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Periconceptional Folic Acid Supplementation and Infant Risk of Congenital Heart Defects in Norway 1999–2009

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Abstract

Background: The birth prevalence of congenital heart defects (CHDs) has decreased in Canada and Europe. Recommended intake of folic acid in pregnancy is a suggestive risk-reducing factor for CHDs. We investigated the association between periconceptional intake of folic acid supplements and infant risk of CHDs.

Methods: Information on maternal intake of folic acid supplements before and during pregnancy in the Medical Birth Registry of Norway 1999–2009 was updated with information on CHD diagnoses from national health registers and the Cardiovascular Diseases in Norway Project. The association between folic acid intake and infant risk of CHD was estimated as relative risk (RR) with binomial log linear regression.

Results: Among 517 784 non-chromosomal singleton births, 6200 children were identified with CHD and 1153 with severe CHD. For all births, 18.4% of the mothers initiated folic acid supplements before pregnancy and 31.6% during pregnancy. The adjusted RR for severe CHD was 0.99 [95% confidence interval [CI] 0.86, 1.13] comparing periconceptional intake of folic acid with no intake. Specifically, RR for conotruncal defects was 0.99 [95% CI 0.80, 1.22], atrioventricular septal defects 1.19 [95% CI 0.78, 1.81], left ventricular outflow tract obstructions 1.02 [95% CI 0.78, 1.32], and right ventricular outflow tract obstructions 0.97 [95% CI 0.72, 1.29]. Birth prevalence of septal defects was higher in the group exposed to folic acid supplements with RR 1.19 [95% CI 1.10, 1.30].

Conclusions: Periconceptional folic acid supplement use showed no association with severe CHDs in the newborn. An unexpected association with an increased risk of septal defects warrants further investigation.

Keywords: *Norway, cohort study, folic acid supplementation, congenital heart defects, epidemiology.*

Introduction

Congenital heart defects (CHDs) are among the most common birth defects and represent an important cause of infant morbidity and mortality, affecting 5–13 per 1000 births worldwide.[1–3] After decades of increasing prevalence of CHDs believed to be explained by improved diagnostics and reporting,[4,5] several studies have shown a changing time trend with decreasing prevalence in Canada and Europe after 1999,[6,7] and also in Norway from 2005.[3] This decline in CHDs has been partly explained by the concurrent introduction of folic acid food fortification or the increasing use of periconceptional folic acid supplements. Folic acid is the synthetic form of folate, which is necessary in DNA, RNA, and protein synthesis, and therefore important during fetal development. Periconceptional intake of folic acid has been shown to reduce the risk for neural tube defects,[8,9] and women worldwide have been recommended to take folic acid supplements before conception and in the beginning of pregnancy. More than 70 countries have also implemented folic acid fortification of grain products,[5,6] whereas health authorities in Norway have refrained from such fortification and recommended periconceptional use of

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folic acid supplements.[10] A possible protective effect of folic acid supplements on CHDs is, however, controversial. While some studies have reported reduced risk of CHDs in children whose mothers have taken multivitamins with folic acid[11,12] or pure folic acid supplements,[13,14] or after folic acid food fortification,[6] other studies have reported no effect on CHDs of folic acid food fortification.[15,16]

In the Medical Birth Registry of Norway, information on the use of folic acid and multivitamin supplements has been recorded for all women giving birth since 1999.[17] We have taken advantage of Norway's national health registries and the Cardiovascular Disease in Norway project (CVDNOR) to investigate infant risk of specific types of CHDs among mothers using folic acid supplements in the periconceptional period.

Methods

Data sources

The Norwegian National Registry contains demographic data and vital status on all residents since 1965. Every resident's unique personal identification number enables linkage of data between national registries and other data sources. The Medical Birth Registry of Norway has since 1967 recorded information on all births (livebirths and stillbirths, since 1999 terminated pregnancies for fetal reasons, and since 2002 all births from 12th week gestation) on the birth notification form, including information on the mother's health, the course of the pregnancy and delivery, and the health of the newborn.[17] Oslo University Hospital's clinical registry for children with heart disease has registered all children with a heart defect admitted to Oslo University Hospital since 1992.[18] The multipurpose research project CVDNOR[19] includes information on discharge diagnoses retrieved from the electronic Patient Administrative Systems of all somatic hospitals in Norway 1994–2009.[19] The Cause of Death Registry records contributing causes of death from death certificates. Statistics Norway provides demographic data for all residents, including educational level, occupation, income, and marital status.[20]

Case ascertainment and classification of congenital heart defects

Information on CHD diagnoses was retrieved from the four data sources mentioned above, as published previously,[3] where each child was assigned a cardiac phenotype with priority corresponding to the timing of presumed errors in fetal heart development[2,3]: *heterotaxia*; *conotruncal defects* [d-transposition of the great arteries (TGAs), tetralogy of Fallot (ToF), double outlet right ventricle, conoventricular ventricle septal defect (VSD), common arterial trunk, interrupted aortic arch (IAA) type B or C]; *atrioventricular septal defect* (AVSD); *anomalous pulmonary venous return* (APVR); *left ventricle outflow tract obstruction* (LVOTO) [coarctation of the aorta (CoA), aortic valve stenosis (vAS), hypoplastic left heart syndrome (HLHS)]; *right ventricle outflow tract obstruction* (RVOTO) [hypoplastic right heart syndrome (HRHS), tricuspid atresia, Ebstein anomaly, pulmonary atresia (PA) or atresia of the pulmonary valve with intact ventricular septum, valvular pulmonary stenosis (vPS)]; *septal defect* [VSD only, atrial septal defect (ASD) only and recorded from postnatal age 6 weeks or with surgical or percutaneous correction, VSD and ASD only]; *other complex heart defect* [single ventricle, congenital corrected transposition of the great arteries (ccTGA)]; *patent ductus arteriosus* (PDA) at postnatal age > 6 weeks or with surgical correction, in livebirths with gestational age 37 weeks or more (term PDA), or with gestational age < 37 weeks (preterm PDA); *other specified heart defect*; and *unspecified heart defect*. *Severe CHD* was defined as heterotaxia, conotruncal defect, AVSD, APVR, LVOTO, RVOTO (except valvular pulmonary stenosis), or other complex defect.

Information on chromosome aberrations and genetic conditions associated with CHD was retrieved using ICD codes [8th revision 759.3–759.5, 9th revision 758.0–759.9, 10th revision D82.1, Q87.1, Q87.2, Q90.0-Q99.9], van Mierop codes [8000–8004, 8009–8025, 8072], and by searching the free text fields for specific disorders (e.g. Down's syndrome, William's syndrome, Noonan's syndrome).

Folic acid and multivitamin supplementation

Since 1999, the Medical Birth Registry of Norway has registered maternal intake of periconceptional vitamins by using five check boxes on the Birth Registry notification form from maternity units; for regular use of folic acid or multivitamins before pregnancy or during pregnancy, or for no supplement use. The embryonic cardiac development is 3–7 weeks after conception, and includes the time period when the mother likely recognises her pregnancy, with subse-

Table 1. Maternal use of folic acid or multivitamin supplements before and during pregnancy in 517 784 births, Medical Birth Registry of Norway, 1999–2009[a]

		Supplement use during pregnancy			
		Folic acid		No folic acid	
Supplement use before pregnancy		Multivitamin No. (%)	No multivitamin No. (%)	Multivitamin No. (%)	No multivitamin No. (%)
Folic acid	Multivitamin	32 477 (6.3)	2196 (0.4)	1172 (0.2)	1538 (0.3)
	No multivitamin	16 485 (3.2)	36 725 (7.1)	1419 (0.3)	3497 (0.7)
No folic acid	Multivitamin	18 539 (3.6)	2572 (0.5)	12 496 (2.4)	1986 (0.4)
	No multivitamin	62 170 (12.0)	80 205 (15.5)	28 959 (5.6)	215 348 (41.6)

[a]Livebirths and stillbirths registered in the Medical Birth Registry with information on supplement use, excluding multiple births, births from in vitro fertilisation, children with chromosomal disorders, and with maternal epilepsy.

quent initiation of folic acid supplementation. We therefore decided to report risk estimates for CHD by any use of folic acid before pregnancy and/or during pregnancy, with or without multivitamin intake, referred to as periconceptional use of folic acid. Risk analyses were also performed for the other combinations of folic acid and multivitamin exposure (Table 1). Over-the-counter folic acid supplements in Norway contained 0.4 mg folic acid and multivitamin tablets 0.0–0.2 mg folic acid during the study period 1999–2009.

Other variables

We included the following covariates as confounders of the association between folic acid intake and infant CHD risk in the multivariable model; year of birth (each year), maternal age (<20, 20–24, 25–29, 30–34 and >34 years), parity (0, 1 or ≥2 previous pregnancies), maternal education (≤10, 11–13, 14–16, ≥17 years, missing (7.8%)), marital status (married/cohabitant, single/other), maternal smoking (regular/occasional, non-smokers, did not consent to register smoking information, missing (2.8%)), and family income (quartiles of mean income of the adults in the family). In initial analyses, we evaluated maternal diabetes (pregestational or gestational) as a confounder; however, diabetes did not affect the association between folic acid and CHD, and was not included in the final adjustment model.

Study population

In the period 1999–2009, 652 977 births were registered in the Medical Birth Registry of Norway. We excluded births with chromosomal disorders ($n = 2245$), multiple births ($n = 23\,815$), births from in vitro fertilisation ($n = 15\,791$), and births with maternal epilepsy ($n = 4978$), in total 41 292 (6.3%) births. Among the remaining 611 685 births, we excluded 93 901 (15.4%) births without information of folic acid or multivitamin supplementation (which included the 1442 pregnancies terminated for fetal reasons), leaving 517 784 livebirths and stillbirths for analyses.

Statistical analysis

The association between maternal periconceptional folic acid supplement use and infant risk of CHD was reported as relative risk (RR); the risk of CHD among the exposed divided by the risk of CHD among the unexposed. Births without maternal intake of folic acid or multivitamin supplements were used as reference group. Crude and adjusted relative risks (aRR) with 95% confidence intervals [CI] were estimated using binomial log linear regression models with a log-link function using STATA version 13 (Stata Corp., Texas, USA).

Results

Among 517 784 individuals, 6200 children had any type of CHD and 1153 had a severe CHD; the birth prevalence was 119.7 per 10 000 births and 22.3 per 10 000 births, respectively. In the period, the birth prevalence increased for total CHD until 2004, and decreased thereafter (Figure 1). The prevalence for severe CHD decreased from 2005. Overall, 95 509 (18.4%) mothers had initiated folic acid supplements

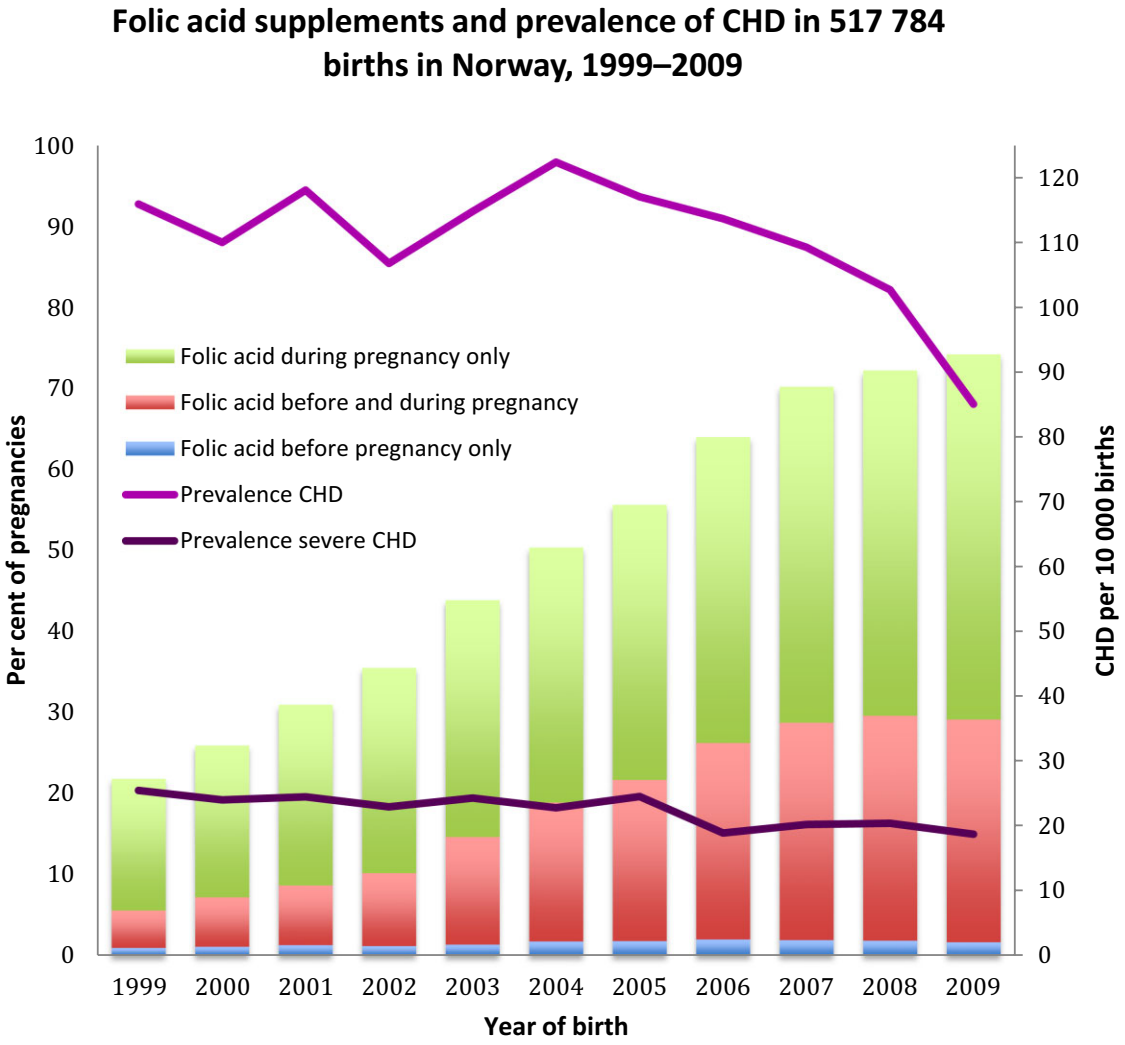

Figure 1. Periconceptional use of folic acid supplements and birth prevalence of severe CHD (heterotaxia, conotruncal defect, AVSD, APVR, LVOTO, RVOTO except valvular pulmonary stenosis, CoA, other complex heart defect) and any CHD except preterm PDA, by year of birth, in 517 784 livebirths and stillbirths registered in the Medical Birth Registry of Norway, 1999–2009, excluding multiple births, births from in vitro fertilisation, children with chromosomal disorders, and with maternal epilepsy. APVR, anomalous pulmonary venous return; AVSD, atrioventricular septal defect; CHD, congenital heart defect; CoA, coarctation of the aorta; LVOTO, left ventricle outflow tract obstruction; PDA, patent ductus arteriosus; RVOTO, right ventricle outflow tract obstruction.

before pregnancy, 163 486 (31.6%) had started during pregnancy, 43 441 (8.4%) used only multivitamins in the periconception period, while 215 348 (41.6%) did not use any folic acid or multivitamin supplements (Tables 1 and 2). Initiation of folic acid before pregnancy increased from 5.5% of all births in 1999 to 29.1% in 2009, while any periconceptional use of folic acid increased from 21.7% in 1999 to 74.2% in 2009.

In Table 2, initiation of folic acid supplements before pregnancy or during pregnancy, use of multivitamins only, and no use of any supplements are shown by year of birth and maternal characteristics. Shorter education, younger age, smoking, previous births, single status, and lower family income were more frequent in mothers who did not use any folic acid or multivitamin supplements.

Maternal periconceptional use of folic acid was not associated with infant risk of severe CHD; the aRR was 0.99 [95% CI 0.86, 1.13] comparing pregnancies exposed to folic acid with non-exposed pregnancies (Table 3). Specifically, aRR for conotruncal defects was 0.99 [95% CI 0.80, 1.22], aRR for AVSD 1.19 [95% CI 0.78, 1.81], aRR for LVOTO 1.02 [95% CI 0.78, 1.32],

Table 2. Birth characteristics according to use of folic acid before or during pregnancy in Norway, 1999–2009

Characteristics	Total births[a] 517 784		Preconceptional folic acid[b] 95 509 (18.4%)		Postconceptional folic acid only[c] 163 486 (31.6%)		Multivitamins only[d] 43 441 (8.4%)		No use of supplements[e] 215 348 (41.6%)	
	No.	% of Births	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Year of birth										
1999	46 520	(9.0)	2563	(5.5)	7558	(16.2)	5783	(12.4)	30 616	(65.8)
2000	48 472	(9.4)	3458	(7.1)	9080	(18.7)	4960	(10.2)	30 974	(63.9)
2001	46 693	(9.0)	4018	(8.6)	10 410	(22.3)	4532	(9.7)	27 733	(59.4)
2002	44 226	(8.5)	4475	(10.1)	11 202	(25.3)	4293	(9.7)	24 256	(54.8)
2003	43 749	(8.4)	6379	(14.6)	12 782	(29.2)	3900	(8.9)	20 688	(47.3)
2004	44 464	(8.6)	8376	(18.8)	13 992	(31.5)	3206	(7.2)	18 890	(42.5)
2005	44 614	(8.6)	9649	(21.6)	15 145	(33.9)	2957	(6.6)	16 863	(37.8)
2006	46 215	(8.9)	12 101	(26.2)	17 444	(37.7)	3523	(7.6)	13 147	(28.4)
2007	48 617	(9.4)	13 946	(28.7)	20 162	(41.5)	3661	(7.5)	10 848	(22.3)
2008	51 142	(9.9)	15 110	(29.5)	21 795	(42.6)	3386	(6.6)	10 851	(21.2)
2009	53 072	(10.2)	15 434	(29.1)	23 916	(45.1)	3240	(6.1)	10 482	(19.8)
Maternal education, y										
≤10	98 808	(19.1)	10 038	(10.2)	27 673	(28.0)	10 228	(10.4)	50 869	(51.5)
11–13	167 510	(32.4)	25 160	(15.0)	52 171	(31.1)	13 961	(8.3)	76 218	(45.5)
14–16	129 257	(25.0)	32 425	(25.1)	46 113	(35.7)	8317	(6.4)	42 402	(32.8)
≥17	81 713	(15.8)	23 618	(28.9)	27 933	(34.2)	4657	(5.7)	25 505	(31.2)
Missing data	40 496	(7.8)	4268	(10.5)	9596	(23.7)	6278	(15.5)	20 354	(50.3)
Maternal age, y										
<20	12 940	(2.5)	402	(3.1)	3475	(26.9)	1640	(12.7)	7423	(57.4)
20–24	79 284	(15.3)	7390	(9.3)	25 824	(32.6)	7940	(10.0)	38 130	(48.1)
25–29	172 574	(33.3)	31 139	(18.0)	56 181	(32.6)	14 050	(8.1)	71 204	(41.3)
30–34	169 622	(32.8)	38 081	(22.5)	52 764	(31.1)	12 798	(7.5)	65 979	(38.9)
>34	83 348	(16.1)	18 494	(22.2)	25 238	(30.3)	7010	(8.4)	32 606	(39.1)
Missing data	16	(0.0)	3	(18.8)	4	(25.0)	3	(18.8)	6	(37.5)
Maternal smoking										
No	357 552	(69.1)	75 196	(21.0)	115 748	(32.4)	28 762	(8.0)	137 846	(38.6)
Yes	94 429	(18.2)	9382	(9.9)	30 093	(31.9)	9777	(10.4)	45 177	(47.8)
No consent	59 007	(11.4)	9911	(16.8)	15 937	(27.0)	4420	(7.5)	28 739	(48.7)
Missing data	6796	(1.3)	1020	(15.0)	1708	(25.1)	482	(7.1)	3586	(52.8)
Parity										
0	209 839	(40.5)	39 570	(18.9)	75 789	(36.1)	17 871	(8.5)	76 609	(36.5)
1	186 530	(36.0)	38 025	(20.4)	56 236	(30.1)	14 290	(7.7)	77 979	(41.8)
≥2	121 415	(23.4)	17 914	(14.8)	31 461	(25.9)	11 280	(9.3)	60 760	(50.0)
Marital status										
Married/cohabiting	476 209	(92.0)	92 043	(19.3)	150 887	(31.7)	38 861	(8.2)	194 418	(40.8)
Single/other	41 575	(8.0)	3466	(8.3)	12 599	(30.3)	4580	(11.0)	20 930	(50.3)
Family income(quartiles)										
1	128 127	(24.7)	12 598	(9.8)	36 160	(28.2)	14 376	(11.2)	64 993	(50.7)
2	130 934	(25.3)	21 176	(16.2)	41 621	(31.8)	10 899	(8.3)	57 238	(43.7)
3	129 512	(25.0)	27 615	(21.3)	42 493	(32.8)	9393	(7.3)	50 011	(38.6)
4	124 504	(24.0)	33 706	(27.1)	42 472	(34.1)	8105	(6.5)	40 221	(32.3)
Missing data	4707	(0.9)	414	(8.8)	740	(15.7)	668	(14.2)	2885	(61.3)

[a]Livebirths and stillbirths registered in the Medical Birth Registry with information on supplement use, excluding multiple births, births from in vitro fertilisation, children with chromosomal disorders, and maternal epilepsy.
[b]Initiation of folic acid supplementation before pregnancy, with or without use of multivitamins.
[c]Initiation of folic acid supplementation during pregnancy, with or without use of multivitamins.
[d]Multivitamin supplements before and/or during pregnancy, with no use of folic acid.
[e]Pregnancies with no use of folic acid or multivitamin supplements as reference group.

Table 3. Congenital heart defects according to use of folic acid before and/or during pregnancy in 517 784 births in Norway, 1999–2009[a]

	Births	Any use of folic acid[b]		RR crude[c]		RR adjusted[d]	
Heart defect phenotype	No.	No.	%	RR	95% CI	aRR	95% CI
Any CHD	6200	3166	(51.1)	1.05	(0.99, 1.10)	1.10	(1.03, 1.16)
CHD excl. preterm PDA	5695	2928	(51.4)	1.07	(1.01, 1.13)	1.13	(1.06, 1.20)
Severe CHD	1153	546	(47.4)	0.89	(0.79, 1.01)	0.99	(0.86, 1.13)
Heterotaxia	71	28	(39.4)	0.69	(0.42, 1.13)	0.80	(0.45, 1.42)
Conotruncal defect	502	240	(47.8)	0.92	(0.77, 1.11)	0.99	(0.80, 1.22)
TGA	179	91	(50.8)	1.07	(0.78, 1.45)	1.10	(0.77, 1.57)
ToF	100	44	(44.0)	0.80	(0.53, 1.20)	0.90	(0.57, 1.44)
Other conotruncal[e]	223	105	(47.1)	0.87	(0.66, 1.15)	0.95	(0.70, 1.30)
AVSD	118	60	(50.8)	0.96	(0.66, 1.39)	1.19	(0.78, 1.81)
APVR	52	21	(40.4)	0.76	(0.42, 1.37)	0.78	(0.40, 1.52)
LVOTO	312	149	(47.8)	0.89	(0.70, 1.12)	1.02	(0.78, 1.32)
HLHS	78	40	(51.3)	0.98	(0.62, 1.55)	1.15	(0.69, 1.94)
CoA + IAA type A	109	53	(48.6)	0.92	(0.62, 1.36)	1.05	(0.67, 1.63)
vAS	125	56	(44.8)	0.80	(0.56, 1.16)	0.92	(0.61, 1.39)
RVOTO	258	120	(46.5)	0.89	(0.69, 1.15)	0.97	(0.72, 1.29)
HRHS	31	17	(54.8)	1.41	(0.65, 3.09)	1.43	(0.59, 3.42)
Ebstein	34	18	(52.9)	1.07	(0.53, 2.15)	0.91	(0.41, 1.99)
vPS	169	75	(44.4)	0.83	(0.60, 1.15)	0.96	(0.67, 1.38)
Other RVOTO[f]	24	10	(41.7)	0.64	(0.28, 1.46)	0.67	(0.26, 1.74)
Septal defect, isolated	3280	1747	(53.3)	1.16	(1.08, 1.25)	1.19	(1.10, 1.30)
ASD	647	345	(53.3)	1.16	(0.99, 1.37)	1.30	(1.08, 1.56)
VSD	2595	1378	(53.1)	1.15	(1.06, 1.25)	1.16	(1.06, 1.27)
Other septal defect	37	23	(62.2)	1.74	(0.85, 3.57)	1.97	(0.89, 4.38)
Other complex CHD[g]	9	3	(33.3)	0.50	(0.12, 2.09)	0.70	(0.15, 3.36)
Isolated PDA	1074	543	(50.6)	1.00	(0.88, 1.13)	1.02	(0.88, 1.17)
At term gestation	569	305	(53.6)	1.16	(0.98, 1.38)	1.23	(1.01, 1.50)
Preterm gestation	505	238	(47.1)	0.85	(0.71, 1.02)	0.82	(0.67, 1.01)
Other specified CHD	285	147	(51.6)	1.03	(0.81, 1.31)	1.17	(0.89, 1.53)
Unspecified CHD	239	108	(45.2)	0.80	(0.62, 1.04)	0.84	(0.62, 1.14)

[a]Livebirths and stillbirths registered in the Medical Birth Registry, excluding multiple births, births from in vitro fertilisation, children with chromosomal disorders, and with maternal epilepsy.

[b]Preconceptional or postconceptional initiation of folic acid, with or without use of multivitamins.

[c]Births with no periconceptional use of folic acid or multivitamin supplements as reference group.

[d]Relative risk adjusted for year of birth, parity, family income, mother's age, education, marital status, and smoking.

[e]Common arterial trunk, double outlet of the right ventricle (not ToF anatomy), conotruncal VSD, aortopulmonary window, supravalvular AS, IAA type B or C.

[f]Valvular or arterial pulmonary atresia.

[g]Single ventricle or ccTGAs.

APVR, anomalous pulmonary venous return; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; CoA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; IAA, interrupted aortic arch; LVOTO, left ventricular outflow tract obstructions; PDA, patent ductus arteriosus; RVOTO, right ventricular outflow tract obstructions; TGA, transposition of the great arteries; ToF, tetralogy of Fallot; vPS, valvular pulmonary stenosis; VSD, ventricular septal defect.

and aRR for RVOTO 0.97 [95% CI 0.72, 1.29]. Septal defects (i.e. ASD, VSD, other septal defects) and term PDA were associated with increased risk in infants whose mothers used folic acid, as compared to non-users; aRRs were 1.19 [95% CI 1.10, 1.30] $P < 0.0001$ and 1.23 [95% CI 1.01, 1.50] $P = 0.04$, respectively.

The increased infant risk of septal defects among folic acid users were similar in categories of maternal education (≤10 years, aRR 1.26 [95% CI 1.05, 1.52]; 11–13 years, aRR 1.09 [95% CI 0.95, 1.26]; 14–16 years, aRR 1.36 [95% CI 1.15, 1.61]; ≥ 17 years, aRR 1.07 [95% CI 0.88, 1.30]), year of birth (1999–2002, aRR 1.24 [95%

Table 4. Congenital heart defects according to use of folic acid before and/or during pregnancy in 517 784 births in Norway, 1999–2009[a]

	Births	Preconceptional folic acid[b] (18.4%)		Postconceptional folic acid only[c] (31.6%)	
Heart defect phenotype	No.	aRR[d]	95% CI	aRR[d]	95% CI
CHD excl. preterm PDA	5695	1.14	(1.05, 1.24)	1.12	(1.04, 1.20)
Severe CHD	1153	1.10	(0.91, 1.33)	0.97	(0.83, 1.12)
Heterotaxia	71	1.14	(0.52, 2.49)	0.75	(0.39, 1.44)
Conotruncal defect	502	1.30	(0.99, 1.71)	0.90	(0.71, 1.14)
AVSD	118	1.07	(0.59, 1.96)	1.18	(0.75, 1.86)
APVR	52	0.70	(0.27, 1.83)	0.82	(0.42, 1.40)
LVOTO	312	0.93	(0.64, 1.36)	1.06	(0.80, 1.12)
RVOTO	258	0.98	(0.65, 1.47)	0.94	(0.68, 1.25)
Septal defect, isolated	3280	1.18	(1.06, 1.32)	1.19	(1.09, 1.31)
Other complex CHD	9	1.52	(0.24, 9.67)	0.44	(0.05, 3.90)
Isolated PDA at term GA	1074	1.16	(0.88, 1.52)	1.24	(1.00, 1.54)
Other specified CHD	285	1.39	(0.96, 2.01)	1.05	(0.77, 1.42)
Unspecified CHD	239	0.67	(0.43, 1.03)	0.91	(0.65, 1.27)

[a]Livebirths and stillbirths registered in the Medical Birth Registry, excluding multiple births, births from in vitro fertilisation, children with chromosomal disorders, and with maternal epilepsy.
[b]Initiation of folic acid supplementation before pregnancy, with or without use of multivitamins.
[c]Initiation of folic acid supplementation during pregnancy, with or without use of multivitamins.
[d]Relative risk adjusted for year of birth, parity, family income, mother's age, education, marital status and smoking. Births with no periconceptional use of folic acid or multivitamin supplements as reference group.
APVR, anomalous pulmonary venous return; AVSD, atrioventricular septal defect; CHD, congenital heart defect; GA, gestational age; LVOTO, left ventricular outflow tract obstructions; PDA, patent ductus arteriosus; RVOTO, right ventricular outflow tract obstructions.

CI 1.09, 1.42]; 2003–2006, aRR 1.19 [95% CI 1.05, 1.35]; 2007–2009, aRR 1.10 [95% CI 0.92, 1.32]), and gestational age (<37 weeks, aRR 1.16 [95% CI 0.94, 1.43]; ≥37 weeks, aRR 1.23 [95% CI 1.12, 1.34]).

In Table 4, the aRRs of the main CHD phenotypes are shown by initiation of folic acid supplementation before pregnancy (preconception) and during pregnancy (postconception). For preconceptional or postconceptional initiation of folic acid, the RRs were similar for severe defects (aRR 1.10 and aRR 0.97, respectively) and for septal defects (aRR 1.18 and aRR 1.19, respectively).

Finally, we estimated RR for CHD by various combinations of folic acid/multivitamin supplement exposures (folic acid only, folic acid and/or multivitamin supplement use before pregnancy, before and during pregnancy, or during pregnancy only) with similar results to those presented above (results not shown).

Comment

In this nationwide study of 517 784 births and 6200 children with CHD, 50% of the mothers had used folic acid supplementation in the periconceptional period. Maternal intake of folic acid supplements was not associated with infant risk of severe CHD, such as conotruncal defects, AVSD, LVOTO, and RVOTO. For septal defects, there was approximately 20% increased risk in children whose mothers had taken periconceptional folic acid supplements.

From mid-2000s there has been a decreasing prevalence of both severe and non-severe CHD in Norway, as in other European countries.[3,7] This downward time trend has been suggested explained by the increasing intake of periconceptional folic acid and multivitamins from 1999 to 2009.[10] In Quebec, Canada, the distinct decreasing prevalence of severe CHD from 1999 coincided with implementation of folic acid fortification of grain products from 1998.[6] In Alberta, Canada,[15] there was a reduction in LVOTO (mainly CoA) in the post folic acid fortification period, but no change in the overall CHD prevalence. There was no corresponding reduction in CHD in Atlanta, Georgia,[5] despite a similar food fortification policy. Such correlating time trends of folic acid supplement use or food fortification and the birth prevalence of CHD in

populations should be interpreted with caution, since the two events do not necessarily show a causal relationship.

Only a few studies have reported individual level information of maternal folic acid supplement use and infant risk of CHD. A Californian case-control study from 1995,[11] based on telephone interviews with the mothers of 207 children with conotruncal heart defects and 481 randomly selected infants without malformations, reported reduced risk for conotruncal heart defects in children of mothers who had taken multivitamins or folic acid fortified cereals. A registry-based case-control study from the Northern Netherlands 1996–2005,[13] including 611 children with CHD, and two control groups; 2401 supposedly non-folate-related birth defects, and 3343 pregnant women participating in previous cross-sectional studies, reported a reduced risk for CHD, mainly septal defects, in offspring of women using periconceptional folic acid supplements. In these studies, the folic acid content was similar to the presumed dose in our study (0.4 mg/d). In a case-control study from Hungary,[14] however, much higher doses were used; the estimated average dose was 5.6 mg/d. This Hungarian study compared 598 children with CHD born in 1980–1996 with 902 matched controls, 20 896 children with other malformations, and 38 151 children without birth defects, and reported a reduced risk for conotruncal heart defect in the group exposed for folic acid supplements. In a Hungarian randomised controlled trial,[12] multivitamin supplements with 0.8 mg folic acid were compared to supplements with other trace elements. There was significantly reduced risk for CHD in the group receiving vitamins with high-dose folic acid, but the numbers were small, with only 10 vs. 20 CHD cases in the exposed and unexposed group, respectively.

A possible risk reduction of CHD by intake of folic acid or multivitamin supplements is likely determined by the extent of dietary vitamin insufficiency in the population. The dietary folate intake reported in pregnant Norwegian women, around 300 μg per day,[21] could be sufficient for fetal cardiac development, as opposed to certain Chinese provinces with a high prevalence of folate deficiency, where the risk of CHD has been significantly reduced when mothers had used periconceptional folic acid supplements.[22] Alternatively, the dose of folic acid supplement in the present study, 400 μg per day, is too small to prevent cardiac malformations, although plasma folate has been found to be significantly higher in women reporting folic acid supplement use.[23] However, no risk reduction was found, even in the group with both folic acid and multivitamin supplements before and during pregnancy (approximately folic acid dose of 0.6 mg/d), suggesting the use of folic acid supplements does not prevent CHD in the Norwegian population. Changes in other risk factors may explain the recent decrease in CHD prevalence.

To our surprise, we found a significantly increased risk for both ASD and VSD if the mother had used folic acid supplements in the periconceptional period, which has not been reported previously. The increased risk of septal defects was not modified by year of birth, maternal education, or prematurity. The positive association between folic acid supplements and risk of septal defects in the present study is unlikely a chance finding but could be caused by an unknown residual confounding. A biological factor cannot be ruled out; in studies of pregnant mice, a moderate to high intake of folic acid had adverse effects on offspring cardiac development. Mikael *et al*. found that mice fed with a diet containing 10 times the recommended rodent folic acid intake showed an increased risk for VSDs and thinner ventricular walls than the control group.[24]

The strengths of our nationwide study were the cohort design, linkage of comprehensive and compulsory registries with reliable information, and minimal loss to follow-up. Ascertainment of CHD cases through four national administrative and clinical registries enabled a virtually complete registration of both severe and minor CHD.[3] A weakness may be related to the validity of the exposure variable, maternal intake of folic acid or multivitamins, as we had no information on dose or duration of intake. However, the only folic acid tablets sold in Norway during the study period contained the recommended daily dose of 0.4 mg folic acid, and the maximum folic acid content in multivitamins was 0.2 mg. Although a large proportion of women started folic acid supplementation during pregnancy in the present study, we know from another Norwegian study in the same period that almost all folic acid users had implemented supplementation at 4 to 5 gestational week, corresponding to 2 to 3 weeks post conception (85 000 pregnancies in the Norwegian Mother and Child Cohort Study, 2001–2008),[25] which should cover most of the heart development period ranging from 3 to 7

weeks post conception. All combinations of folic acid or multivitamin intake before pregnancy or during pregnancy showed consistent findings; the association between folic acid or multivitamin supplement use and severe CHD was null, and for septal defects, there was a slightly increased risk after folic acid supplement use. Other concerns might be lack of details on additional confounders of the association between maternal supplementation and maternal/offspring outcome, such as other dietary nutrients, or maternal pre-pregnancy weight. We did not have such information. Information on supplement use was missing in 15% of all births; these births were excluded from the study population. However, the prevalence of severe defects and septal defects were similar among births with missing folic acid information and the study population, except for the terminated pregnancies (0.2% of all births). The prevalence of CHD was increased in all terminated pregnancies (144 per 1000), but the proportion of terminated pregnancies among all births with any CHD (2.7%) or severe CHD (9.3%) was low, and amounted to a relatively small part of the births with CHD.

In conclusion, periconceptional use of folic acid or multivitamin supplements was not associated with risk of severe CHDs in infants. The association with a 20% increased risk of septal defects may be due to unknown common factors for folic acid use and CHD risk, or an adverse effect from folic acid, and warrants further investigation.

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Disclosures

The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the manuscript and its final contents.

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