	238	161	290
1989	163	41	204	163	243
1990	170	61	231	185	269
1991	163	37	187	152	227
1992	172	114	286	211	319
1993	160	60	220	193	264
1994	162	113	275	235	355
1995	174	133	307	263	396
1996	153	116	269	233	345
1997	180	126	306	268	380
1998	154	100	254	220	319

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Chapter 8

Periconceptional folic acid use and the prevalence of neural tube defects in the Netherlands

K.M. van der Pal-de Bruin, P.G.M. van der Heijden, S.E. Buitendijk, A. L. den Ouden

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Abstract

Objective: To study the effect of increased folic acid intake on the prevalence of neural tube defects (NTD) in the Netherlands.

Study design: Using the capture-recapture method, the prevalence of NTD was estimated on the basis of five different registries on births affected by NTD.

Results: Total prevalence over the 1988-1998 period varied between 1.43 to 1.96 per 1,000 live and stillbirths. No decrease in total prevalence was found to have taken place during that period. Scrutiny of the last two years, 1997 and 1998, in which increased folic acid intake might be expected to have had an effect, did not give any indication that the prevalence of NTD was falling.

Conclusions: A decrease in the Dutch prevalence of NTD during the study period could not be demonstrated due to the relatively small number of women using folic acid periconceptionally. This does not mean automatically that periconceptional folic acid use is ineffective in reducing the Dutch prevalence of NTD. Further monitoring is needed.

Introduction

Neural tube defects (NTD) are among the most frequent birth defects contributing to infant mortality and serious disability. The two most common types of NTD are anencephaly and spina bifida. A child with anencephaly cannot survive, and dies before birth or shortly afterwards. A child with spina bifida can survive, but often has serious functional impairments, and may be mentally retarded. In the Netherlands, at least 27% of the children registered with a neural tube defect during the last decade died within the first month of life. [1]

Observational studies [2-5] and randomised trials [6,7] have shown that folic acid supplementation in the periconceptional period reduces the occurrence of spina bifida and anencephaly. In the autumn of 1995, a national and a local Folic Acid Campaign were conducted in the Netherlands to provide information on periconceptional folic acid use to healthcare professionals and women wishing to conceive. A year later, 77.3% of the pregnant women had heard of folic acid use before their last menstrual period, and 21% had actually used folic acid throughout the entire recommended period (i.e. from four weeks before conception until eight weeks after it). [8] By the end of 1998, appropriate folic acid use had risen to 35.5%. [9]

It was not known whether this increased folic acid intake influenced the prevalence of NTD in the Netherlands. In this country, newborns with neural tube defects are registered in several national and regional databases. However, none of these databases is complete. On the basis of regional data collected for EUROCAT, a programme for the epidemiologic surveillance of congenital anomalies in Europe, it is estimated that approximately 260 children are born annually with a neural tube defect, including 125 live births with spina bifida. [1]

Using the capture-recapture method, it is possible to estimate the prevalence of NTD on the basis of available databases. This method was originally developed by ecologists to assess the size of animal populations in the wild; [10] the population size is estimated from the degree of overlap between two or more samples obtained from the same population. This method has been applied in epidemiology to study for example birth defects, cancer, drug use, infectious disease, injuries, and insulin dependent diabetes mellitus.[11]

In order to study the effect of the increased folic acid intake since 1994, we estimated the prevalence of NTD in the period before and during the increase in folic acid use. Prevalence was estimated for the period 1988 through 1998. A distinction was made between births that took place before 24 weeks of gestation (i.e. the legal limit for pregnancy termination), and from 24 weeks. To estimate the prevalence of NTD in the Netherlands, five different sources of information were included in the capture-recapture analysis.

Methods

Registries

NTD was defined as anencephaly, meningocele, meningomyelocele and encefalocele. Information on cases with NTD was obtained from four different registries in the Netherlands, and from the Dutch Parent Association (BOSK). These five sources of information are briefly described below:

1. *The Dutch Perinatal Database 1 (LVR1)* is an anonymous pregnancy and birth registry of low-risk pregnancies and births. In the Netherlands, the midwife is responsible for care in such cases (primary care), which constitute approximately 60% of all births. In our study, we used data from the period 1988 through 1998. During this period, participation in the LVR1 increased from approximately 75% of midwife practices in 1988 to over 90% in 1998.
2. *The Dutch Perinatal Database 2 (LVR2)* registers anonymous data concerning the birth of the child in secondary care. Our study used data from the period 1988 through 1998. During this period, participation in the LVR2 increased from approximately 75% in 1988 to nearly 100% in 1998. It should be noted that if a woman is referred from primary care to secondary care, she may be registered in the LVR1 as well as in the LVR2.
3. *The National Neonatal Database (LNR)*, which started its work in the course of 1991, contains anonymous information on all admissions and re-admissions of newborns to paediatric departments within the first 28 days of life. Our study used data from the period 1992 through 1998. During this period, all ten neonatal intensive care units

(NICU) and 50% of the remaining general paediatric departments participated in the registration.

4. *The Dutch Paediatric Surveillance Unit (DPSU)* registers infants born alive with an NTD upon the occasion of their first visit to a paediatrician. 95% of all paediatric departments participate. NTDs have been registered by the DPSU since 1993; in our analysis, we used data from 1993 through 1998.
5. *Dutch Parents Association of children with an NTD (BOSK)* In our study, we sent a short questionnaire to every member of BOSK who had had an NTD-affected child born between 1988 and 1998. Information was obtained on the mother's date of birth, on the date of birth, initials, gender and place of birth of the child; and on the hospital in which the child was being treated. This information was sufficient to identify records that were duplicated in the other registries.

Identifying duplicate records

Infants with NTD can be registered in more than one of the above registries; in many cases, they are registered several times within the same registry. To make a valid estimate of the prevalence of NTD in the Netherlands, these duplicate records therefore had to be identified very carefully, since non-identified double counts would result in an overestimation of the prevalence.

A set of key variables identified duplicate records within and between the registries. A record was considered identical if all the key variables were identical. Allowing for discrepancies in the set of key variables, each variable was omitted once from the set. Additional variables, such as gestational age, birth weight, and hospital, were used to increase the validity of our identification of duplicate records.

The set of key variables depended on the information that was available in the registries. When the LVR1 and LVR2 were combined, the set of key variables consisted of the year of registration, the first three digits of the zip code, the mother's date of birth, and the birth-date and gender of the child. While the LNR contained information on these variables, only the first two digits of the zip code were available, and solely the mother's year of birth (i.e. rather than the precise date). The DPSU contained all the variables except the mother's date

of birth. The data in the BOSK registry also included all variables and the first two digits of the zip code.

We identified duplicate records across the five registries for each year between 1988 and 1998, systematically following the same approach for each year. Duplicate records were first identified by computer. If the total set of key variables was identical, the records were marked as duplicate. If there was a discrepancy within the set of key variables, the match found by the computer was checked by both the researcher and a paediatrician to ensure that no records had incorrectly been marked as identical. Once all duplicate records had been identified, the records were reduced to a single entry, thus creating a combined database based on five registries that contained a single entry for each NBD.

Statistical method

Capture-recapture methods (also known as multiple record systems estimation) were originally developed to estimate the size of a closed animal population. In such cases, the first stage of this procedure, the so-called capture stage, involves the capture of as many animals as possible in a particular area. These are then tagged and released. In a second stage (the recapture stage), as many animals as possible are captured in the same area. The number of animals in each sample, and the number common to both, are used to estimate the number in the total population. In this process, two assumptions are made: firstly, capture and recapture are assumed to be independent; and secondly, it is assumed that all animals have the same probability of being captured. Violation of these assumptions might lead the true population size to be overestimated or underestimated.

In our case, the number of infants with NTD were estimated, and five sources were used rather than two. Furthermore, separate estimates were made of the number of infants with NTD born before 24 weeks of gestation, and of those born from 24 weeks of gestation. Our reasoning was that births before 24 weeks of gestation include a relatively high number of induced abortions, and that these appeared only in the LVR1 and LVR2 registries. Loglinear models were then fitted to estimate the number of births before 24 weeks of gestation, where in each year the cell for being neither in lvr1 and lvr2 is structurally zero. The final model chosen was lvr1+lvr2+year+(lvr1+lvr2)*yearlin. Here yearlin is a linear term to account for a change in capture probabilities that is linear in the logarithm. The

product term (lvr1+lvr2)*yearlin is shorthand for a linear change through time of the capture probability of lvr1 and a linear change through time of the capture probability of lvr1. For this model the deviance is 23.1 with 18 degrees of freedom, so this model fits adequately. It should be noted that, since there are only two sources, the model assumes that lvr1 and lvr2 are independent.

The number of infants with NTD born from 24 weeks' gestation was estimated using five registries. The standard approach to estimating the number of NTD would be to fit loglinear models with a structural zero cell for observations that are in none of the registries. [13] In this situation, however, the usual approach could not be adopted, as some of the registrations were not available for all of the years: as stated above, the number of available registries increased from three before 1992, to four in 1992, and then to five after 1992. For this reason, we used the Expectation-Maximisation (EM) algorithm to estimate the number of NTD-affected infants who were not registered in the first few years because the registry did not yet existed (Little and Rubin 1987). A loglinear model was fitted the M-step of the algorithm. In this model we did not have to assume that all registrations were are independent. To account for unobserved heterogeneity, we followed the procedure proposed by the IWGDMF, by including a term for the heterogeneity of capture probabilities.The final model we chose was (lvr1+lvr2)*year+lvr1*(lvr2+bosk+lnr+dpsu) +lvr2*(bosk+lnr+dpsu)+(bosk*lnr), where, for example, lvr1*(lvr2+bosk+lnr+dpsu) is shorthand for the two-factor interactions lvr1*lvr2, lvr1*bosk, lvr1*lnr and lvr1*dpsu. The deviance of this model of 151.2 for 192 degrees of freedom is adequate.

To obtain the total number of infants born with NTD for each of the years in the 1988-1998 period, we summed the observed number of infants and the number of missing infants we had calculated via the capture-recapture analysis. The parametric bootstrap was used to calculate confidence intervals for the total number of infants for each year. [14] The advantage of the bootstrap method over asymptotic methods is that formulae for asymptotic standard errors are available only in the usual approach to multiple record systems estimation, not in situations such as ours, in which some of the registries were missing for some years. In addition, the bootstrap can yield confidence intervals that are non-symmetric. In the parametric bootstrap method, random samples are drawn from an estimated probability distribution derived from a fitted model. For this purpose, we used the

Table 1: Number of newborn with NTD per year in the Netherlands, 1988-1998

Year	Number of reported newborns with NTD [1]	Number of known newborns with NTD (corrected for duplicates)	Percentage of duplicates	Added number of newborns with NTD based on availability of registrations in later years	Total number of known newborns with NTD
1988	233	186	25.3	18	204
1989	281	202	39.1	8	210
1990	308	220	40.0	12	232
1991	314	214	46.7	7	221
1992	333	228	46.0	13	242
1993	368	214	72.0	n.a.	214
1994	349	203	71.9	n.a.	203
1995	368	215	71.2	n.a.	215
1996	359	201	78.6	n.a.	201
1997	376	226	66.4	n.a.	226
1998	350	203	72.4	n.a.	203

1 1988-1991: Sources:LVR1, LVR2, BOSK; 1992-1993: Sources:LVR1, LVR2, BOSK, LNR; 1994-1998 Sources:LVR1, LVR2, BOSK, LNR, DPSU

two models specified above. As we did not condition on years, the number of observations for each year may fluctuate across bootstrap samples.

The prevalence rate of NTD was calculated as the total number of estimated NTD divided by the total number of live and stillbirths per year as reported by the National Bureau of Statistics. [15-17] The confidence interval of the prevalence was calculated in the same way, using the number of NTD for the upper and lower limit as estimated by the bootstrap.

Results

The number of reported newborns with NTD increased from 233 in 1988 to 350 in 1998. This rise in reported numbers was due to the increase in the number of registries used in that period, and to the higher participation rate within registrations over the years (table 1).

Table 2: Estimated prevalence of NTD in the Netherlands using capture-recapture analysis, 1988-1998

	Number of observed and estimated newborns with NTD (95% CI)						
Year	<24 weeks of gestation		≥ 24 weeks of gestation		Total		Total number LB and SB in the Netherlands
1988	98	(65,156)	238	(161,290)	336	(250,405)	187.685
1989	87	(59,131)	204	(163,243)	291	(240,343)	190.079
1990	103	(76,146)	231	(185,269)	334	(276,390)	199.104
1991	98	(75,127)	187	(152,227)	285	(244,331)	199.732
1992	101	(79,125)	286	(211,319)	387	(307,420)	197.848
1993	92	(75,115)	220	(193,264)	312	(282,363)	196.819
1994	66	(52,82)	275	(235,355)	341	(303,419)	196.666
1995	66	(53,81)	307	(263,396)	373	(328,462)	191.376
1996	70	(57,84)	269	(233,345)	339	(301,420)	190.405
1997	64	(51,78)	306	(268,380)	370	(334,443)	193.428
1998	65	(54,81)	254	(220,319)	319	(288,388)	200.378

	Prevalence rate of NTD per 1,000 LB and SB (95% CI)					
Year	<24 weeks of gestation		≥ 24 weeks of gestation		Total	
1988	0.52	(0.35,0.83)	1.27	(0.86,1.55)	1.79	(1.33,2.16)
1989	0.46	(0.31,0.69	1.07	(0.86,1.28)	1.53	(1.26,1.80)
1990	0.52	(0.38,0.73)	1.16	(0.93,1.35)	1.68	(1.39,1.96)
1991	0.49	(0.38,0.64)	0.94	(0.76,1.14)	1.43	(1.22,1.66)
1992	0.51	(0.40,0.63)	1.45	(1.07,1.61)	1.96	(1.55,2.12)
1993	0.48	(0.38,0.58)	1.12	(0.98,1.34)	1.59	(1.43,1.84)
1994	0.34	(0.26,0.42)	1.40	(1.19,1.81)	1.73	(1.54,2.13)
1995	0.34	(0.28,0.42)	1.60	(1.37,2.07)	1.95	(1.71,2.41)
1996	0.37	(0.30,0.44)	1.41	(1.22,1.81)	1.78	(1.58,2.21)
1997	0.33	(0.26,0.40)	1.58	(1.39,1.96)	1.91	(1.73,2.29)
1998	0.32	(0.27,0.40)	1.27	(1.10,1.59)	1.59	(1.44,1.95)

LB=live births, SB=stillbirth

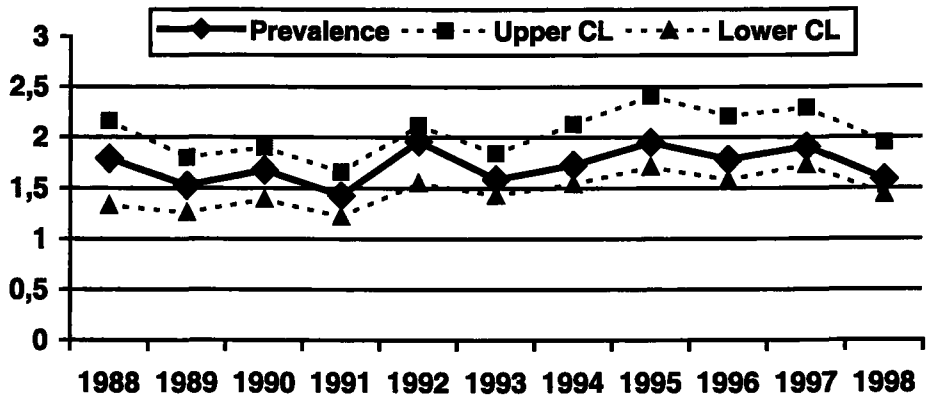
In the same period, the overlap between registrations rose from 25.3% to 72.4%, resulting in an annual average of 210 known newborns with NTD. The lowest number of known NTD newborns was registered in 1988 (n=186); the highest was in 1992 (n=228). The seeming increase in known cases over this period was in fact the product of the increase in the number of registrations. With the EM algorithm the number of newborns with NTD who had been missed in the years the LNR and DPSU did not exist was estimated. This estimation was based on the relations of these registries with the other registries in the years all five registries were available. Depending on the year of registration, this resulted in an increase of between seven and 18 newborns with NTD (table 1).

Separately capture-recapture analysis was used to estimate the number of newborns with NTD for < 24 weeks and ≥ 24 weeks of gestation. The results are presented in table 2. In the 1988-1993 period, the number of NTD < 24 weeks of gestation was nearly 100. From 1994, this number dropped to a level between 64 and 70 per year. Before 1994, about 29.8% of all newborns with NTD were born before < 24 weeks gestation. From 1994 onwards, this was about 19.0%. In the 1988-1998 period, the number of NTD ≥ 24 weeks of gestation fluctuated between 187 and 307, and does not seem to have decreased over time. The total number of NTD was found to be highest in 1992 (with 387 cases), and lowest in 1989 (with 291).

The capture-recapture analysis showed that approximately 40% of the newborns with NTD had not been registered in any of the registries covered in the study period. For example, in 1998 it is estimated that 319 newborns were born with NTD, whereas only 203 newborns were registered; in other words, 36% of such newborns were not registered.

Each year, approximately 200,000 live and stillbirths are registered by the National Bureau of Statistics. In 1988, the prevalence of NTD was 1.79 per 1,000 live and stillbirths; in 1998, the figure was 1.59 per 1,000. In the intervening years, the total prevalence of NTD varied from 1.43 to 1.96 per 1,000 live and stillbirths (figure 1). No decrease was found in the total prevalence in this period. When we focus on the years 1997 and 1998, the years in which the effect of increased folic acid use would be expected, there is no indication of a lowering of NTD prevalence.

Figure 1: Prevalence per 1.000 live and stillbirths of NTD in the Netherlands, 1988-1998.



Discussion

The prevalence of NTD in the Netherlands was estimated for the 1988-1998 period. Newborns with NTD were collected from five different registries, and those that had been registered more than once were identified. Capture-recapture analysis was used to estimate the number of newborns that had not been registered in any one of the registries, and showed that approximately 40% had not been registered. Our study shows that the number of new NTD cases in the Netherlands varied between 291 and 373 over the period. We find no decrease in the prevalence of NTD.

Five different registries were used in the analysis, as each represented a portion of the infants born with an NTD. In our capture-recapture analysis, it was of the utmost importance that the same infants were identified within and between the registries used: otherwise the prevalence of NTD would have been heavily overestimated. The method used by the researcher to search for duplicate entries was systematically carried out by computer, and was checked by a paediatrician. We are therefore confident that few duplicates are likely to have been missed. Furthermore, as the same procedure was followed for the entire study period, it is unlikely that more duplicates will have been missed for some years than for others. This therefore allows for evaluation of the trend in NTD.

Our estimate of the prevalence of NTD had to be based on a very time-consuming procedure (i.e. the combination of five different registries and the use of capture-recapture analysis). It would be much easier and less time consuming if the number of cases of babies born with NTD was registered in a national database. The disadvantage, however, would be that one would be unable to estimate the number of missed cases, as the capture-recapture method needs at least two different registries. Having only one national database would probably result in a rather large underestimation of the prevalence of NTD, as it was shown that about 40% of the cases of NTD were not registered in either one of the five registries. A comparable percentage of missed cases was also found by Dorrepaal et al, who reported that approximately 70% of the NTD's are registered in the Dutch perinatal databases. [18]

Studies of the prevalence of NTD in other countries show the high impact of pregnancy terminations on the prevalence of live births with an NTD. [19-24] In England, for instance, antenatal screening and subsequent termination of the pregnancy means that there is a low prevalence of live NTD births. [23] In the Netherlands, antenatal screening for NTD takes place only if there is an indication of increased risk; pregnancy termination is allowed only until 24 weeks of gestation. The distribution of the prevalence of NTD shows a peak before 24 weeks of gestation and around 38 weeks of gestation. The peak before 24 weeks of gestation is due to spontaneous preterm births but especially by induced pregnancy termination. These pregnancy terminations are registered in the LVR1 and LVR2 but are not specified as such. We were, therefore, unable to distinguish between medically-induced terminations and instances of spontaneous very preterm births but were able to present the prevalence of NTD including pregnancy terminations. The prevalence thus reflects the total prevalence of NTD which is important for the evaluation of the effect of increased folic acid intake. A possible side effect of the attention for the prevention of NTD by folic acid use may be that antenatal screening and subsequent pregnancy termination has also been increasing. This would also result in a decrease in the prevalence in NTD. Our data show no evidence of an increase in births before 24 weeks of gestation in the study period, meaning that a decrease in NTD prevalence will be related to increased folic acid use.

Previous estimates of the prevalence of NTD in the Netherlands were based on the regional registry of EUROCAT in the northern Netherlands. From the EUROCAT registry it is estimated that the prevalence of NTD was 1.1 per 1,000 live and stillbirths in the 1981-

1998 period, which would correspond with approximately 220 NTD newborns each year. [25] On the basis of the five registries, we established a likely NTD prevalence of 1.7 per 1,000 live and stillbirths, i.e. approximately 340 newborns with NTD each year. This difference can only partly be explained by the rejection of parents to include the data on their child in the EUROCAT registry. Neither is the difference explained by non-confirmation of the initial diagnosis, which occurred occasionally in the EUROCAT region. Approximately five of the infants with NTD identified in one or more of the five registries in the EUROCAT region each year were not known to EUROCAT, suggesting an underestimation of about 18%. This may mean that a small underestimate in a region can lead to an important underestimation in the whole country.

The prevalence of NTD in the Netherlands, as reported by EUROCAT, is in the intermediate compared to other European countries. [26] Based on our finding, the prevalence of NTD would be one of the highest compared to other European countries, but one should be cautious with such a comparison. It is likely that also in other countries the prevalence of NTD is underestimated because of missed cases in the registration. Therefore, for fair international comparisons one should use data that are obtained in a comparable way.

Periconceptional folic acid use reduces the occurrence and recurrence risk of a child with a NTD considerably. [2-7] In many countries, including the Netherlands, women wishing to conceive are advised to use folic acid. [27] Up until the middle of 1996 no change in time trend attributable to the introduction of national folate supplementation policies was measured using data of 11 registries participating in the International Clearinghouse for Birth Defects Monitoring System. [28] It should be noted that since the early 1990's folic acid use has been increasing only slowly in many countries and that in most countries half of the pregnancies seem to be unplanned. [28] Therefore, it is very difficult the find a change in time trend attributable to increased folic acid use until mid 1996. In the United Stated enrichment of food with folic acid was introduced, partially because of the high percentage of unplanned pregnancies. On the basis of birth-certificate data, Honein found a 19% decline in the birth prevalence of neural tube defects following the folic acid fortification of the US food supply. [29] Unfortunately this does not give a complete picture, as birth certificate data do not include foetal deaths, stillbirths and pregnancy terminations taking

place after prenatal screening programs, which are all common in pregnancies affected by a neural tube defect. [30]

In the Netherlands, unplanned pregnancies are far less common and proper folic acid use has been increasing since the recommendations of the Health Authorities in November 1993. Due to a national folic acid campaign, proper folic acid use in the Netherlands increased to 21.0% by the end of 1996 [8]. At present the national figure may even be higher: by the end of 1998 proper folic acid use was 35.6% in the northern Netherlands. [9] Although the Dutch conditions seem more favourable than in other European countries, it remains difficult to detect a reduction in the prevalence of NTD with a large degree of certainty. Theoretically, on the basis of the percentage of proper folic acid use in 1996 (21.0%) [8] and on a risk reduction of 60-70%, a reduction in the prevalence of NTD of about 13.0% can be expected from mid-1997. [2-7] This theoretical reduction may be an underestimation, however, as the use of folic acid during a shorter period than advised will inevitably bring about some reduction in risk. With regard to the Netherlands, while the effect of increased folic acid use should be noticeable from mid-1997, this may be very difficult to ascertain with certainty, due to the natural variance in the prevalence of NTD and the relatively small number of women using folic acid periconceptionally. At this moment, we were unable to show a lowering of the prevalence rate from 1997, though the prevalence rate in 1998 is one of the lowest measured in the time period studied. This does not mean that periconceptional folic acid use is not effective in reducing the prevalence of NTD but indicates that the preventive effect is not larger in the general population than demonstrated in specific populations. [2-7] Further monitoring of the prevalence of NTD in the Netherlands is needed to answer the question of folic acid use can reduce the prevalence of NTD in the Netherlands. In the mean time, public health interventions to increase folic acid intake should be continued.

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Chapter 9

Discussion

In the Netherlands, approximately 2.5% of babies are born with a congenital anomaly. [1] These anomalies constitute a large proportion of perinatal death. Antenatal screening makes it possible to detect a number of these anomalies, including neural tube defects. If a serious congenital anomaly is detected, pregnancy termination often follows, and if this is conducted before the lower limit of the registration threshold for perinatal death, it is not recorded as a death in the national statistics. Different countries have different practices with regard to antenatal screening and the termination of pregnancy due to congenital anomalies.

In chapter 2 we show that these differences contribute to the variations in overall perinatal mortality rate between European regions and countries. In regions where antenatal screening and pregnancy termination are common, the difference between the regular perinatal mortality rate and the 'natural' perinatal mortality rate (i.e. the perinatal mortality rate that would occur if no medical interventions took place) is greater than in regions where they are less common. This implies that the impact of congenital anomalies in terms of total foetal and neonatal mortality is greater than can be measured in the perinatal mortality rate alone.

The focus of this thesis is the primary prevention of neural tube defects, a congenital anomaly with high mortality and morbidity. Until some years ago the only way of prevention was to offer antenatal screening to pregnant women. This can be followed by pregnancy termination when a neural tube defect is detected. In the Netherlands antenatal screening for neural tube defects is only offered to women with a known increased risk of bearing a child with this defect and to women over 35 years of age. With this prevention strategy only a small number of cases are detected as the majority of cases occur in the general population.

Antenatal screening does not prevent the occurrence of a neural tube defect but offers the possibility to terminate the pregnancy, which is a very drastic matter. Since the early 1990s, there is convincing evidence that periconceptional folic acid use reduces the risk of the occurrence of neural tube defects [2], although there is some criticism regarding methodology

and the interpretation of outcomes. [3,4] The possibility to prevent the occurrence of a neural tube defect marks a big step forward for the prevention of this serious defect. In many countries, women of child bearing age or women planning pregnancy are currently advised to take 400 μg of folic acid daily in the period around conception to prevent the first occurrence of a neural tube defect. [5] In the Netherlands, a Joint Committee of the Health Council and Food Council of the Netherlands recommended that women in the general population should take folic acid when planning pregnancy. [6] Supplementation was considered to be a temporary measure as legislation did not yet allow fortification of food with folic acid. To reduce the risk of first occurrence of a neural tube defect, women planning pregnancy were advised to take a supplementary daily dosage of 400 μg folic acid orally. This recommendation was followed by the Chief Inspector of Health, who informed health professionals about this, by letter. [7]

The current strategy: increased folic acid intake by supplementation

To stimulate the implementation of the recommendation, two Folic Acid Campaigns – one at the national level, and one at the local level – were initiated by the Ministry of Health and carried out by the Nutrition Bureau and Dutch Alliance of Parent and Patient Organisations of genetic and non-genetic congenital disorders. in 1995. [8] The two campaigns targeted health-care professionals and women planning pregnancy. In addition, the local campaign specifically targeted women from the lower socio-economic group, both because these women appear to be at greater risk of bearing a child with a neural tube defect, and because they are more difficult to reach through public health campaigns.

The first phase of the campaign, first half of 1995, focused on health-care professionals, such as general practitioners, midwives, obstetricians and pharmacists, who were informed about folic acid through their professional associations, in publications in national medical journals, and in personal correspondence. In this way they were provided with educational materials intended to establish a positive attitude towards folic acid use.

The second phase of the Folic Acid Campaign, September 1995, was to inform the general population combine. The aim was to reach at least 70% of women, 65% of whom were

expected to use folic acid in the recommended period. In other words, at the end of the Folic Acid Campaign, 46% of all pregnant women were expected to use folic acid in the recommended period.

Chapter 3 describes the effect of the Folic Acid Campaign on healthcare professionals. The majority of general practitioners (87%) and midwives (94%) were familiar with the Folic Acid Campaign. Half the general practitioners and two-thirds of midwives considered the use of folic acid by women planning pregnancy to be important. Although most general practitioners (82%) and midwives (93%) were anxious that pregnant women who knew the folic acid recommendations but did not use it might develop feelings of guilt, 64% of each group recommended the use of folic acid. Almost 60% of the general practitioners reported that they voluntarily discussed the preventive effect of folic acid use with women who might contemplate a pregnancy. Almost half the midwives stated that, during the contraceptive advice they gave to women after birth, they mentioned folic acid use in the context of a subsequent pregnancy (although 35% indicated they sometimes forget to do so).

So in theory, general practitioners and midwives were willing to comply to the recommendations but their practice leaves scope for improvement. There seems to be enough support to bring such improvements about: a survey among 100 midwives showed that many thought preconception advice and counselling would be a valuable addition to the care they provided (although 70% of them believe it should be provided by the general practitioner). [9] Another survey among 100 general practitioners showed that while 93% of them considered preconception advice and counselling to be part of their duties, 53% of them believed they had insufficient knowledge about it, and 30% that they had insufficient time to provide it. [10]

Chapter 4 describes the development of a framework, comparable to the central constructs of the Theory of Reasoned Action, to improve our understanding of determinants that influence folic acid use in the Netherlands. Subjective norm, perceived safety and attitude appear to have a direct relation with folic acid use. Awareness knowledge was mediated through the above mentioned determinants. The framework was developed using data of 1995; the

model was confirmed by the data of 1996. The relation between the determinants and folic acid use appeared to be independent of level of education.

The framework is comparable to the central constructs of the Theory of Reasoned Action but is less complete than the model introduced by Fishbein and Ajzen. Data concerning intention to use folic acid periconceptionally were only available for non-users. One may assume that once a woman uses folic acid during pregnancy she will use it again in a subsequent pregnancy, although it may very well be that there are reasons not to use folic acid. Complete information about intention to use may have improved the model as well as our understanding of periconceptional folic acid use considerably and should be included in further studies. Furthermore there may be perceived barriers as suggested by Bandourra's self-efficacy theory that were not measured in this study. Information about these barriers may help us to understand why many women do not start folic acid use four weeks before conception.

Overall, the framework can be used for explaining folic acid use by women planning pregnancy and for studying the effectiveness of interventions promoting the use of folic acid.

In chapter 5 we report on the overall effect of the campaign on women. We found that the first objective (inform 70% of women planning pregnancy) was attained without difficulty: the percentage of women who had heard of folic acid increased from 41% before the Folic Acid Campaign to 77% a year after it had been conducted. The actual use of folic acid was also found to have increased. Use during at least some of the period around conception increased from 25.1% before the campaign to 53.5% one year after it; proper folic acid use, i.e. from four weeks before conception until eight weeks after it, increased from 4.8% to 21.0%. Although this was a tremendous increase for just one campaign, the initial aim of 46% proper folic acid use was not reached. In the regions with the additional local campaign a comparable proportion of women used folic acid to the regions with the national campaign (adjusted odds ratio=1.0; 95% confidence interval=0.7-1.4). No additional effect of the local campaign on folic acid use was found.

It is known that women in the low socio-economic groups are harder to reach and less willing to change their behaviour. In chapter 6 we describe divergences in the knowledge and use of folic acid use between women of different socio-economic levels, and study whether the local Folic Acid Campaign specifically aimed at women from the lower socio-economic groups was more successful in reaching the women in question.

Before the Folic Acid Campaign, women with a lower educational level reported less often than their better-educated counterparts that they had heard of folic acid and its use. In the year following the campaign, folic acid use during at least some of the period around conception had increased in both groups from 9.2% to 39.6% in women with a low level of education and from 30.9% to 59.6% in women with a high level of education. Thus while there was still a difference in folic acid use between the two groups, it had not increased in the regions with only the national Folic Acid Campaign. This means that the Folic Acid Campaign succeeded in halting the pattern of increasing differences in its use between women of different level of education, which had been noted in the period following the release of the recommendations and preceding the Folic Acid Campaign. It also appeared that, regardless of educational level, once a woman had heard of folic acid, her knowledge of it was accurate. This implies that the dissemination of information leads to accurate knowledge in all women.

Hearing of folic acid use is one thing, using it in the recommended period is another. Several determinants were identified that predict folic acid use; the best of these were attitude and subjective norm. Furthermore, women's attitudes were strongly grounded in beliefs about the health benefits and safety of folic acid use. Overall, the scores on the attitude and subjective norm of women with a high educational level were higher than those for women with a low level. The local campaign did not affect attitude more than only the national campaign. With regard to subjective norm, women with a low level of education benefited as much from the local campaign as women with a high level. In the region with only the national campaign, women with a high level of education benefited more compared to women with a low level of education.

Folic acid use has increased ever since women planning pregnancy were first told they should use folic acid around conception. Though this increase was small in the period between the initial publication of the recommendations and the onset of the campaign, it was much larger after the campaign had taken place. This was clear from the responses of all women, regardless of their level of education. In 1998, three years after the Folic Acid Campaign ended, folic acid use had further increased in the northern Netherlands region. Use at some period around conception had increased to 62.5%; proper use was 35.5% and the difference between women with a low level of education and those with a high level had widened. [11] In 2000, the increase in folic acid use levelled off in the northern Netherlands. Folic acid use at any period around conception was still 61.0%, and proper use 35.6%. [12] This shows that if no specific health education is offered, as at present, folic acid use will not continue to increase. In addition, surveys conducted in the northern Netherlands region in 1998 and 2000 suggest that differences between women of different level of education are already increasing.

Despite the considerable difference in folic acid use between women across educational groups, the impact on public health of the rise in use may be greater that one might expect at first sight. More than one third of Dutch women have a low level of education, and approximately 17% have a high level. This means that a small increase in folic acid use in the larger group (i.e. women with a low level of education) would have a greater effect on public health than a large increase in folic acid use by women in the smaller group. Furthermore, women with a low level of education appear to be at greater risk of having a child with a neural tube defect. Being able to reach more women with a low level of education would therefore further increase the impact on public health.

Recommendation concerning the current strategy: supplementation of folic acid

The results presented in chapter 3-6 of this thesis indicate that folic acid use can effectively be promoted by mass-media campaigns, certainly in a large group of women who have no prior knowledge of the health benefits associated with periconceptional folic acid use. A common feature of health promotion is that changing health behaviour is a slow process, and that a long time elapses before the target behaviour comes about. [13] If, at the very minimum, one

wishes to maintain the level of awareness that has been established with regard to folic acid and of its use, repeated campaigns are necessary.

Furthermore, the prevention strategy should be improved. In order to achieve more equal health outcomes among women of socio-economic levels, tailored interventions are needed for women of the lower socio-economic group. To design such interventions, it is necessary to research the determinants of folic acid use by women of each group. The study design for establishing these determinants should involve focus group interviews and lead to the formulation of a questionnaire that can be used for this purpose. The existence of different determinants may explain why information on folic acid use does not always reach women with a low socio-economic level. A prevention strategy designed to overcome the obstacles to reaching such women may reduce the difference in awareness and in the use of folic acid.

Furthermore, using new channels of information may also extend the prevention strategy. Information about a healthy lifestyle before and during pregnancy – which should include a component on folic acid use – should be taught at school: it might, for example, be incorporated into the curriculum under 'personal health' which is now a core subject in secondary education. Folic acid use should also become a standard component of any preconception advice and counselling given by general practitioners. A formal preconception counselling programme is planned for inclusion in the standard care of general practitioners.

An alternative strategy: fortification of food with folic acid

So far we have not discussed the possibility of increasing folic acid intake via the fortification of food. Both inside Europe and beyond, enrichment of food with folic acid is already taking place, or plans to implement it are being developed. In the United States, the Food and Drug Administration (FDA) decided to fortify enriched flour with 140 μg folic acid per 100g, effective as of January 1, 1998. [14] There are indications that blood levels of folate have since increased. [15,16] On the basis of birth-certificate data, Honein found a 19%

decline in the birth prevalence of neural tube defects following the folic acid fortification of the US food supply. [17] Unfortunately this does not give a complete picture, as birth certificate data do not include foetal deaths, stillbirths and pregnancy terminations taking place after prenatal screening programs, which are all common in pregnancies affected by a neural tube defect. [18]

In the UK, the government is advised by the Committee on Medical Aspects of Food and Nutrition Policy (COMA) to fortify at 240 μg per 100g flour in foods. According to the Committee, this will have a significant effect in preventing conceptions affected by a neural tube defect, without leading to unacceptably high intakes in any group of the population. [19] Recently the UK Board of the Food Standards Agency decided against mandatory folic acid fortification. [20]

In the middle of 1998, the Health Council of the Netherlands was asked to advise on the risks to public health of the fortification of food with folic acid. The Health Council's recommendations, which clearly show that their work was seriously affected by the lack of studies on the safety of folic acid use, state that fortification of food provides only limited scope for the prevention of neural tube defects, especially in the Netherlands, where an alternative is available in the form of vitamin supplements containing folic acid. [21] This increased the Council's reluctance to accept health risks of food fortification: not only was there a danger that vitamin B12 deficiency may be masked, there was also a possibility that, in certain groups of the wider population, the general fortification of food might raise folic acid intake above the acceptable daily limit. Therefore, the Health Council recommended that, if fortification was considered, it should be limited to special products intended for women planning pregnancy. The introduction of these products should take place only in conjunction with the appropriate advice and labelling, such that the women in question would be sure to recognise them, and would not use them with supplements that might lead to the over-consumption of folic acid.

Recommendation concerning fortification of food with folic acid

It is unlikely that a restricted food fortification programme would lead to a higher intake of folic acid by women planning pregnancy than is currently reached. Like the use of folic acid supplements, the purchase of special food products presupposes that the individual women will undertake positive action – in other words, that they will deliberately choose to buy them. Moreover, not all women will want their shopping to reveal their desire to conceive. Besides, special products are generally more expensive, which may become a barrier to women of a lower socio-economic status, and thus further increase the difference in folic acid use between women of low and high socio-economic levels. Introducing special products fortified with folic acid might lead to confusion about what should be used, and may also result in the over-consumption of folic acid by women who use supplements as well as special products. The introduction of special products would also call for health education programmes like the current strategy. For all these reasons, the current strategy to increase folic acid intake by supplementation should not be changed, but should instead be continued and maximised in the ways we specified in section 9.1.1. After all, the initial strategy has already achieved a considerable increase, both in awareness and in folic acid use.

Effect of increased folic acid intake on the prevalence of neural tube defects

The aim of the Folic Acid Campaign was to raise both the awareness and the use of folic acid in order to reduce neural tube defects. Therefore the ultimate objective is to bring about a significant decrease in their prevalence. In chapter 7 and 8 we describe the prevalence of neural tube defects since the Folic Acid Campaign was conducted. Since a national database of the prevalence of neural tube defects is not available in the Netherlands, we used capture-recapture analysis to estimate their prevalence on the basis of available databases.

In chapter 7 we describe the method used to estimate the prevalence of neural tube defects in the Netherlands. In capture-recapture analysis, also known as multiple records systems estimation, it is usually assumed that all registrations relate to the same population. In this

chapter we describe the development of a method which can be used when the registrations relate to different populations and show that the Expectation-Maximisation (EM) algorithm can be used to estimate the population size.

Chapter 8 presents the estimated prevalence of neural tube defects in the Netherlands over the period 1988-1998. The analysis included five different sources of information to estimate this prevalence. A distinction was made between births that took place before or from 24 weeks of gestation (i.e. the legal limit for pregnancy termination).

Total prevalence over the 1988-1998 period varied between 1.43 and 1.96 per 1,000 live and stillbirths. The highest number of neural tube defects occurred in 1992, with 387 cases, and lowest in 1989, with 291 cases. The capture-recapture analysis showed that approximately 40% of the newborns with a neural tube defect had not been registered in any of the registries covered in the study period.

No decrease in total prevalence was found to have taken place during that period. Our data do not show a lower prevalence rate in 1997 than in the preceding years. Though the prevalence rate in 1998 was one of the lowest measured in the time-period studied, which is in accordance with our expectations, there is no proof that this marked the onset of a downward trend. In itself, this is not surprising. On the basis of the percentage of proper folic acid use in 1996 (i.e. 21.0%), and of a risk reduction of 60-70%, we calculate that a reduction in the prevalence of neural tube defects of about 13.0% can be expected starting mid-1997. This equals an approximate decrease of 43 cases per year. The natural variance of the prevalence was 96 cases between the lowest and highest number of neural tube defects in the 1988-1996 period. A decrease of 43 cases would therefore not be noticeable. Only when proper use exceeds 48% will it be possible to show the preventive effect of folic acid use in the Netherlands. In the meantime, if proper folic acid use is currently increasing, the onset of a downward trend should become visible.

Recommendations concerning monitoring and the prevalence of neural tube defects

At present it is not possible to quantify the impact of increased folic acid intake in the Netherlands. The study period included data for the period up to 1998. It has been reported that proper folic acid increased further after the Folic Acid Campaign, levelling off at 35.5% in 2000. [12] To demonstrate convincingly that it has a preventive effect, folic acid use should exceed 48%; however, the onset of a downward trend should become visible at an earlier stage. At present, on the basis of 35.5% proper use in 2000, we can expect a risk reduction of 21%. A continuation of monitoring until 2001 should give further information on the preventive effect of increased folic acid intake. Thus, to study the effect of the current strategy and its continuation, sustained periodic folic acid campaigns should be accompanied by monitoring of the prevalence of neural tube defects. Using the capture-recapture method has the advantage that the estimation of prevalence is more complete, since it also includes an estimate of the number of cases that are not registered in one of the existing registries.

Antenatal screening of neural tube defects

Not all neural tube defect are related to folate status. Therefore, even with supplementation, neural tube defects will still occur, albeit at a substantially lower level. At present, about 40% of the women planning pregnancy do not use folic acid, and another 25% do not use it as advised. While non-use will decrease if health education is continued, it will never reach zero. Inappropriate folic acid use may also decrease, but again it is impossible to achieve 100% compliance.

As stated above, the mortality and morbidity are high in children with a neural tube defect. Therefore, routine antenatal screening should be an option for pregnant women, whether or not they used folic acid. In case of detection of a neural tube defect, the pregnant woman and her partner may decide to terminate the pregnancy. In any case, the decision to end a pregnancy because of congenital anomalies of the baby is very difficult. Therefore, routine antenatal screening and subsequent termination are at most an additional strategy, and could never be the preventive measure of choice. As folic acid use is not common yet, a considerable number of neural tube defect affected pregnancies will be detected by routine

antenatal screening. If folic acid use increases further and the occurrence of neural tube defects is prevented, a lesser number of affected pregnancies will be detected. Recently, the Health Council of the Netherlands recommended the introduction of such a routine antenatal screening for neural tube defects and Down's syndrome for all pregnant women. [22] This advice is now under consideration by the Minister of Health.

Other preventive effects of folic acid use

Czeizel reported that folic acid use had a preventive effect not only on the occurrence of neural tube defects, but also on other congenital anomalies. [23,24] This reports were followed by observational studies reporting that the use of multivitamins containing folic acid had a preventive effect on cardiac defects, orofacial defects, urinary tract defects, limb reduction defects and Down's syndrome. [25-36] In addition, folic acid use may also reduce the risk of cardiovascular diseases in adults, especially strokes and heart attacks. Although there are several indications that the relationship is causal, confirmation can be supplied only by an intervention study and by evidence from randomised trials showing that reducing homocysteine levels with folic acid reduces the incidence of cardiovascular disease. No such trials have yet been reported. [19] If this information becomes available, the potential impact on public health may be great enough to reconsider the fortification of food with folic acid.

Conclusion

As neural tube defects are a very serious congenital anomaly, prevention should be given a high priority in public health policy. There is convincing evidence that periconceptional folic acid use considerably reduces the occurrence and recurrence risk of neural tube defects. This implies that primary prevention is possible by increased intake of folic acid. In this thesis it is shown not only that periconceptional folic acid use can be increased by supplementation, but also that health-care professionals are willing to inform women about the positive effects of its use, and that they are willing to prescribe folic acid. It is also

shown that the majority of women were informed about folic acid use, and that folic acid use did increase after the campaign (although not by as much as hoped).

The first step – to establish increased folic acid intake by women planning pregnancy – has now been taken. While the results of this single Folic Acid Campaign are encouraging, it takes time and substantial effort to change health behaviour. As proper folic acid use is practised by a minority of the pregnant women, it is still impossible to prove that folic acid use reduces the prevalence of neural tube defects.

The current prevention strategy should be continued and maximised, thereby increasing periconceptional folic acid intake via tablets containing folic acid. Mass media campaigns should be repeated at regular intervals, and information on folic acid use should be incorporated into the secondary-level school curriculum in the courses on personal health. It should also become a standard component in the preconception advice and counselling provided by general practitioners. In order to achieve more equal health outcomes among women of divergent socio-economic status, more tailored interventions are needed for women from the lower socio-economic groups. Studies to identify how such women may best be approached should become a matter of priority.

In order to obtain information on the effectiveness of the current prevention strategy, the two major outcome measures of the public health education – i.e. folic acid use and the prevalence of neural tube defects – should be monitored on a regular basis. In the long run, we have to justify the continuation of the prevention strategy by demonstrating its effectiveness.

Since it is a very drastic matter to end a pregnancy because of a congenital anomaly, antenatal screening and subsequent termination are an additional strategy. Therefore, antenatal screening should not be the preventive measure of choice. Because folic acid use is not yet common, routine antenatal screening should be offered. And even if folic acid use becomes common, antenatal screening should remain available, as not all neural tube defects are folate related and full compliance of folic acid use is unattainable.

At some time in the future, new understanding of the preventive effect of folic acid on other diseases (especially on cardiovascular diseases), and also of the safe upper intake limit and the long-term effects of folic acid use, may necessitate reconsidering the current prevention strategy. Until that time, the current prevention strategy to increase folic acid intake by supplementation should be continued and maximised.

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Summary

In the Netherlands, approximately 2.5% of newborns – about 5,000 babies per year – are born with a congenital anomaly. A neural tube defect is a very serious congenital anomaly of the central nervous system with high morbidity and mortality. Since the early 1990s, convincing evidence has been emerging that periconceptional folic acid use reduces the risk of the occurrence of neural tube defects. Since the end of 1993, periconceptional folic acid use is being advised to Dutch women planning pregnancy. In 1995, the recommendations were accompanied by a public health campaign to inform caregivers and women planning pregnancy. This thesis evaluates the current strategy for prevention of neural tube defects, i.e. the periconceptional use of tablets containing 0.4mg folic acid. The most important outcome measures are proper folic acid use (4 weeks before until 8 weeks after conception) and the prevalence of neural tube defects.

Chapter 2 describes the prevalence of termination of pregnancy for eight serious congenital anomalies of nine regional EUROCAT-registries from five European countries and the impact of pregnancy termination on the perinatal mortality rate. Large differences in the prevalence of pregnancy terminations before 24 weeks of gestational age were found between the EUROCAT-registries. The difference between regular and 'natural' perinatal mortality rate (calculated for the hypothetical situation that no pregnancy terminations have taken place) is larger in regions where the reported frequency of pregnancy terminations is higher. This indicates that the regular perinatal mortality rate (used in international statistics) will decrease if the number of pregnancy terminations increases. Therefore, differences in antenatal screening and subsequent pregnancy termination contribute to differences in the regular perinatal mortality rate between regions and countries.

In **chapter 3** the attitude of general practitioners and midwives towards periconceptional folic acid use is presented. A survey among general practitioners was carried out in 1996; a survey among midwives was carried out in 1997. In both studies the response exceeded 80%. The majority of the general practitioners (87%) and midwives (94%) were aware of the Folic Acid Campaign. Half of general practitioners and two thirds of midwives indicated they found folic acid use important. Both the general practitioners and midwives reported they were afraid of feelings of guilt in women who did not use folic acid (82% and

93% respectively). Almost two thirds of the general practitioners and midwives advised the use of folic acid, although they indicated they forgot to do so on a regular basis. Overall, the general practitioners and midwives reported a positive attitude towards folic acid use, although the frequency of advising women about folic acid use can be improved.

Chapter 4 describes the development of a framework, comparable to the central constructs of the Theory of Reasoned Action, in order to increase our understanding of determinants of folic acid use. Subjective norm, perceived safety and attitude appear to have a direct relationship with folic acid use. Awareness knowledge was mediated through the above mentioned determinants. The framework was developed using data of 1995; the model was confirmed by the data of 1996. The relationship between the determinants and folic acid use appeared to be independent of level of education. The framework is comparable to the central constructs of the Theory of Reasoned Action but is less complete than the model introduced by Fishbein and Ajzen. Data concerning intention to use folic acid periconceptionally were only available for non-users. One may assume that once a woman uses folic acid during pregnancy she will use it again in a subsequent pregnancy, although it may very well be that there are reasons not to use folic acid. Overall, the framework can be used for explaining folic acid use by women planning pregnancy and for studying the effectiveness of interventions promoting the use of folic acid.

Chapter 5 describes the evaluation of the overall effect of the national and the additional local Folic Acid Campaign on awareness and folic acid use of women wishing to conceive. Furthermore, the additional effect of the local folic acid campaign is evaluated. The results show that one year after the campaign 77.3% of the women had heard of folic acid compared to 41.7% before the campaign. Folic acid use at some period around conception had increased from 25.1% before to 53.5% after the campaign. An increase in proper folic acid use (four weeks before until eight weeks after conception) from 4.8% before to 21.0% after the campaign was found. The percentage of women that had heard of folic acid is higher than the target of 70%. Although proper folic acid use has been increasing considerably, the target of the campaign had not been met at this point. In the regions with the additional local campaign a comparable proportion of women used folic acid to the

regions with the national campaign (adjusted odds ratio=1.0; 95% confidence interval=0.7-1.4). No additional effect of the local campaign on folic acid use was found.

In **chapter 6** the differences in knowledge and use of folic acid use between women of different socio-economic levels is being described. Further, it describes whether the local Folic Acid Campaign specifically aimed at women from the lower socio-economic groups was more successful in reaching the women in question. Before the Folic Acid Campaign, women with a lower educational level reported less often than their better-educated counterparts that they had heard of folic acid and its use. In the year following the campaign, folic acid use during at least some of the period around conception had increased in both groups with 30%. In other words, the difference in folic acid use between both groups had not increased further, but had not diminished either. Overall, the scores on attitude and subjective norm of women with a high educational level were higher than those for women with a low level. The local campaign did not affect attitude more than only the national campaign. With regard to subjective norm, in the regions with the national and local campaign women with a low level of education benefited as much as women with a high level. In the region with only the national campaign, women with a high level of education benefited more compared to women with a low level of education.

Chapter 7 describes the use of capture-recapture analysis in estimating prevalence of neural tube defects in the Netherlands in the period 1988-1998. In the Netherlands no national registry exists that registers all cases of neural tube defects. Therefore we used several registries that register neural tube defects. An adjusted method of capture-recapture analysis was developed because not all used databases were available for the complete time period. It was shown that this adjusted method provides a correct estimate of the prevalence. This method was subsequently used to estimate the prevalence of neural tube defects in the Netherlands.

In **chapter 8** the trend in prevalence of neural tube defects in the Netherlands in the period 1988-1998 is being presented. Data concerning neural tube defects were obtained from the three national perinatal databases (LVR1, LVR2, LNR) and the Dutch Paediatric

Surveillance Unit (DPSU). Further members of the Dutch Parents Association (BOSK) who have a child with spina bifida were contacted. The prevalence of neural tube defects varied between 1.43 and 1.96 per 1,000 stillbirths and live births in the period 1988-1998. A downward trend could not be found because of the relatively low percentage of women using folic acid. This does not necessarily mean that folic acid use is ineffective in decreasing the prevalence of neural tube defects. The monitoring should be continued in order to follow the effect of folic acid use on the prevalence of neural tube defects.

In **chapter 9** the results of this thesis are discussed in relation to potential avenues for the continuation of primary prevention of neural tube defects. It is concluded that the current prevention strategy, periconceptional folic acid supplementation, should be continued and improved. Mass media campaigns should be repeated at regular intervals, and information on folic acid use should be incorporated into the secondary-level school curriculum in the courses on personal health. It should also become a standard component of the preconception advice and counselling provided by general practitioners. In order to achieve more equal health outcomes among women of different socio-economic status, more tailored interventions are needed for women from the lower socio-economic groups. Studies to identify how such women may best be approached should become priority.

In order to obtain information on the effectiveness of the current prevention strategy, the two major outcome measures of the public health education – i.e. folic acid use and the prevalence of neural tube defects – should be monitored on a regular basis. In the long run, continuation of the prevention strategy can only be justified by demonstrating its effectiveness.

Since it is a very drastic matter to end a pregnancy because of a congenital anomaly, antenatal screening and subsequent termination are an additional strategy. Therefore, antenatal screening should not be the preventive measure of choice. Because use of folic acid is not yet common practice, routine antenatal screening should continue to be offered. However, even if folic acid use becomes common practice, antenatal screening should

remain available, as not all neural tube defects are folate related and full compliance to folic acid use is likely unattainable.

At some time in the future, new understanding of the preventive effect of folic acid on other diseases (especially on cardiovascular diseases), and also of the safe upper intake limit and the long-term effects of folic acid use, may necessitate reconsidering the current prevention strategy. Until that time, the current prevention strategy to increase folic acid intake by supplementation should be continued and maximised.

Samenvatting

In Nederland wordt naar schatting 2,5% van de pasgeborenen geboren met een aangeboren afwijking. Jaarlijks zijn dit ongeveer 5.000 kinderen. Een neuralebuisdefect is een zeer ernstige aangeboren afwijking van het centrale zenuwstelsel die gepaard gaat met hoge mortaliteit en morbiditeit. Begin jaren negentig werd overtuigend aangetoond dat door het gebruik van foliumzuur rond de conceptie het risico op het ontstaan van een neuralebuisdefect aanzienlijk werd verminderd. Op grond hiervan wordt sinds eind 1993 in Nederland aan vrouwen met zwangerschapswens geadviseerd om dagelijks 0,4 mg foliumzuur in tabletvorm te gebruiken. Om dit advies te verspreiden onder zorgverleners en vrouwen met zwangerschapswens is in 1995 een voorlichtingscampagne uitgevoerd. In dit proefschrift wordt de huidige preventiestrategie voor neuralebuisdefecten, namelijk het gebruik van foliumzuur rondom de conceptie middels tabletten, geëvalueerd. De belangrijkste onderzochte effecten zijn foliumzuurgebruik gedurende de gehele aanbevolen periode (4 weken vóór tot 8 weken na conceptie) en veranderingen in de prevalentie van neuralebuisdefecten.

Hoofdstuk 2 beschrijft de frequentie van zwangerschapsafbreking voor acht ernstige aangeboren aandoeningen in negen regionale EUROCAT-registraties uit vijf Europese landen en de invloed hiervan op de perinatale sterfte. Tussen de registraties bestonden grote verschillen in het percentage zwangerschapsafbrekingen. Verschillen tussen de geregistreerd perinatale sterfte en 'natuurlijke' perinatale sterfte (berekend voor het hypothetische geval dat er geen zwangerschapsafbrekingen zouden zijn uitgevoerd) waren groter naar mate het aantal zwangerschapsafbrekingen groter was. Dit geeft aan dat door een toename in prenatale screening en daaruit volgende zwangerschapsafbreking, de geregistreerde perinatale sterfte (zoals gebruikt in internationale statistieken) zal dalen. Verschillen in mate van prenatale screening en daaruit volgende zwangerschapsafbrekingen dragen dus bij aan verschillen in perinatale sterfte tussen regio's en landen.

In **hoofdstuk 3** wordt de mening van huisartsen en van verloskundige over het gebruik van foliumzuur door vrouwen met zwangerschapswens beschreven. Het onderzoek onder huisartsen is uitgevoerd in 1996; het onderzoek onder verloskundigen in 1997. In beide onderzoeksgroepen was de respons ruim 80%. De meerderheid van de huisartsen (87%) en van

de verloskundigen (94%) gaf aan op de hoogte te zijn van de foliumzuurcampagne. Ook vond de helft van de huisartsen en tweederde van de verloskundigen het gebruik van foliumzuur door vrouwen met zwangerschapswens belangrijk. Een ruime meerderheid van de huisartsen en verloskundigen verwachtte dat vrouwen die van foliumzuur hebben gehoord maar het niet hebben gebruikt, hier gevoelens van spijt over kunnen ontwikkelen (respectievelijk 82% en 93%). Bijna tweederde van de huisartsen en verloskundigen gaf aan het gebruik van foliumzuur te adviseren, al gaven zij ook aan dat zij het adviseren over foliumzuur nog regelmatig vergeten. Al met al staan de huisartsen en verloskundigen positief tegenover het gebruik van foliumzuur. Wel is er nog ruimte voor verbetering van de mate waarin zij vrouwen met zwangerschapswens adviseren over foliumzuurgebruik.

Hoofdstuk 4 beschrijft de ontwikkeling van een raamwerk om de kennis over determinanten van foliumzuurgebruik te vergroten. Dit raamwerk is vergelijkbaar met de centrale constructen van de Theory of Reasoned Action. Subjectieve norm, gepercipieerde veiligheid en attitude bleken een rechtstreekse relatie te hebben met het gebruik van foliumzuur. Gehoord hebben van foliumzuur beïnvloedt het gebruik van foliumzuur via de eerder genoemde determinanten. Het model is ontwikkeld met de data van het onderzoek van 1995 (de voormeting vóór de foliumzuurcampagne) en is bevestigd met de data van het onderzoek van 1996 (de nameting). De relatie tussen de determinanten en foliumzuurgebruik bleek onafhankelijk van het opleidingsniveau. Het ontwikkelde model is minder uitgebreid dan de Theory of Reasoned action. Data over de intentie van foliumzuurgebruik bij een eventuele volgende zwangerschap ontbraken voor de vrouwen die foliumzuur hadden gebruikt. Het lijkt aannemelijk dat vrouwen die eerder foliumzuur hadden gebruikt dit bij een volgende zwangerschap ook zullen doen, maar er kunnen redenen zijn dat zij niet opnieuw foliumzuur gaan gebruiken. Het ontwikkelde model kan worden gebruikt bij het begrijpen van het gebruik van foliumzuur door vrouwen met zwangerschapswens. Tevens is het model bruikbaar voor het evalueren van de effectiviteit van interventies ter bevordering van het gebruik van foliumzuur.

In **hoofdstuk 5** wordt het effect van de landelijke foliumzuurcampagne in 1995 op kennis en gebruik van foliumzuur beschreven, evenals het additionele effect van een regionale

foliumzuurcampagne. Vlak voor de landelijke voorlichtingscampagne was het percentage vrouwen dat gehoord had van foliumzuur 41,7%. Eén jaar na de foliumzuurcampagne was het percentage vrouwen dat aangaf gehoord te hebben van foliumzuur gestegen naar 77,3%. Het gebruik van foliumzuur gedurende een deel van de aanbevolen periode is gestegen, namelijk van 25,1% voor de landelijke voorlichtingscampagne naar 53,5% één jaar na de landelijke voorlichtingscampagne. Ook is er een stijging in het juist gebruik van foliumzuur (vanaf 4 weken voor tot 8 weken na de conceptie) van 4,8% naar 21,0%. Het percentage vrouwen dat gehoord heeft van foliumzuur is hoger dan de vooraf gestelde doelstelling, namelijk dat 70% van de vrouwen met zwangerschapswens van het advies over foliumzuur heeft gehoord. Het juist gebruik van foliumzuur is na de foliumzuurcampagne aanzienlijk toegenomen, maar de doelstelling dat 46% van de zwangere vrouwen foliumzuur op de juiste manier heeft gebruikt, is niet bereikt. Verder is bestudeerd of de uitgevoerde regionale campagne een additioneel effect laat zien op het gebruik van foliumzuur. Het gebruik van foliumzuur was vergelijkbaar tussen de regio's met alleen de landelijke campagne en die met de landelijke en regionale campagne (adjusted odds ratio=1.0; 95% betrouwbaarheidinterval=0.7-1.4). Een additioneel effect van de regionale campagne is dus niet gevonden.

In **hoofdstuk 6** is het effect van de landelijke en regionale campagne bij vrouwen met verschillend opleidingsniveau bestudeerd. Hiervoor is het ontwikkelde model van determinanten van foliumzuurgebruik gebruikt (zie hoofdstuk 4), Voor de start van de foliumzuurcampagne gaven vrouwen met een lage opleiding minder vaak aan gehoord te hebben van foliumzuur en foliumzuur te gebruiken, dan vrouwen met een hoge opleiding. Eén jaar na de campagne (1996) was het gebruik van foliumzuur in beide groepen met 30% gestegen. Dit betekent dat het verschil in foliumzuurgebruik tussen vrouwen met een laag en hoog opleidingsniveau niet kleiner is geworden, maar ook niet groter. Wel zijn er verschillen in de hoogte van de score op determinanten tussen vrouwen met een verschillend opleidingsniveau. Vrouwen met een hoog opleidingsniveau gaven een hogere score voor gepercipieerde veiligheid en attitude, terwijl vrouwen met een laag opleidingsniveau een hogere score gaven voor subjectieve norm. Tussen de regio's met alleen de landelijke campagne en de regio's met de landelijke en regionale campagne zijn er geen verschillen gevonden in effect op

attitude en gepercipieerde veiligheid. Wel was er een verschil in het effect op subjectieve norm, de ingeschatte verwachting van wat de directe omgeving over het gebruik van foliumzuur vindt. In de regio's met de landelijke campagne stegen de scores van vrouwen met een hoog opleidingsniveau meer dan die van vrouwen met een laag opleidingsniveau. Met andere woorden, voor subjectieve norm profiteerden vrouwen met een hoog opleidingsniveau meer van de campagne. In de regio's met de landelijke en regionale campagne stegen de scores voor subjectieve norm evenveel voor vrouwen met een verschillend opleidingsniveau, waardoor het verschil tussen beide groepen niet is toegenomen. Beide groepen vrouwen hebben daar evenveel van de campagnes geprofiteerd.

Hoofdstuk 7 beschrijft hoe de capture-recapture methode is toegepast om de prevalentie van neuralebuisdefecten in Nederland voor de periode 1988-1998 te schatten. Er is in Nederland geen landelijke registratie van neuralebuisdefecten. Daarom is gebruik gemaakt van verschillende registraties waarin neuralebuisdefecten worden geregistreerd. Omdat niet alle gebruikte registraties gedurende de hele periode beschikbaar zijn, is een aangepaste vorm van de capture-recapture methode ontwikkeld. Aangetoond wordt dat deze methode een correcte schatting van de populatiegrootte geeft. Deze methode is daarna toegepast bij de schatting van de landelijke prevalentie van neuralebuisdefecten.

In **hoofdstuk 8** is de trend in neuralebuisdefecten in Nederland in de periode 1988-1998 beschreven. Voor het schatten van de prevalentie is gebruik gemaakt van data over neuralebuisdefecten van de drie perinatale databases (LVR1, LVR2, LNR) en het Nederlands Signalerings Centrum Kindergeneeskunde (NSCK). Daarnaast zijn via de oudervereniging de BOSK alle leden met een kind met spina bifida aangeschreven. Met behulp van de capture-recapture methode, zoals beschreven in hoofdstuk 7, is de prevalentie van neuralebuisdefecten geschat. In de periode 1988-1998 varieerde de prevalentie tussen 1,43 en 1,96 per 1.000 levend- en doodgeborenen. Een daling in de prevalentie van neuralebuisdefecten vanaf half 1997 kon niet worden bewezen. Wel is de prevalentie in 1998 een van de laagste in de bestudeerde periode. Op populatieniveau is het gebruik van foliumzuur rond de conceptie nog niet bewezen effectief. Voortzetting van het monitoren van de prevalentie, bijvoorkeur

vergezeld van structurele voorlichting over foliumzuurgebruik, is van belang om het effect van foliumzuurgebruik op de prevalentie van neuralebuisdefecten te kunnen volgen.

In **hoofdstuk 9** zijn de belangrijkste bevindingen samengevat en worden aanbevelingen gedaan over de voortzetting van primaire preventie van neuralebuisdefecten in Nederland. Geconcludeerd wordt dat de huidige preventiestrategie, periconceptioneel foliumzuurgebruik middels tabletten, duidelijk effect begint te vertonen. Om dit effect te behouden en te laten toenemen zijn de volgende maatregelen nodig. Ten eerste, het regelmatig herhalen van de landelijke campagne via de massamedia. Ten tweede zou informatie over het gebruik van foliumzuur opgenomen kunnen worden in het lesprogramma van het voortgezet onderwijs. Ten derde dient voorlichting over foliumzuurgebruik een standaard onderdeel van de preconceptie-advisering door huisartsen te zijn. Tevens zijn specifieke interventies nodig om vrouwen met een laag opleidingsniveau te bereiken.

Om het volledige effect van de huidige preventiestrategie te beoordelen is monitoring van foliumzuurgebruik en van de prevalentie van neuralebuisdefecten van belang. Uiteindelijk ligt het rechtvaardigen van het doorgaan met de primaire preventie van neuralebuisdefecten in het aantonen van een daling in de prevalentie.

Overigens kunnen door foliumzuurgebruik niet alle gevallen van neuralebuisdefecten worden voorkomen. Prenatale screening met de mogelijkheid tot zwangerschapsafbreking zal dan ook noodzakelijk blijven. Bij volledig gebruik van foliumzuur zal dit echter veel minder vaak nodig zijn waardoor ook het verdriet dat met een dergelijke ingrijpende gebeurtenis gepaard gaat wordt voorkomen.

Mogelijk dat in de toekomst, door het beschikbaar komen van nieuwe inzichten (zoals het preventief effect van foliumzuur op hart- en vaatziekten), heroverweging van de huidige preventiestrategie gewenst is. Tot die tijd dient de huidige strategie voortgezet en verbeterd te worden.

Nawoord

Nawoord

Mijn eerste project bij TNO was de evaluatie van de foliumzuurcampagne. Dat dit project het begin van mijn promotieonderzoek zou zijn was toen nog onduidelijk. Wel sprak het onderwerp mij vanaf het begin bijzonder aan vanwege de mogelijkheid om een ernstig aangeboren afwijking te voorkómen door 'simpelweg' een bepaald vitaminetabletje rond de conceptie te gebruiken. Dat dit niet zo simpel is, heeft dit onderzoek mij wel geleerd.

De evaluatie van de foliumzuurcampagne was niet gelukt zonder de inzet van de verloskundigen, gynaecologen en huisartsen die in het najaar van 1995 en 1996 aan alle zwangere cliënten die voor de eerste of tweede controle kwamen hebben gevraagd of ze aan dit onderzoek wilden meewerken. Nogmaals mijn hartelijke dank hiervoor. Ook bedank ik alle zwangere vrouwen die na de zwangerschapscontrole de vragenlijst in de wachtkamer hebben ingevuld. Doordat zij hiervoor 20 minuten de tijd namen was het mogelijk de foliumzuurcampagne te evalueren.

Vele verloskundigen, gynaecologen en kinderartsen hebben door hun deelname aan verschillende registraties waarin kinderen met neuralebuisdefect zijn opgenomen ongemerkt een belangrijke bijdrage aan het onderzoek naar de prevalentie van neuralebuisdefecten geleverd. Mijn dank gaat uit naar de Landelijke Verloskunde Registratie 1ste lijn, de Landelijke Verloskunde Registratie 2de lijn, en de Landelijke Neonatologie Registratie. Tevens wil ik alle kinderartsen bedanken die vanaf 1993 maandelijks aan het Nederlands Signalerings Centrum Kindergeneeskunde pasgeborenen met een neuralebuisdefect hebben gemeld en daarna onze vragenlijst invulden. Ook wil ik Ina Kloosterboer bedanken die de laatste jaren de gegevens van de kinderen in de database heeft ingevoerd.

Graag wil ik de Bond voor Ouders met Spastische Kinderen (BOSK) bedanken voor het toesturen van een vragenlijst aan hun leden met een kind met spina bifida en alle leden die de vragenlijst ingevuld aan ons terugzonden. Zo leverde zij een belangrijke bijdrage aan het beantwoorden van de vraag hoeveel kinderen met een neuralebuisdefect er jaarlijks in Nederland geboren worden.

Het opmaken van het manuscript en het 'boekje' is meer werk dan het op het eerste gezicht misschien lijkt. Jolanda Anthonissen en Tineke de Graaf dank ik voor alle inspanningen om alles op tijd af te hebben.

Verder gaat mijn dank uit naar Marian van Elk en Odile de Groot, die door de liefdevolle opvang van mijn kinderen mij in de gelegenheid hebben gesteld dit onderzoek uit te voeren.

Lieve mama en papa, jullie gaven mij de gelegenheid om zonder zorgen te kunnen studeren wat ik wilde en mezelf te ontwikkelen op een manier die bij mij past. Waardevolle fundamenten, en niet alleen voor een onderzoek als dit.

Lieve Jack, het is niet in woorden uit te drukken hoe belangrijk jouw liefde en steun is geweest voor het tot stand komen van dit proefschrift en voor zoveel meer...

En nu ... lieve Femke en Manouk, laten we lekker gaan spelen, want het boekje is klaar!

Curriculum Vitae

Karin Maria van der Pal-de Bruin werd geboren op 18 september 1968 te Amsterdam. Zij volgde daar de lagere school en het VWO. In 1986 begon zij in Leiden met de studie Biomedische Wetenschappen. In 1991 behaalde zij het doctoraalexamen. Na haar studie werkte zij een jaar als statisticus bij Solvay Duphar, waarna zij ruim 3 jaar als epidemioloog bij het centrum voor Volksgezondheid Toekomstverkenningen van het Rijksinstituut voor Volksgezondheid en Milieu werkte. Sinds augustus 1995 is zij werkzaam bij TNO Preventie en Gezondheid. Bij de sector Voortplanting en Perinatologie van de divisie Jeugd verrichtte zij onder andere het onderzoek dat in dit proefschrift is beschreven.


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