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

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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 and 1.96 per 1000 live and still births. No decrease in total prevalence was found to have taken place during that period. Scrutiny of the last 2 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.

Keywords: Prevalence NTD; Trend; Folic acid use

1. 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 health care 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 4 weeks before conception until 8 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 [11,12].

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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.

2. Methods

2.1. 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 period 1988 to 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 10 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. Ninety-five percent of all paediatric departments participate. NTDs have been registered by the DPSU since 1993; in our analysis, we used data from 1993 to 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 1997. 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.

2.2. 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.

2.3. 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 d.f., 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 [13]. 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 d.f. 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 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.

3. 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). 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 7 and 18 newborns with NTD (Table 1).

Separately capture–recapture analysis was used to estimate the number of newborns with NTD for <24 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

Table 1
Number of newborn with NTD per year in The Netherlands, 1988–1998

Year	Number of reported newborns with NTD[a]	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

[a] 1988–1991: sources—LVR1, LVR2, BOSK; 1992–1993: sources—LVR1, LVR2, BOSK, LNR; 1994–1998: sources—LVR1, LVR2, BOSK, LNR, DPSU.

Table 2
Estimated prevalence of NTD in The Netherlands using capture–recapture analysis, 1988–1998

Year	Number of observed and estimated newborns with NTD (95% CI)			Total number LB and SB in The Netherlands	Prevalence rate of NTD per 1000 LB and SB (95% CI)		
	<24 weeks of gestation	≥24 weeks of gestation	Total		<24 weeks of gestation	≥24 weeks of gestation	Total
1988	98 (65, 156)	238 (161, 290)	336 (250, 405)	187.685	0.52 (0.35, 0.83)	1.27 (0.86, 1.55)	1.79 (1.33, 2.16)
1989	87 (59, 131)	204 (163, 243)	291 (240, 343)	190.079	0.46 (0.31, 0.69	1.07 (0.86, 1.28)	1.53 (1.26, 1.80)
1990	103 (76, 146)	231 (185, 269)	334 (276, 390)	199.104	0.52 (0.38, 0.73)	1.16 (0.93, 1.35)	1.68 (1.39, 1.96)
1991	98 (75, 127)	187 (152, 227)	285 (244, 331)	199.732	0.49 (0.38, 0.64)	0.94 (0.76, 1.14)	1.43 (1.22, 1.66)
1992	101 (79, 125)	286 (211, 319)	387 (307, 420)	197.848	0.51 (0.40, 0.63)	1.45 (1.07, 1.61)	1.96 (1.55, 2.12)
1993	92 (75, 115)	220 (193, 264)	312 (282, 363)	196.819	0.48 (0.38, 0.58)	1.12 (0.98, 1.34)	1.59 (1.43, 1.84)
1994	66 (52, 82)	275 (235, 355)	341 (303, 419)	196.666	0.34 (0.26, 0.42)	1.40 (1.19, 1.81)	1.73 (1.54, 2.13)
1995	66 (53, 81)	307 (263, 396)	373 (328, 462)	191.376	0.34 (0.28, 0.42)	1.60 (1.37, 2.07)	1.95 (1.71, 2.41)
1996	70 (57, 84)	269 (233, 345)	339 (301, 420)	190.405	0.37 (0.30, 0.44)	1.41 (1.22, 1.81)	1.78 (1.58, 2.21)
1997	64 (51, 78)	306 (268, 380)	370 (334, 443)	193.428	0.33 (0.26, 0.40)	1.58 (1.39, 1.96)	1.91 (1.73, 2.29)
1998	65 (54, 81)	254 (220, 319)	319 (288, 388)	200.378	0.32 (0.27, 0.40)	1.27 (1.10, 1.59)	1.59 (1.44, 1.95)

LB: live births, SB: still birth.

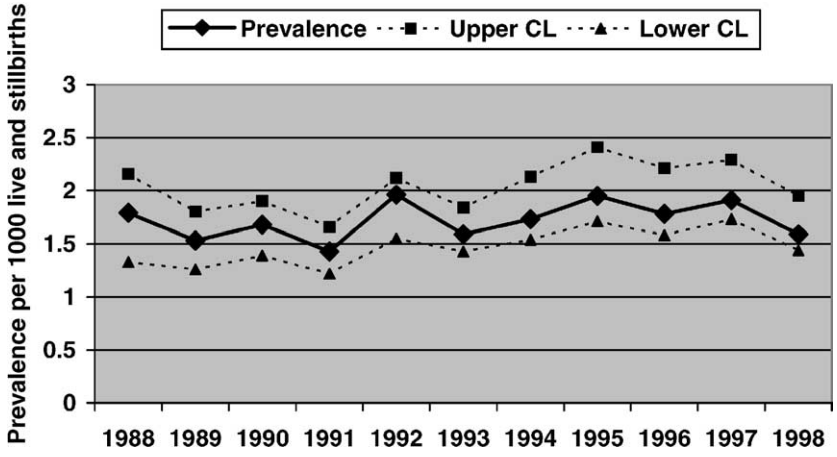

Fig. 1. Prevalence of NTD in The Netherlands, 1988–1998.

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 $\geq$ 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 still births are registered by the National Bureau of Statistics. In 1988, the prevalence of NTD was 1.79 per 1000 live and still births; in 1998, the figure was 1.59 per 1000. In the intervening years, the total prevalence of NTD varied from 1.43 to 1.96 per 1000 live and still births (Fig. 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.

4. 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 1000 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 1000 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 et al. 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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