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Benefits and risks with folic supplementation in persons using antiseizure medication in pregnancy – neurologist perspective

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www.scanaed.org

Conflicts of interests

- I am the Norwegian PI on the EUPAS34201, and my institution has received payment from the MAH of valproate (Sanofi) for the conduction of the study

- Previous speaking and/or consultancy honoraria from: Eisai, Novartis Norway, Jazz Pharmaceuticals, Angelini Pharma, AbbVie, Teva, Lilly, and Lundbeck

Hot topics

Should women using antiseizure medication take folic acid supplementation?

How much?

Are there real benefits or risks?

For the child?

For the mother?

Pediatric News

High-dose folic acid during pregnancy tied to cancer risk in children

Pediatric News , 03 Oct 2022

Prenatal exposure to high-dose folic acid is associated with a greater than twofold increased risk for cancer in children of...

Medscape

High-Dose Folic Acid During Pregnancy Tied to Cancer Risk in Kids

Medscape, 03 Oct 2022

Prenatal exposure to high-dose folic acid is associated with a greater than twofold increased risk for cancer in children of...

WooDZog

Prenatal exposure to high doses of folic acid associated with increased cancer risk in children of mothers with epilepsy

WooDZog.com, 02 Oct 2022

1. The risk of cancer was higher in children of mothers with epile compared to...

Topics

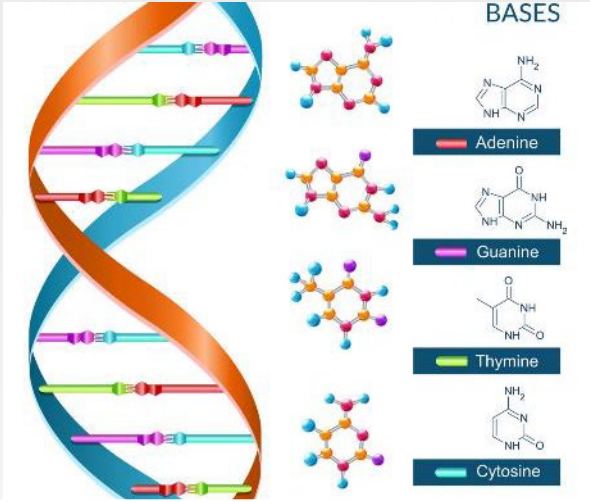
- **Importance of folate in pregnancy**
- Benefits of folic acid supplementation in pregnant women using antiseizure medication
- Risks of high dose folic acid

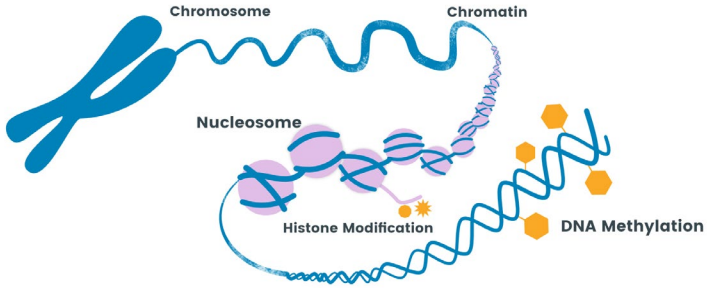
Folate is required in one-carbon metabolism

Transfer and utilize one-carbon units in DNA and RNA biosynthesis, amino acid metabolism, methylation processes

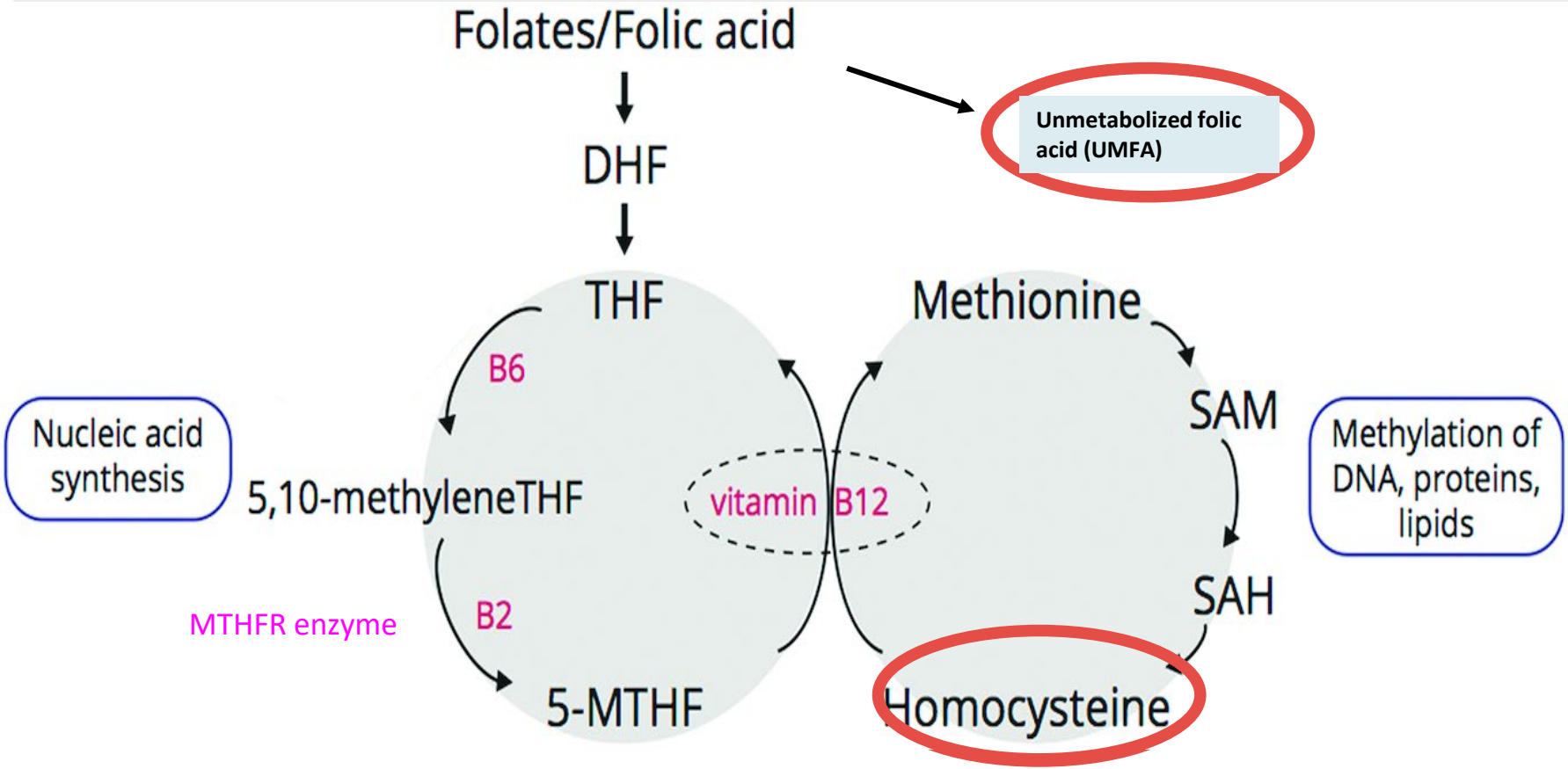
→ cell division and specialization

Folate requirements 5-10-fold increased in pregnancy





One-carbon metabolism



Adapted from Naninck et al. *Adv Nutrition* 2019

Folic acid is important for normal fetal growth and brain development

Brain myelin formation and maintenance

Folate deficiency is common in women of childbearing age

Dietary, genetic or medical cause

low folate concentration

Congenital malformations

Neural tube and cardiac defects

Pregnancy complications

preterm birth, fetal growth retardation

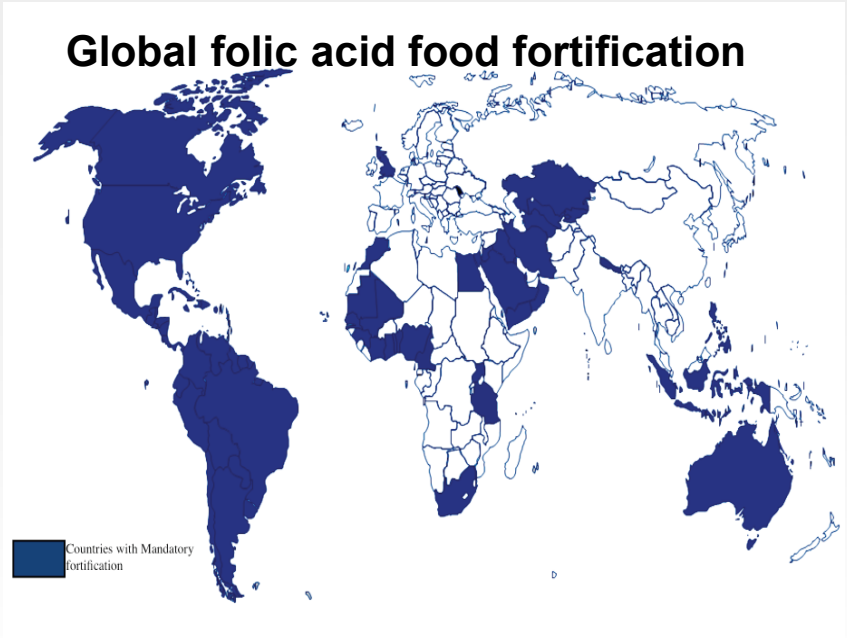
Adverse neurodevelopment

Autism spectrum disorders

Czeizel et al. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med.* 1992
Naninck et al. The Importance of Maternal Folate Status for Brain Development and Function of Offspring *Adv Nutrition* 2019

How much folate is needed for persons of childbearing potential?

- Folate concentrations depend on
  - Type and dose of antiseizure medications
  - intake of vegetables, fruits, seafood, eggs, dairy products, meat, grains
  - Genetic polymorphisms (MTHFR genotype)
  - Concentration of other B-vitamins
  - ethnicity, country of habitation, body mass index, somatic health, socioeconomic status
- WHO recommends RBC folate >906 nmol/L (≈ s-folate > 28 nmol/L) to avoid neural tube defects
- Healthy persons reach s-folate > 906 within 4 weeks of 0.8 mg folic acid supplement.



Cordero AM et al. *Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects: World Health Organization guidelines*. MMWR Morb Mortal Wkly Rep. 2015. **Wilson RD, O'Connor DL.** J Obstet Gynaecol Can. 2022. **Brämswig S et al.** Int J Vitam Nutr Res. 2009

Critical for brain development
Folate defiency harmful
Supplementation above need
– uncertain benefit

- Importance of folate in pregnancy
- Benefits of folic acid supplementation in pregnant women using antiseizure medication
- Risks of high dose folic acid

Women with epilepsy are recommended folic acid supplements to prevent child neural tube defects - However the guidelines differ…

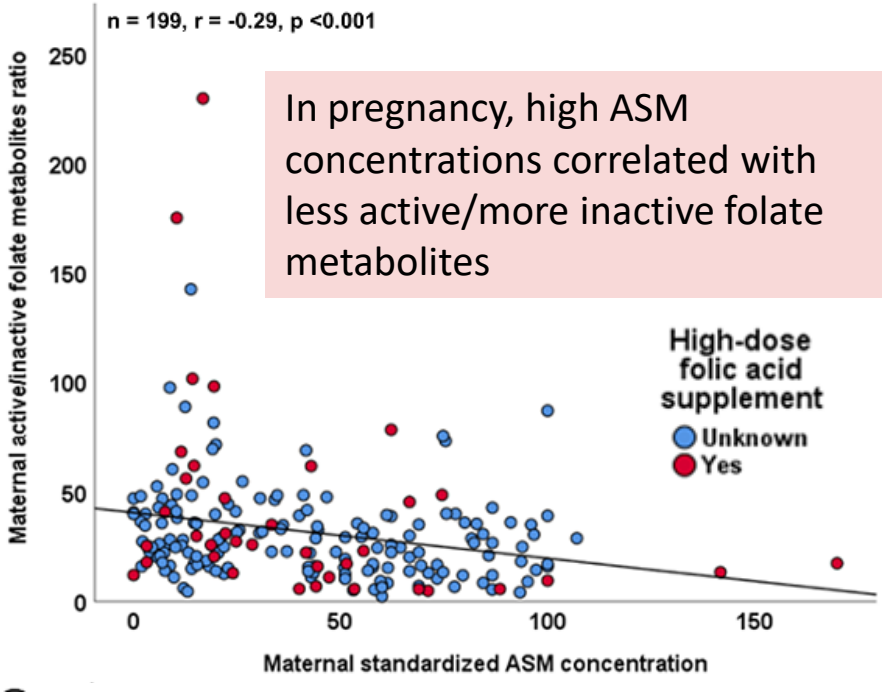
Adapted from Bjørk et al. Pregnancy, folic acid, and antiseizure medication. Clinical Epileptology 2023

Antiseizure medication (ASM) and folate

ASM interfere with folate metabolism

Associated with lower folate

Mechanisms probably different for different drugs



Linnebank et al. **Antiepileptic drugs interact with folate and vitamin B12 serum levels** *Ann Neurol* 2011

Husebye et al. **Vitamin B status and association with antiseizure medication in pregnant women with epilepsy**. *Epilepsia* 2021

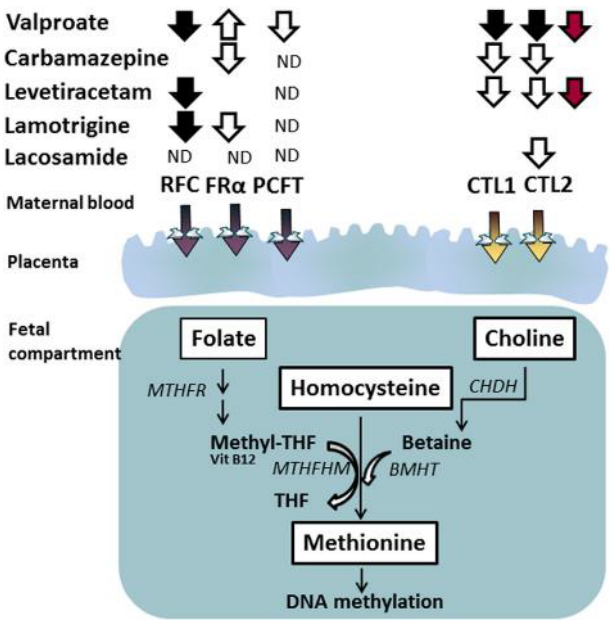
Antiseizure medication (ASM) affects placental folate transport.

Embryo receives folate via placenta transporters

ASMs affect folate transporters in

- Placental cell cultures
- Mice models
- Human placental explants

Most prominent findings for valproate



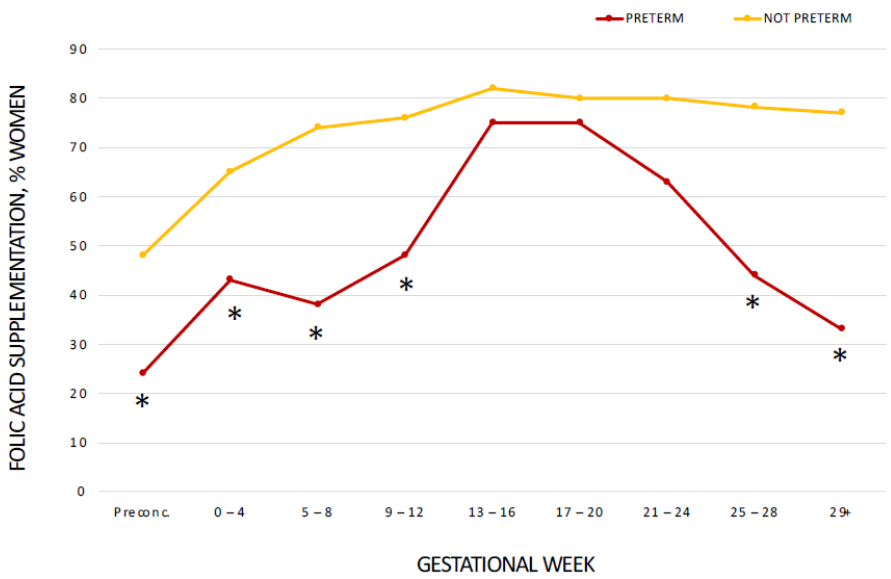
Tetro et a. Epilepsia 2021, Tetro et al. Epilepsia 2019, Meir et al. Epilepsia 2016
Rubinchik-Stern et al. Epilepsia 2015

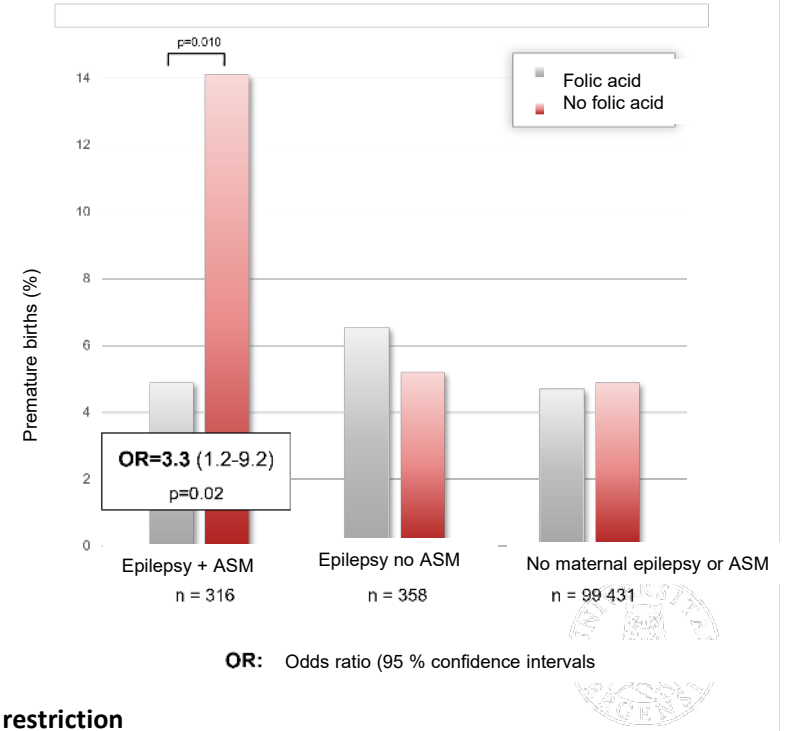
No-use of periconceptional folic acid associated with spontaneous abortions in some (but not all) studies

	Polytherapy	Monotherapy	VPA monotherapy
Spontaneous abortion/ delivery (n)			
Without folic acid supplementation	2/52 (3.7 %)	28/140 (16.5 %)	15/43 (25.4 %)
With folic acid supplementation	1/29 (3.3 %)	8/120 (6.2 %)	1/43 (2.3 %)
Odds Ratio			
OR	1.1	2.9	14.5
95 % CI	0.1–12.5	1.3–6.8	1.8–115.8

Pittschieler et al. **Spontaneous abortion and the prophylactic effect of folic acid supplementation in epileptic women undergoing antiepileptic therapy** *J Neurol,* 2008

Folic acid supplementation throughout pregnancy associated with lower risk of premature birth





OR: Odds ratio (95 % confidence intervals

Alvestad et al. **Folic acid and risk of preterm birth, preeclampsia and fetal growth restriction among women with epilepsy: A prospective cohort study**. *Neurology* 2022

Folic acid supplementation and congenital anomalies

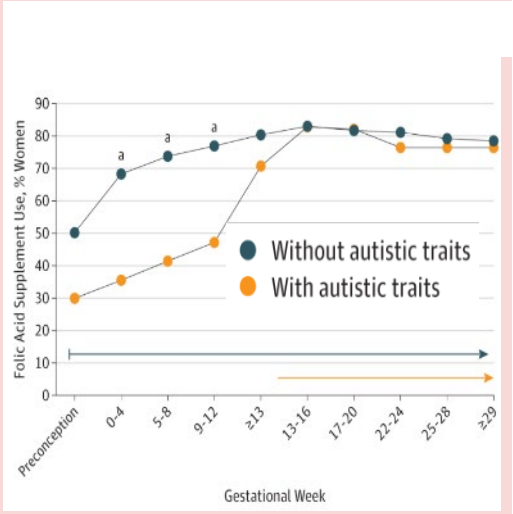
EURAP
Tomson et al
Lancet Neurol
2011

Risk of congenital anomalies increased: Appropriate folic acid use *vs* inappropriate	Odds ratio: 1.4 (1.02–1.82)

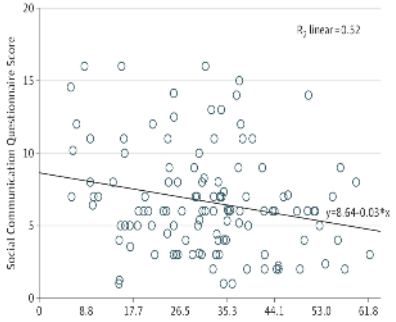
UK Epilepsy and Pregnancy Registry Morrow et al. JNNP 2009

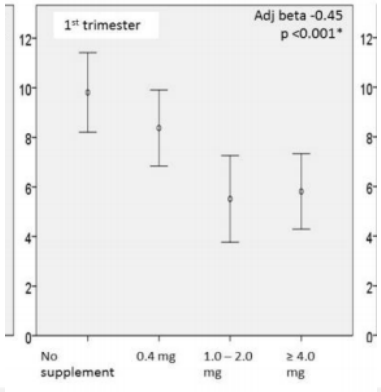
	Congenital malformations				Neural tube defects			
	Folic acid		No Folic acid		Folic acid		No Folic acid	
	N (%)	***95 % CI***	***N (%)***	***95 % CI***	***N (%)***	***95 % CI***	***N (%)***	***95 % CI***
Carbamazepine	14 (2.4 %)	1.4 - 4.0	11 (2.3 %)	1.3 - 4.0	3 (0.5 %)	0.0 -1.5	0	0 - 0.8
Lamotrigine	16 (2.5 %)	1.5 – 4.0	7 (1.9 %)	0.9 – 3.9	1 (0.2 %)	0.0 – 0.9	0	0 – 1.1
Valproate	21 (5.3 %)	3.5 – 8.0	18 (4.3 %)	2.8 – 6.8	3 (0.8 %)	0.3 – 2.2	7 (1.7%)	0.7 – 3.4
All	76 (3.9 %)	3.1 – 4.9	53 (2.2 %)	1.0 – 3.3	8 (0.4 %)	0.2 – 0.8	8 (0.3 %)	0.2 – 0.7

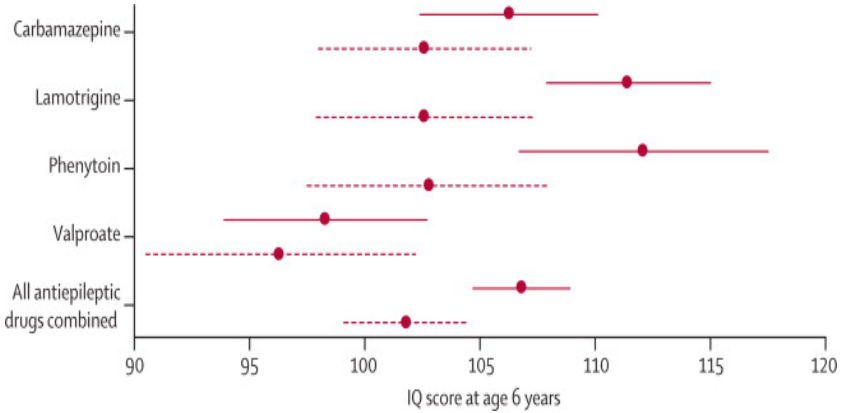
Periconceptional folic acid associated with reduced risk of autistic traits, impaired verbal function and low IQ and verbal IQ after prenatal antiseizure exposure in some studies (not in UK)



Meador et al. Lancet 2013 and Neurology 2020
Bjørk et al. JAMA Neurology 2017
Husebye et al. Neurology 2018
Husebye et al. Eur J Clin Neurol 2019



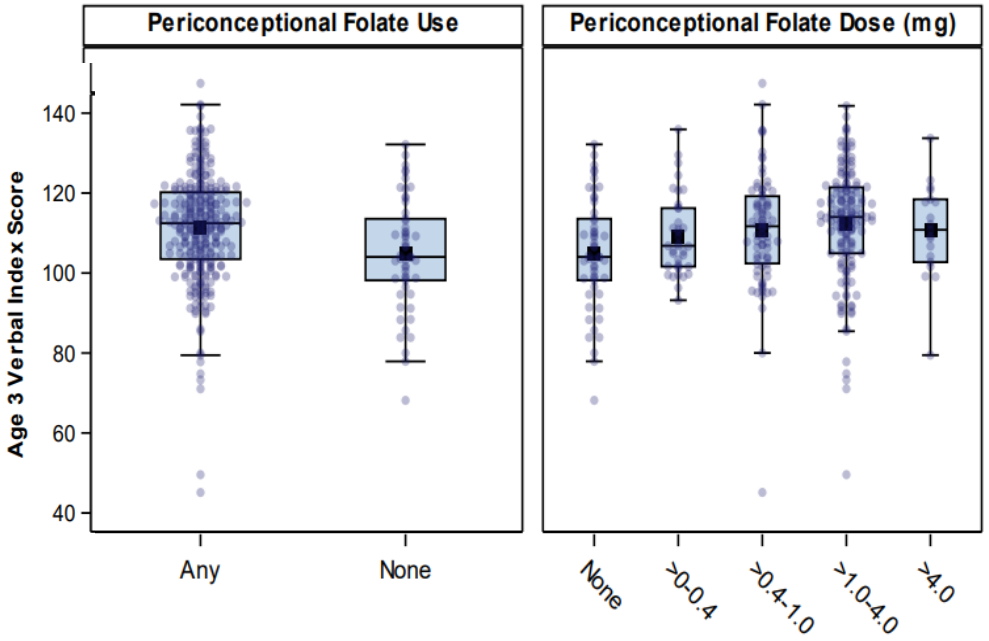




no folic acid
folic acid

Folic acid dose: 95.5 % of children exposed to more than 0.4 mg, 40.5 % ≥ 4.0 mg

Folic acid dose and verbal funcion age 3



Meador et al. Lancet neurology 2023.

Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study

→ newer antiseizure medications

Folic acid use and dose in women using newer ASM significantly associated with improved verbal function in unadjusted but not adjusted models

Critical for brain development
Folate defiency harmful
Supplementation above need – uncertain benefit and risk

ASMs interfere with folate metabolism
Folic acid supplements possibly beneficial for neurodevelopment

Importance of folate in pregnancy

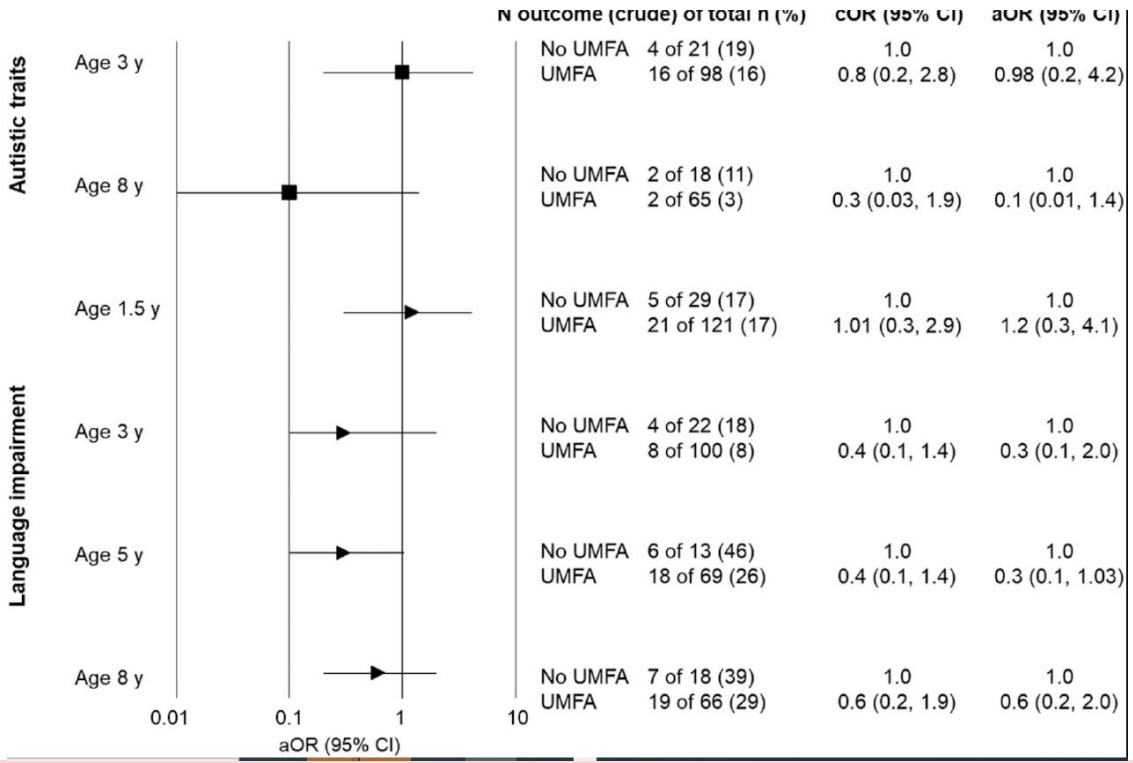
- Benefits of folic acid supplementation in pregnant women using antiseizure medication
- Risks of high dose folic acid

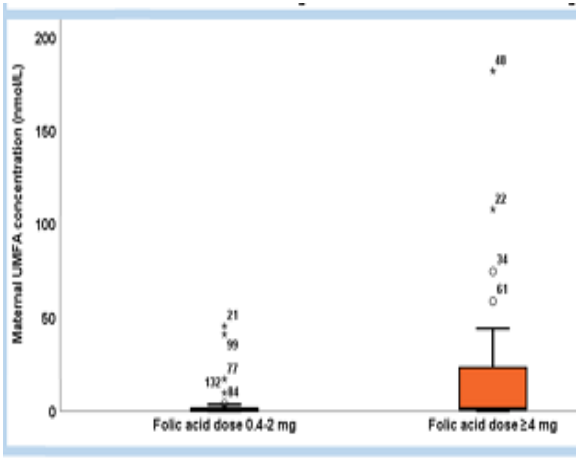
Adverse health effects of high dose folic acid

- Can mask and worsen **B12 deficiency**
- Possibly related to **hypersensitivity disorders** in children (eczema)
- Preclinical data: may enhance **carcinogenesis**. Most clinical studies do not show increased risk, some show protection
- Concerns for increased **unmetabolized folic acid (UMFA)**
  - Cancer
  - Prenatal exposure to very high doses and high folate levels increased risk of autism spectrum disorders in general population

European Administration for Food Safety Scientific Opinion on Dietary Reference Values for folate, 2014. Raghavan et al. *Am J Clin Nutr* 2020. Dunstan et al. Allergy 2012. Dwyer et al. BMI 2022.

Unmetabolized folic acid is no associated with autistic traits or language delay in children of women with epilepsy





Huseby …. Bjørk, Am J Clin Nutr 2022

Adjusted odds ratio for autistic traits and language impairment for ASM exposed children (n=227) of mothers with UMFA (n=50) vs. no UMFA (177)

Cancer Risk in Children of Mothers With Epilepsy and High-Dose Folic Acid Use During Pregnancy

Håkon Magne Vegrim, MD[1]; Julie Werenberg Dreier, PhD[1,2]; Silje Alvestad, MD, PhD[1,3]; Erik Gilhus, MD, PhD[1,4]; Mika Gissler, PhD[5,6]; Jannicke Igland, PhD[1]; Maarit K. Leinonen PhD[5]; Torbjörn Tomson, MD, PhD[7]; Yuelian Sun, MD, PhD[2,8,9,10]; Helga Zoega, MA, PhD Jakob Christensen, MD, PhD, DrMedSci[2,8,9]; Marte-Helene Bjørk, MD, PhD[1,4,13]

» Author Affiliations | Article Information

JAMA Neurol. 2022;79(11):1130-1138. doi:10.1001/jamaneurol.2022.2977

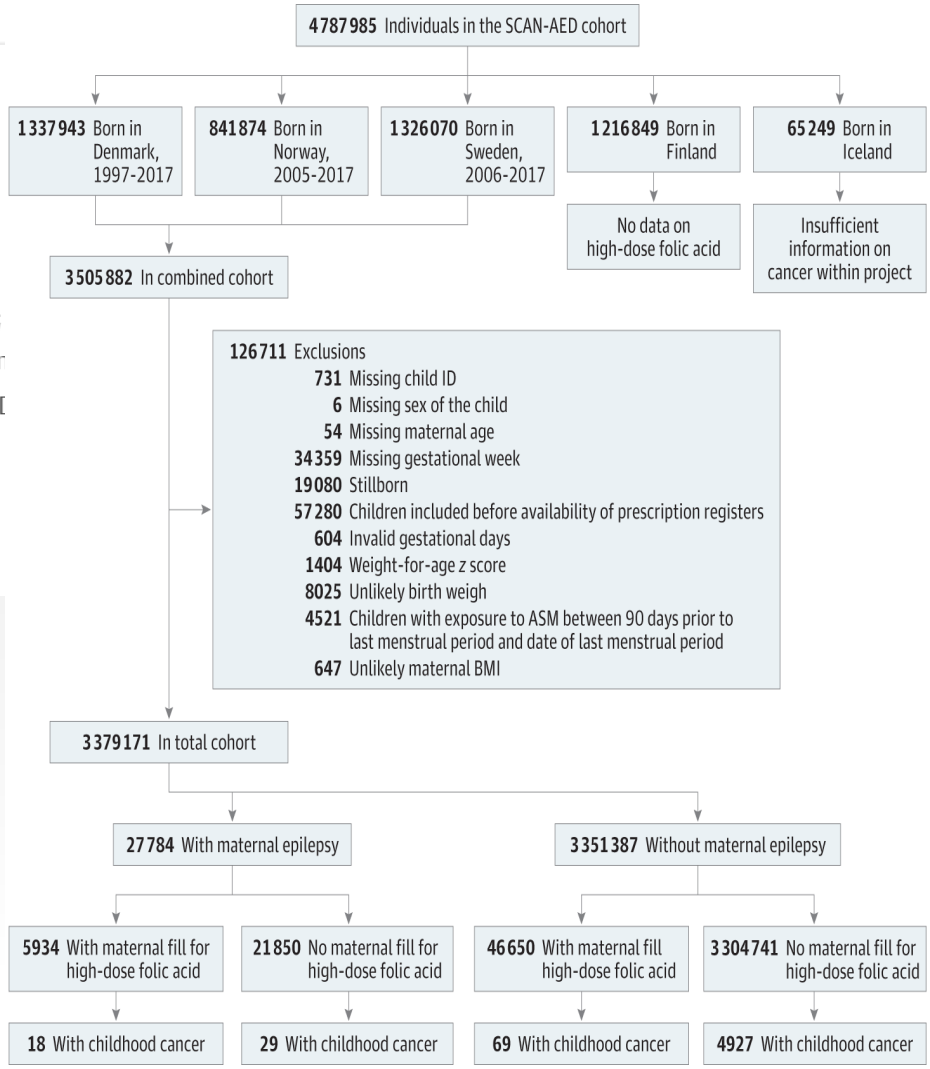


Table 3. Association Between Maternal Epilepsy, Maternal Prescription Fill for Antiseizure Medication (ASM), High-Dose Folic Acid, and Risk of Childhood Cancer in the Offspring[a]

Maternal epilepsy	Maternal ASM	High-dose folic acid	Live births	Incidence rate per 100 000 person-years (95% CI)	Cumulative incidence at 20 y (95% CI)[b]	Crude HR (95% CI)	aHR 1 (95% CI)[c]	aHR 2 (95% CI)[d]
Yes	Yes	Yes	5531	43.0 (26.8-69.2)	1.4 (0.5-3.1)	2.9 (1.1-7.5)	2.9 (1.1-7.7)	3.0 (1.1-7.9)
		No	5195	19.1 (9.5-38.1)	0.6 (0.2-0.13)	1 [Reference]	1 [Reference]	1 [Reference]
	No	Yes	403	NA	NA	NA	NA	NA
		No	16 655	18.2 (11.8-27.9)	0.6 (0.3-1.1)	1 [Reference]	1 [Reference]	1 [Reference]
No	Yes	Yes	819	NA	NA	NA	NA	NA
		No	6045	23.0 (11.5-46.0)	0.4 (0.1-1.0)	1 [Reference]	1 [Reference]	1 [Reference]
	No	Yes	45 827	19.7 (15.4-25.1)	0.4 (0.3-0.5)	1.1 (0.8-1.4)	1.1 (0.8-1.4)	1.1 (0.8-1.4)
		No	3 298 696	18.9 (18.4-19.5)	0.4 (0.4-0.4)	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: aHR, adjusted hazard ratio; aHR 1, first model with basic adjustment; aHR 2, second model including adjustment for antiseizure medication prescription fill; NA, not available.

[a] Birth year, sex of the child and source country were applied as stratum for all models.

[b] The cumulative incidence at age 10 years was 0.4 (95% CI, 0.2-0.6) for maternal epilepsy yes, maternal ASM yes, and high-dose folic acid yes; 0.1 (95% CI, 0.1-0.3) for maternal epilepsy yes, maternal ASM yes, and high-dose folic acid no; 0.2 (95% CI, 0.1-0.3) for maternal epilepsy yes, maternal ASM no, and maternal high-dose folic acid no; 0.2 (95% CI, 0.1-0.6) for maternal epilepsy no, maternal ASM yes, and maternal high-dose folic acid no; 0.2 (95% CI, 0.1-0.3) for maternal epilepsy no, maternal ASM no, and maternal high-dose folic acid yes; and 0.2 (95% CI, 0.2-0.2) for maternal epilepsy no, maternal ASM no, and maternal high-dose folic acid no.

[c] Adjustment for maternal age and educational level.

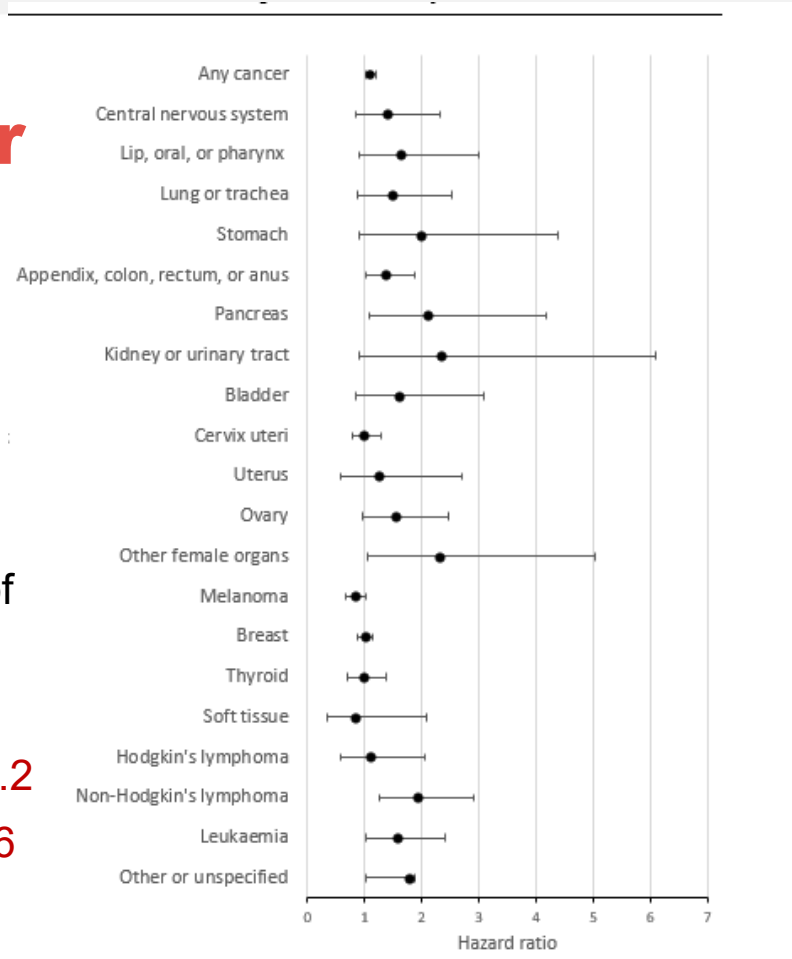
[d] Including adjustment for maternal body mass index, prior births with major congenital anomalies, smoking during pregnancy, and number of hospitalizations.

Vegrim, Dreier....Bjørk, JAMA Neurology, 2022

Risk of maternal cancer

- Nullipara women included week 22
- High dose (≥ 1 mg) Folic acid prescriptions measured as a time varying covariate
- Adjusted for antiseizure medication, diabetes mellitus, inflammatory bowel disease, obesity, smoking
- Followed until cancer, death, emigration or end of follow up (mean 7 years)
- Risk of any cancer: aHR 1.2, 95%CI 1.1-1.2
- 6 months lag time subtracted: aHR 1.1 CI 1.02-1.2
- Antiseizure medications users aHR 1.2 CI 0.9-1.6

Vegrim, Dreier….Bjørk. Unpublished results from SCAN AED



Critical for brain development
Folate defiency harmful
Supplementation above need – uncertain benefit and risk

Importance of folate in pregnancy

ASMs interfere with folate metabolism
Folic acid supplements probably beneficial for neurodevelopment but not for congital malformations

Folic acid supplementation in pregnant women using antiseizure medication (ASM)

No harmful effect of UMFA shown, possibly increase of childhood and maternal cancer

Harmfulness of high dose folic acid

Conclusions

Should women using antiseizure medication take folic acid supplementation? Yes

When and how much? Childbearing age: 0,4 mg.

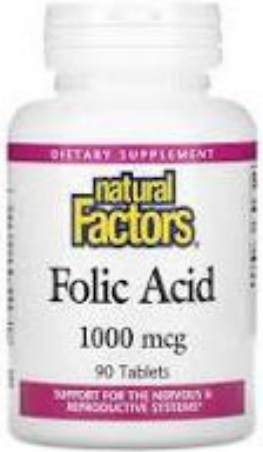
Preconception and pregnancy. 1mg?

Consider measuring folate before and during pregnancy

Are there real benefits:

For the child? Possibly benefit neurodevelopment

Are there risks? Possibly for childhood and maternal cancer



Thank you for the attention

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Elisabeth Husebye

SCAN AED consortium

Bettina Riedel

Håkon Vegrim

Folic acid and autism

- Genetic polymorphisms in folate pathways associated with autism
- Periconceptional folic acid supplements reduced risk of autism in general population in Norway and the US
- Some have found no effect or increased risk with high

	No. (%)		OR (95% CI)	
Folic Acid Use	Total	Autistic Disorder	Unadjusted	Adjusted[a]
No	24 134 (28.3)	50 (0.21)	1 [Reference]	1 [Reference]
Yes	61 042 (71.7)	64 (0.10)	0.51 (0.35-0.73)	0.61 (0.41-0.90)

Abbreviation: OR, odds ratio.

Shaik et al. *Psychiatr Genet*. 2016. Súren et al. JAMA 2013. Valera-Gran. JAMA Pediatrics 2014
Schmidt et al. Am J Clin Nutr 2012. Egorova et al. Mol autism 2020

Folate in pregnancy and cognition in children

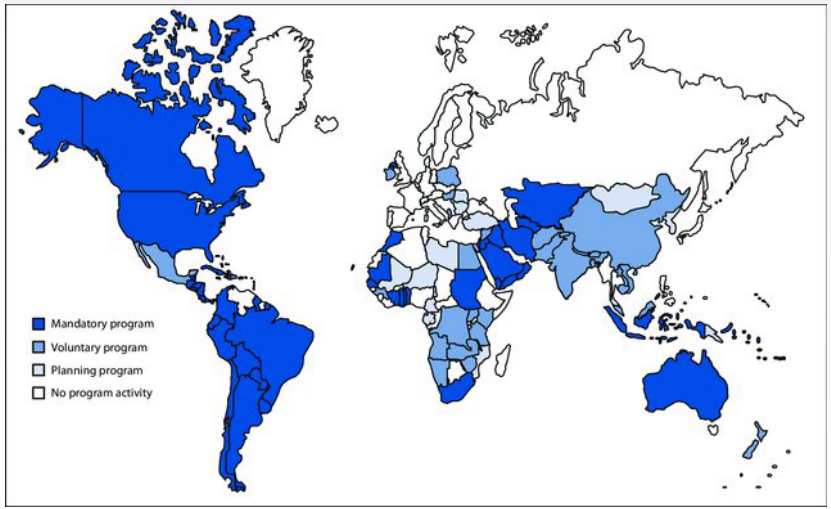
- Children of mothers with folate deficiency compared to infants of mothers with normal folate
  - abnormal neurodevelopment, impaired cognitive abilities

- Observational studies: folic acid supplement in general population: Mixed results
  - 50 % show improvement, 50 % no effect
  - Some show U shaped association (excessive folic acid harmful)
  - Randomized placebo-controlled trial of 400 ug supplementation in 2-3 trimester (n=226) showed beneficial effects on cognition at 3, 7 and 11 years

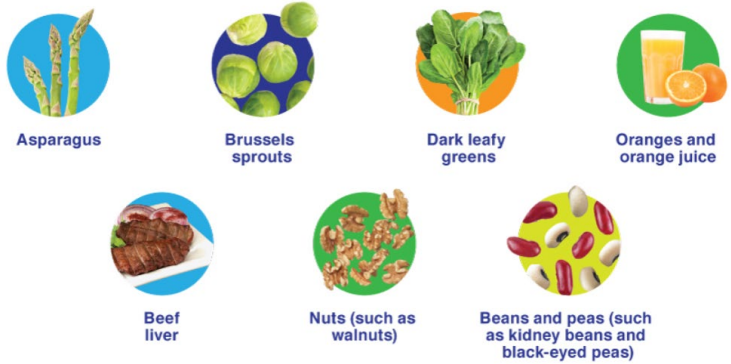
Gross et al. Nutr Rep Int. 1974, Ars et al. Br J Nutr. 2019, Caffrey et al. BMC Medicine 2021, Naninck et al. *Adv Nutrition* 2019

Folate and folic acid

- Folate → naturally occuring
- Folic acid → synthetic form
  - Supplements, food fortification



Natural sources of folate



Folic acid fortified products (US)

Source: US Food & Drug Administration (FDA)

Risk of neurodevelopmental disorders (NDD) in ASM exposed children according to high dose folic acid supplements in Scandinavian population registries - SCAN AED study

	Periconceptional folic acid ≥ 1 mg	Number NDD cases	Adjusted hazard rate NDD (95% CI)
Any antiseizure medication	No n = 10,900	300 (2.8 %)	1 (ref)
	Yes n = 4,700	110 (2.3 %)	0.95 (0.8- 1.2)
Lamotrigine monotherapy	No n = 4,600	90 (2.0 %)	1 (ref)
	Yes n = 1,800	20 (1.1 %)	0.73 (0.4-1.3)
Carbamazepine monotherapy	No n = 700	30 (4.2 %)	1 (ref)
	Yes n = 800	20 (2.5 %)	0.78 (0.4-1.6)
Valproate monotherapy	No n = 500	40 (8 %)	1 (ref)
	Yes n = 400	30 (7.5 %)	0.82 (0.5 - 1.5)
No antiseizure medication	No n = 3,249,000	49,470 (1.5 %)	1 (ref)
	Yes n = 25,200	390 (1.6 %)	1.03 (0.9-1.2)

Alvestad et al. 2021 Unpublished data

World Health Organization

WHO recommendations

All women, from the moment they begin trying to conceive until 12 weeks of gestation, should take a folic acid supplement (400 µg folic acid daily).

Women who have had a fetus diagnosed as affected by a neural tube defect or have given birth to a baby with a neural tube defect should:

- receive information on the risk of recurrence;
- be advised on the protective effect of periconceptional folic acid supplementation;
- be offered high-dose supplementation (5 mg folic acid daily); and
- be advised to increase their food intake of folate.

WHO e-Library of Evidence for Nutrition Actions (eLENA) 2019