From inadequacy to possible excess: discrepancy in folate and vitamin B12 status of pregnant women across population groups and their possible implications on child outcomes

Yvonne Lamers, PhD

Canada Research Chair in Human Nutrition and Vitamin Metabolism

Associate Professor, The University of British Columbia

Investigator, BC Children's Hospital Research Institute

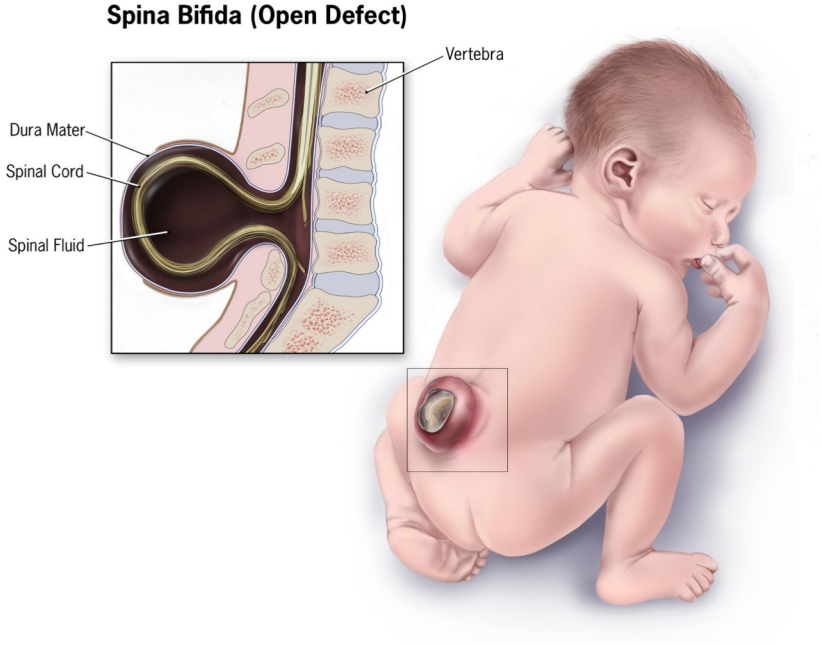
a place of mind

THE UNIVERSITY OF BRITISH COLUMBIA

BC Children's Hospital Research Institute

WOMEN'S HEALTH RESEARCH INSTITUTE AT BC WOMEN'S

Folate / Folic Acid in Pregnancy - Knowns



https://commons.wikimedia.org/w/index.php?curid=30509337

Folate / Methyl Nutrients in Pregnancy & DOHaD Theory

Support mothers to secure future public health

Barker et al. Nature 2013

OUTLINE Folate, Folic Acid, and Vitamin B12 during Pregnancy

Folate/folic acid – current recommendations and status

- Periconceptional folic acid supplementation – evidence & practice
- Cutoff for folate sufficiency related to NTD prevention
- Current folate status in reproductive-aged and pregnant women

Emerging questions since release of guidelines

- Is there a too much of folic acid?
- Supplement use in post-fortification era
- Discrepancies between recommendations and practice
- Identification of at-risk population groups

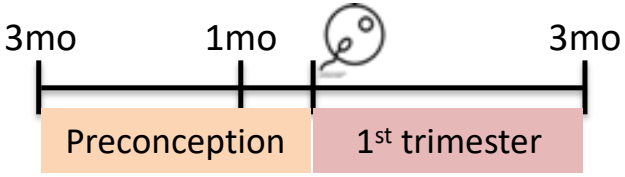
Vitamin B12 – the interplayer with folate

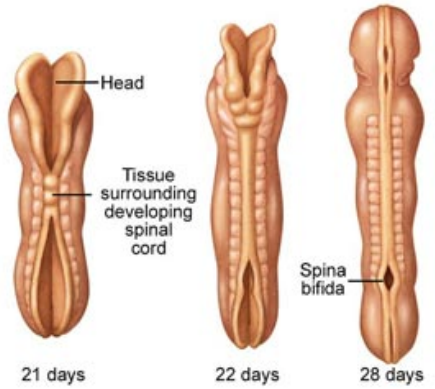
- Dietary B12 requirements for pregnant women
- Vitamin B12 status in pregnant women
- B12 and birth outcomes
- Open questions and knowledge gaps

Key facts on evidence-based recommendations

Periconceptional folic acid supplementation:

*"Women of reproductive age are recommended to take **400µg/d folic acid** starting ≥1 month before conception until 12 weeks of gestation." (**low NTD risk**)*





Neural tube closure in 1st month of pregnancy

Key Facts:

Release of recommendations: 1992 in US; 1993 Canada and Europe

Basis of recommendations: **randomized controlled trials** (high-level evidence)
>90% reduction in NTD incidence in low-risk women

- ❑ Dose: at doses of 400µg/d or higher
- ❑ Folate form: using folic acid as the supplemental folate form
- ❑ Independent: with or without other vitamins and minerals

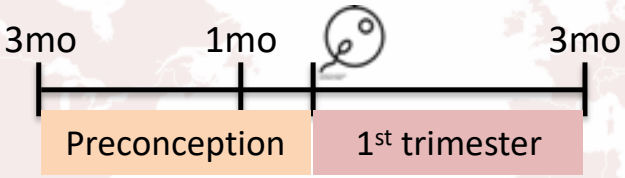
Czeizel 2009 Birth Defects Research; De-Regil et al. 2015 Cochrane Reviews; Berry et al. 1999 NEJM

Recommendations – Consensus and Deviations

<u>Consensus:</u> WHO recommendation, most countries

*"Women of reproductive age are recommended to take **400µg/d folic acid** starting ≥1 month before conception until 12 weeks of gestation." (**low NTD risk**)*

"Women at risk of an NTD affected pregnancy recommended to supplement with 4 or 5mg/day." (high NTD risk)



<u>Deviations:</u>

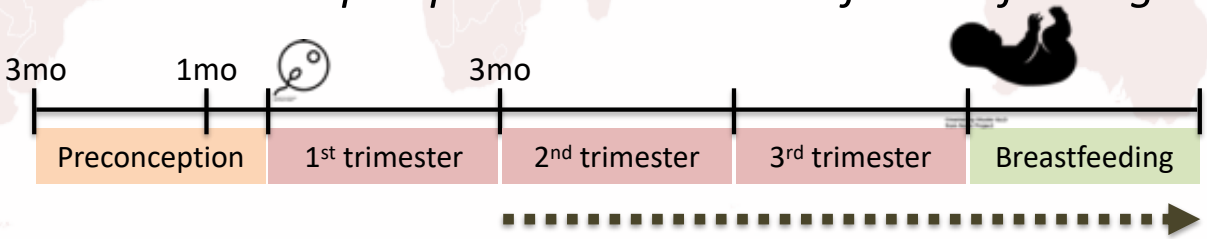
New Zealand, Ministry of Health:

Dose: *800µg/d folic acid*

Canada, Society for Obstetricians and Gynaecologists (SOGC):

Intermediate risk group: *moderate risk (1,000-4,000µg/d folic acid)*

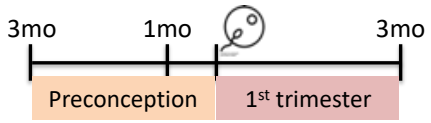
Duration: *until 1 month postpartum or the end of breastfeeding*



Recommendations versus Practice

Compliance of folic acid supplement use at preconception:

USA/Canada	14-60%	*Masih et al. 2015, Chalmers et al. 2009*
Europe	12-20%	*McNulty et al. 2011, Nilson et al. 2006*



Characteristics of women taking supplements at preconception

- Higher maternal age
- Married
- Higher income
- Higher education
- Planned pregnancies
- Infertility treatment
- Chronic disease
- European ethnicity

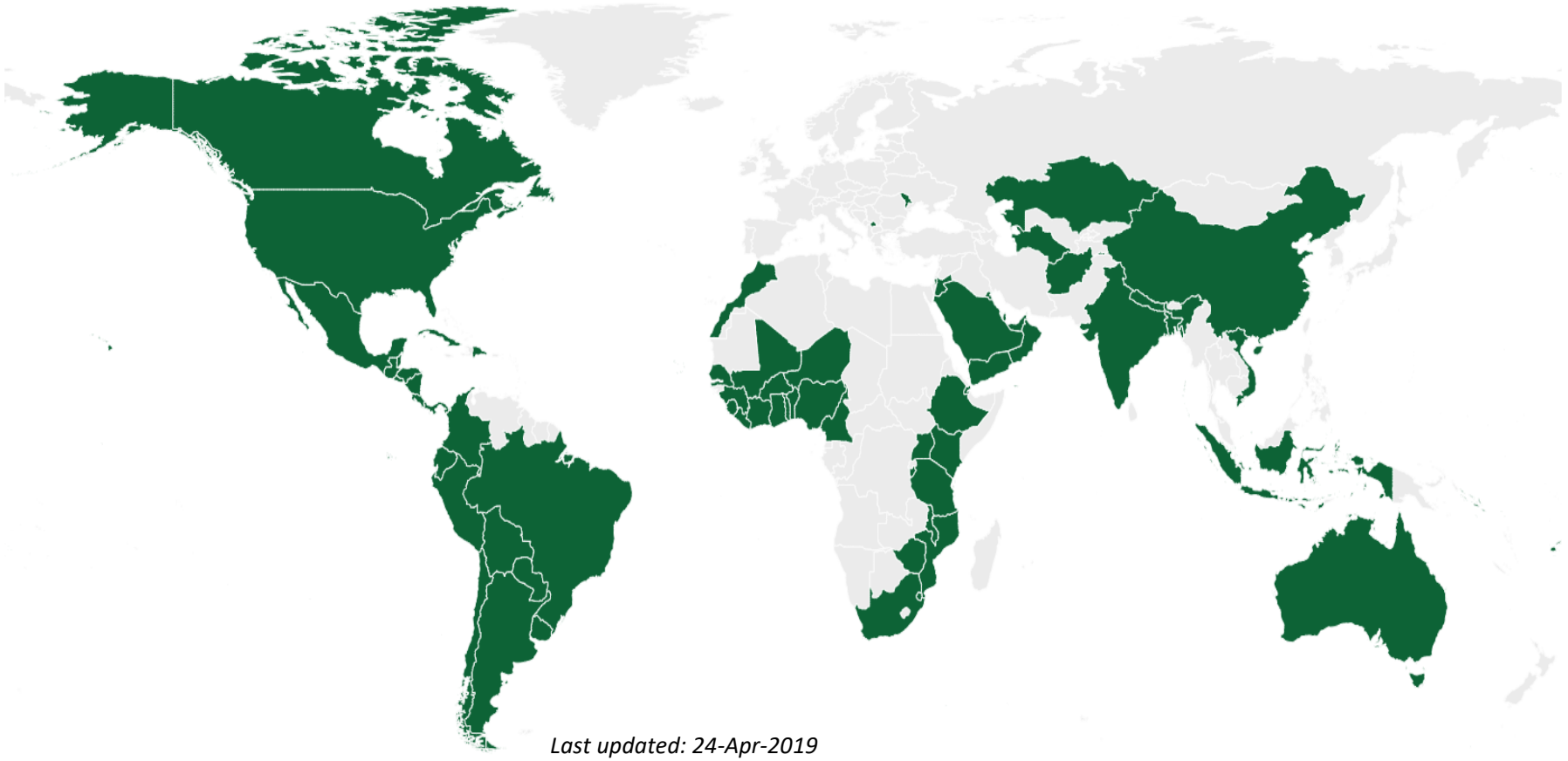
Masih et al. 2015, Nilsen et al. 2006

Prevalence and determinants of unintended pregnancies

- **45% in US** in 2011 *(Finer and Zolna 2016 NEJM)*
  highest prevalence in women of low income, aged 18-24y, not married, lower education status, non-European ethnicity
- **27% in Canada** in 2006 *(Oulman et al. 2015 BMC Pregnancy and Childbirth)*
  higher odds if <20y, first generation immigrant, lower education, no partner, experienced violence or abuse

Population-based NTD prevention strategy

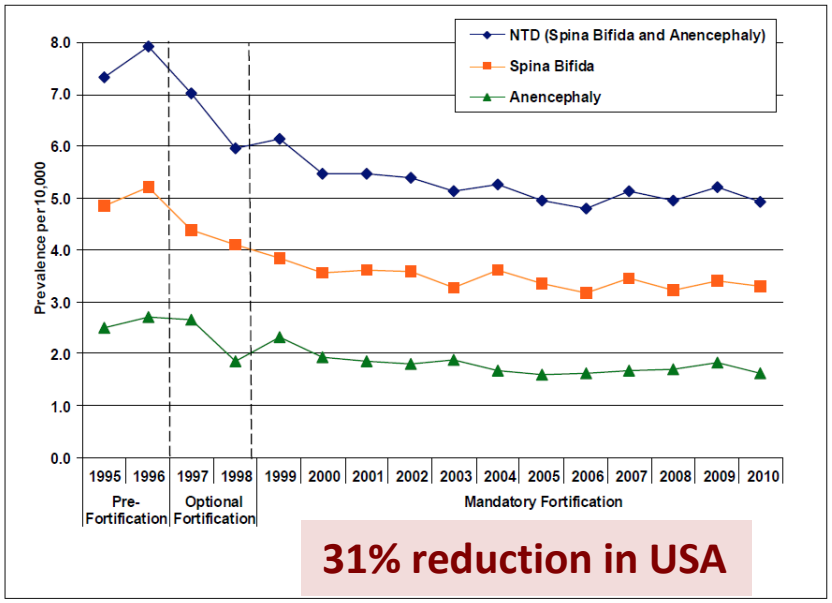
Legislation for mandatory food fortification with folic acid
wheat flour/maize flour/rice
→ **now implemented in 71 countries**



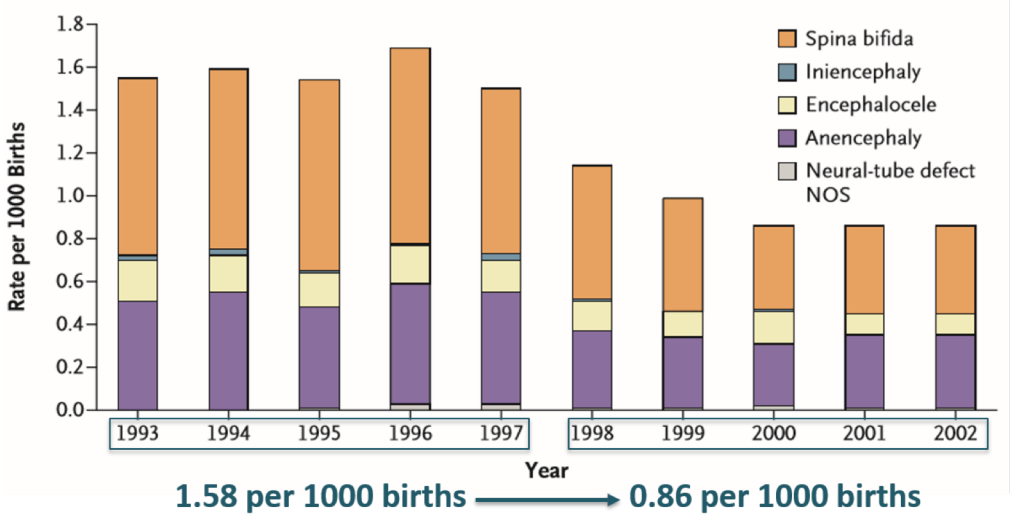
Last updated: 24-Apr-2019
https://fortificationdata.org/map-number-of-nutrients/#

Population-based NTD prevention strategy

Reduction in NTD occurrence in countries with mandatory fortification



31% reduction in USA



1.58 per 1000 births → 0.86 per 1000 births

46% reduction in NTD rate **Canada**

No implementation because of concerns of possible adverse health consequences

- New Zealand
- UK Food Standard's Agency
- Ireland
- other European countries

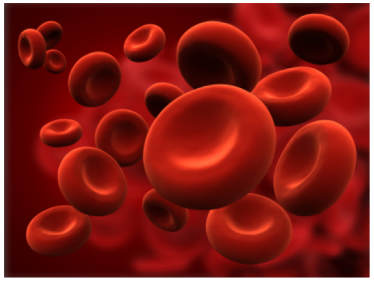
Prevention of neural tube defects in the UK: a missed opportunity

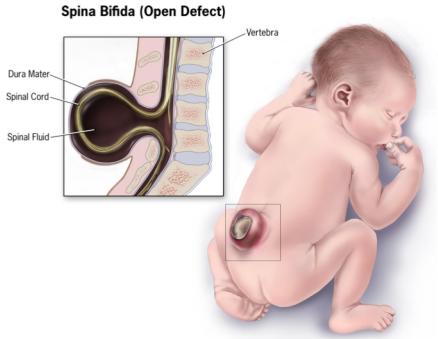
JK Morris,[1] J Rankin,[2] ES Draper,[3] JJ Kurinczuk,[4,5] A Springett,[1,5] D Tucker,[6] D Wellesley,[7] B Wreyford,[5,8] NJ Wald[1]

De Wals et al. NEJM 2007; Williams et al. 2002 (updated 2013); Morris et al. 2016 Arch Dis Child

Biomarker for NTD risk assessment

400µg/day of folic acid: NTD risk reduction by >90%

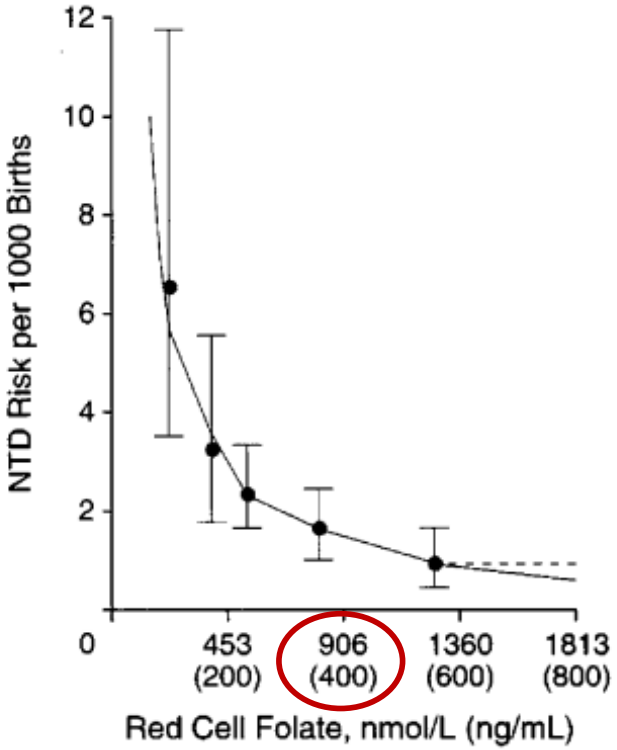




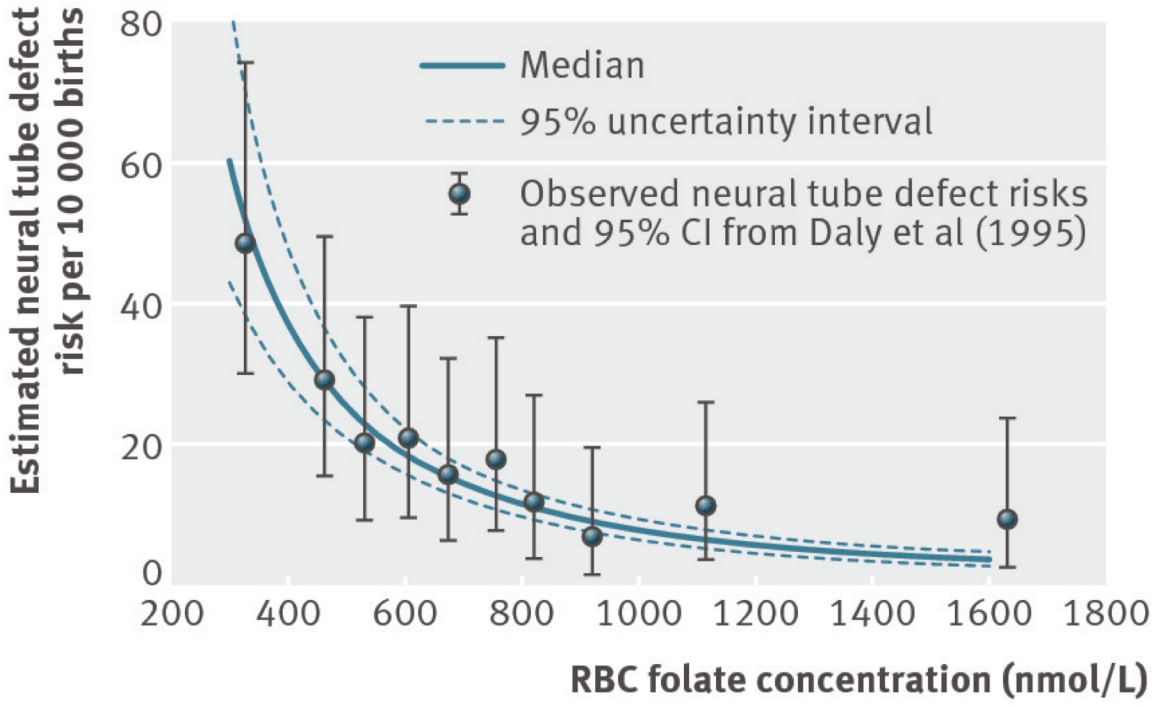
RBC folate
= established biomarker
for NTD risk assessment
in the establishment and
monitoring of prevention programs

Crider et al. 2014 BMJ

Biomarker for NTD risk assessment



Daly et al. 1995 Lancet



Crider et al. 2014 BMJ

Folate sufficiency in reproductive-aged women (WHO Guidelines 2015):

906nmol/L as RBC folate cutoff for optimal NTD prevention (748nmol/L using CDC assay)

Cordero et al. 2015 MMWR Morb Mortal Wkly Rep, Pfeiffer et al. 2016 Am J Clin Nutr

Population-based median **plasma folate cutoff ~25.5 nmol/L** corresponding to RBC folate of 906nmol/L

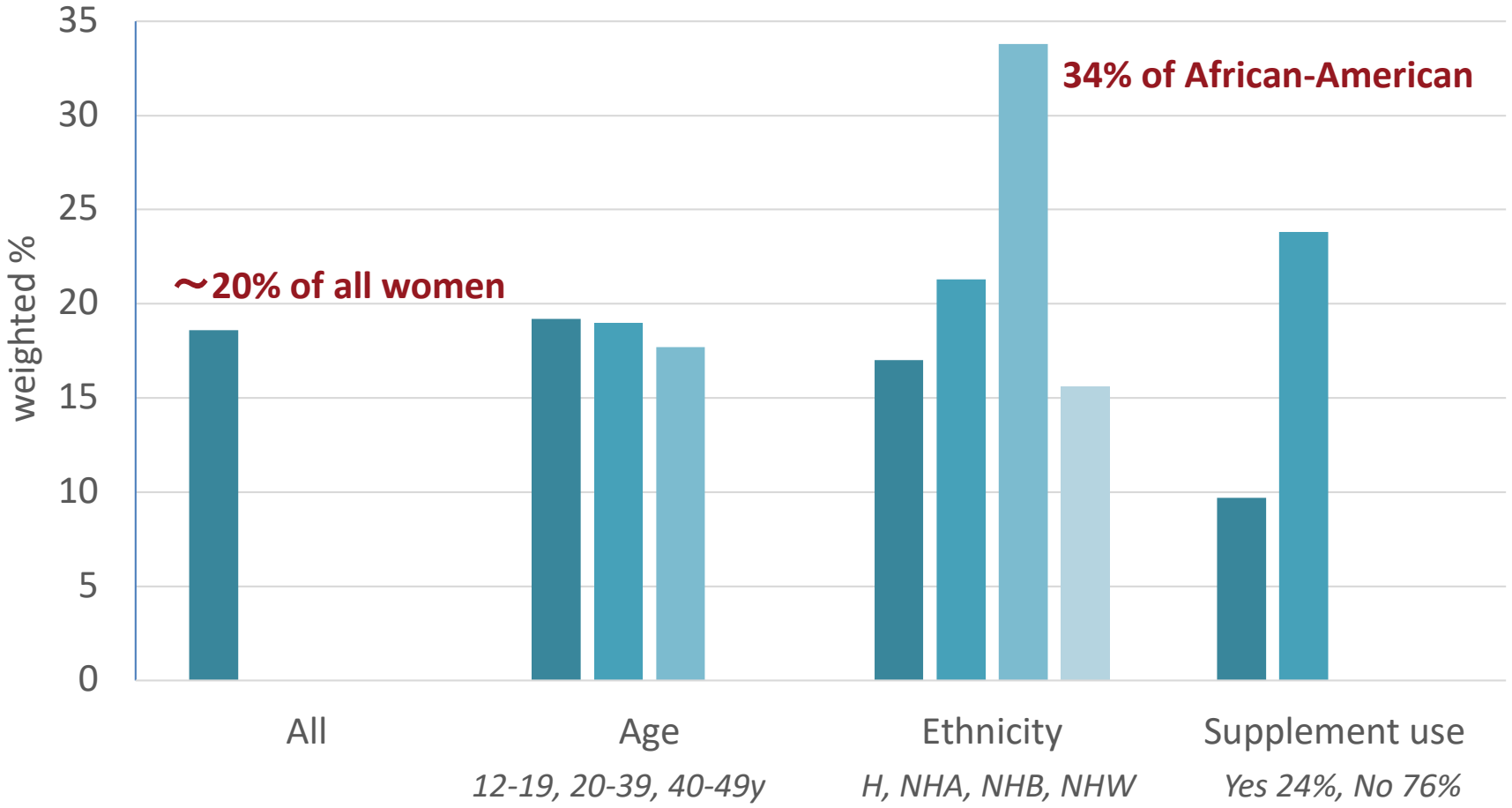
Chen et al. 2019 Am J Clin Nutr

FOLATE STATUS

RBC folate concentration in US women

Prevalence of RBC folate < cutoff for optimal NTD prevention in non-pregnant women

NHANES 2011–2016; 5583 non-pregnant women aged 12–49 years



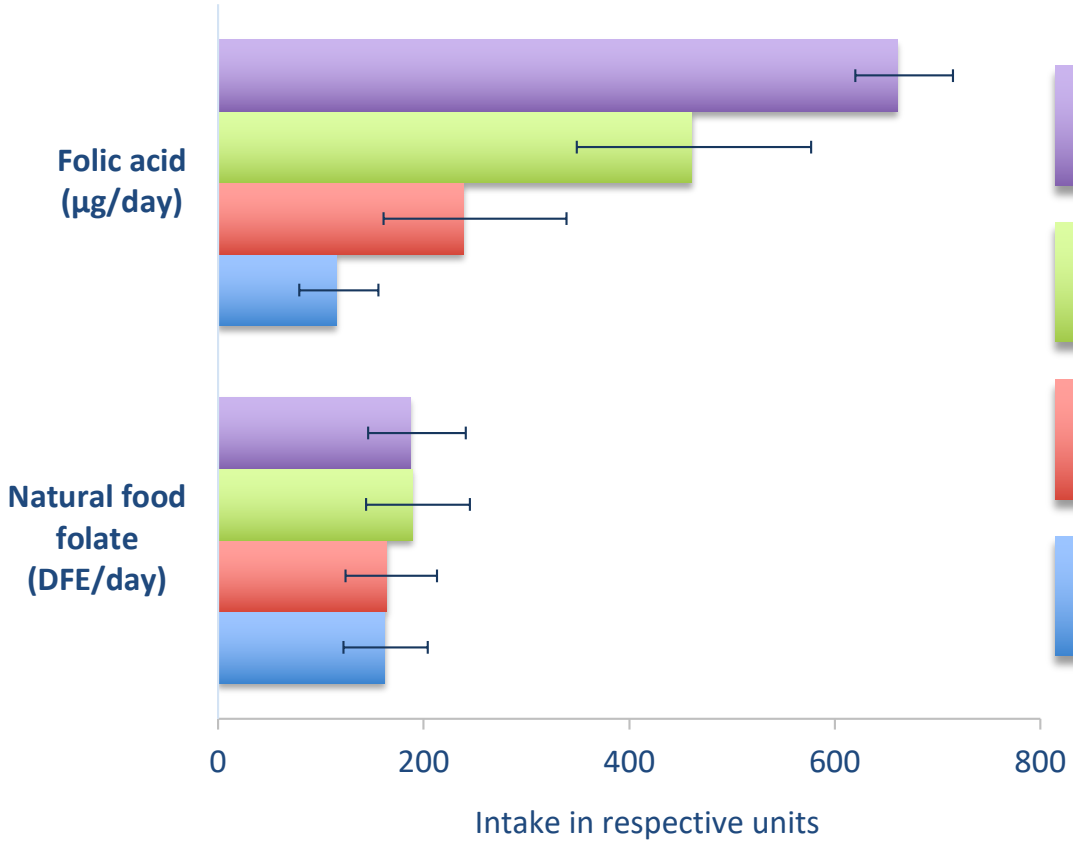
Yvonne Lamers UBC 2020-01-29

Pfeiffer et al. 2019 Am J Clin Nutr

Folate/folic acid intake in US women

Usual daily intakes of folic acid and natural food folate in US non-pregnant women

NHANES 2007–2012; 4783 nonpregnant women aged 12–49 years; data: median (IQR)



Additional NTDs prevented / year

701 (242, 1189)

503 (39, 966)

345 (0, 821)

Crider et al. 2018 Am J Clin Nutr

FOLATE STATUS

Folate/folic acid intake in US women

Prevalence of usual dietary intake distribution in pregnant women

NHANES 2001–2014; 1003 pregnant women aged 20–40 years

Dietary inadequacy

Total dietary folate intake <EAR

16% all pregnant women

supplement users and non-users

Folic acid intake >1000ug/day

33% all pregnant women

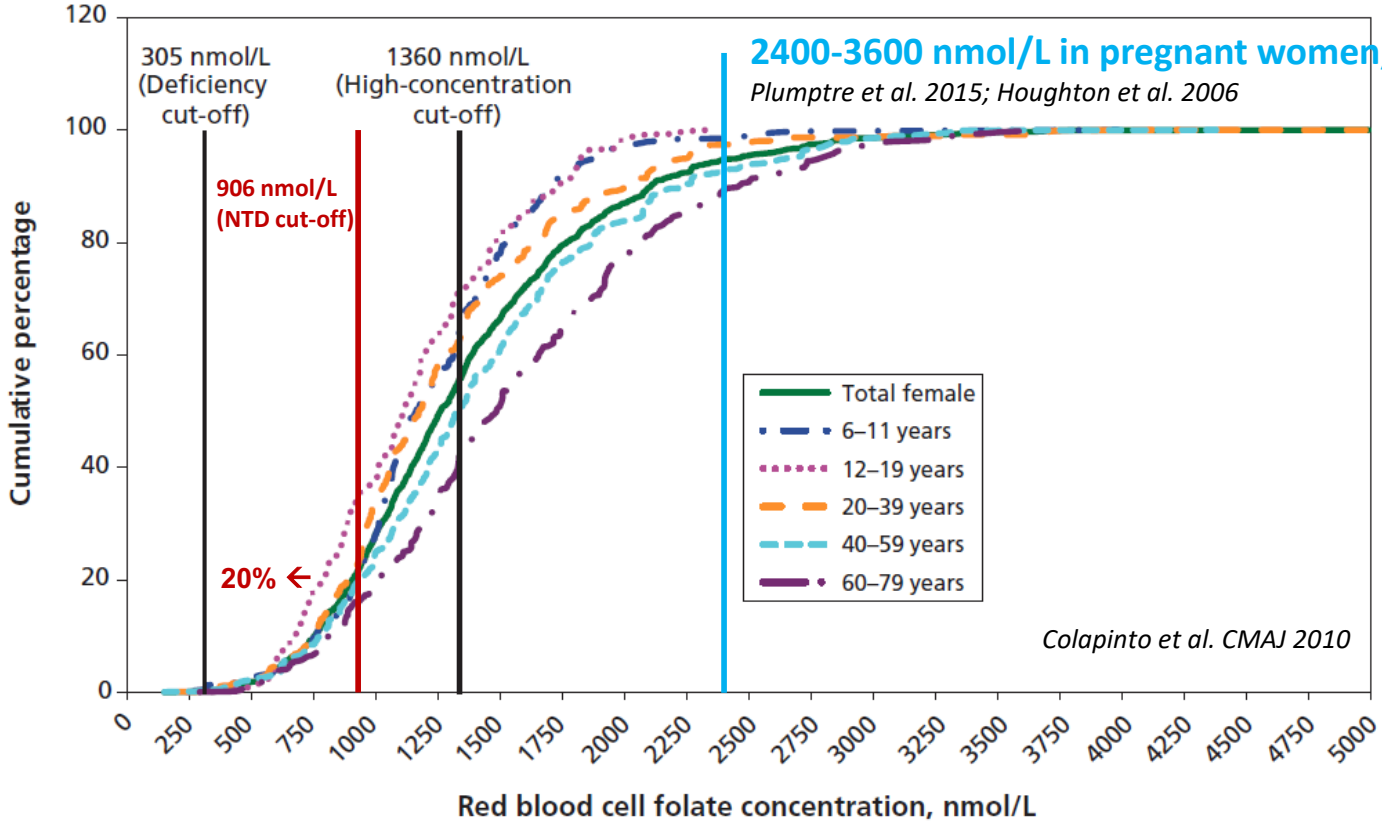
48% supplement users

inadequacy ⟷ **possible excess**

Bailey et al. 2019 JAMA Netw Open

FOLATE STATUS

RBC folate in Canadian women



20% of non-pregnant women with RBC folate below cutoff for lowest NTD risk (CHMS 2007-2009)

Folate status in pregnant women above physiological levels observed in non-pregnant women

FOLATE STATUS Folate/folic acid intake in Canadian women

What leads to the high folate status?

Low folic acid intake from fortified foods:

132µg folic acid/day (n=61 pregnant women)

Sherwood et al. 2006

High folic acid intake from prenatal supplements:

Median folic acid intake from supplements in APrON study

1000µg folic acid/day (n=387/502); 2000µg folic acid/day (n=115/502) *Fayyaz et al. 2014*

Preconception (3mo)	1st trimester	2nd trimester	3rd trimester
Prevalence: 58-60%	**90-97%**	**95%**	**90-92%**
Masih et al. 2015 *Chalmers et al. 2009*	PREFORM Cohort Study, Ontario *Masih et al. 2015* APrON Cohort Study, Alberta *Gomez et al. 2015* Canadian Maternity Experience Survey 2007-09 *Chalmers et al. 2009*		

Support The Guardian | Subscribe | Find a job | Sign in | Search

News | Opinion | Sport | Culture | Lifestyle | More

World | UK | **Science** | Cities | Global development | Football | Tech | Business | Environment | Obituaries

Nutrition

Researchers link asthma risk to folic acid during pregnancy

- **Study showed no hazard from leafy vegetables**
- **UK experts emphasise benefits of supplements**

Babies born to women who have taken folic acid supplements during their pregnancy are up to 30% more likely than other children to develop asthma, researchers have found.

Risky foods: Folic acid supplements increases allergy risk in babies

Folic acid, a type of B Vitamin, is widely used to prevent neural tube defects in the foetus, and to aid in the development of the central nervous system.

FITNESS Updated: Dec 23, 2017 16:10 IST

Asian News International

You may want to avoid taking folic acid supplements during late pregnancy if you do not want your baby to be at risk(Shutterstock)

You may want to avoid taking folic acid supplements during late pregnancy if you do not want your baby to be at risk, a study has said.

University of Adelaide researchers said taking folic acid supplements in late pregnancy may increase risk of allergies in babies affected by growth restriction during pregnancy.

Folic acid, a type of B Vitamin, is widely used to prevent neural tube defects in the foetus, and to aid in the development of the central nervous system. The team conducted a study on sheep, which were born from normal or growth-restricted pregnancies, to measured skin reactions to two common allergens: dust mites and egg whites.

QUESTIONS Is there a too much folic acid?

Birth outcomes and childhood diseases associated with prenatal folic acid intake?

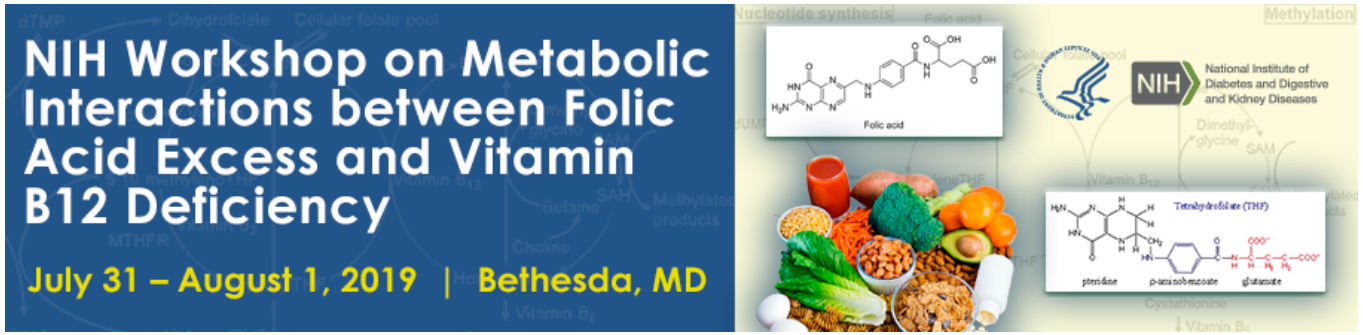
Outcome / level of evidence	Findings
Birth outcomes Cochrane review *Lassi et al. 2013*	**no association** of prenatal FA supplementation with birthweight or risk for preterm birth, stillbirths/ neonatal deaths, or low birthweight
Small-for-gestational-age (SGA) Meta-analysis/systematic review *Hodgetts et al. 2015*	**reduced risk of SGA** if supplemented before conception (adjusted OR 0.80, 95% CI 0.71–0.90, P < 0.01)
Low birth weight Meta-analysis/systematic review *Hodgetts et al. 2015*	**reduced risk of LBW** if supplemented before conception (adjusted OR 0.75, 95% CI 0.61–0.92, P < 0.01)
Asthma/allergic diseases Meta-analysis *Crider et al. 2013*	**no association** between 1st trim. FA use and risk of asthma; **conflicting results** for 2nd and 3rd trimester FA use and asthma
Autism spectrum disorder Systematic review *Gao et al. 2016*	**beneficial effect** of FA on risk of autism (n=15 studies); no significant findings (n=6); negative association (n=1)
Obesity/insulin resistance Systematic review *Xie et al. 2016*	**inconsistent findings**; decreased risk of metabolic syndrome and no/positive association between late-pregnancy maternal folate status and HOMA-IR

Lamers, MacFarlane, O'Connor, Fontaine-Bisson 2018 Am J Clin Nutr

QUESTIONS Is there a too much folic acid?

- Relationships are **associational**; challenged by biases and confounding.
- No agreed upon definition of a “high” or excessive folic acid intake.
- **Available evidence is inconsistent and equivocal**.
- **Evidence lacking** to confirm a **potential dose-dependent adverse effect** of folic acid when supplemented across all trimesters.
- **Precautionary principle to be considered**, i.e., a preventive measure in case of scientific uncertainty.

Lamers, MacFarlane, O’Connor, Fontaine-Bisson 2018 Am J Clin Nutr

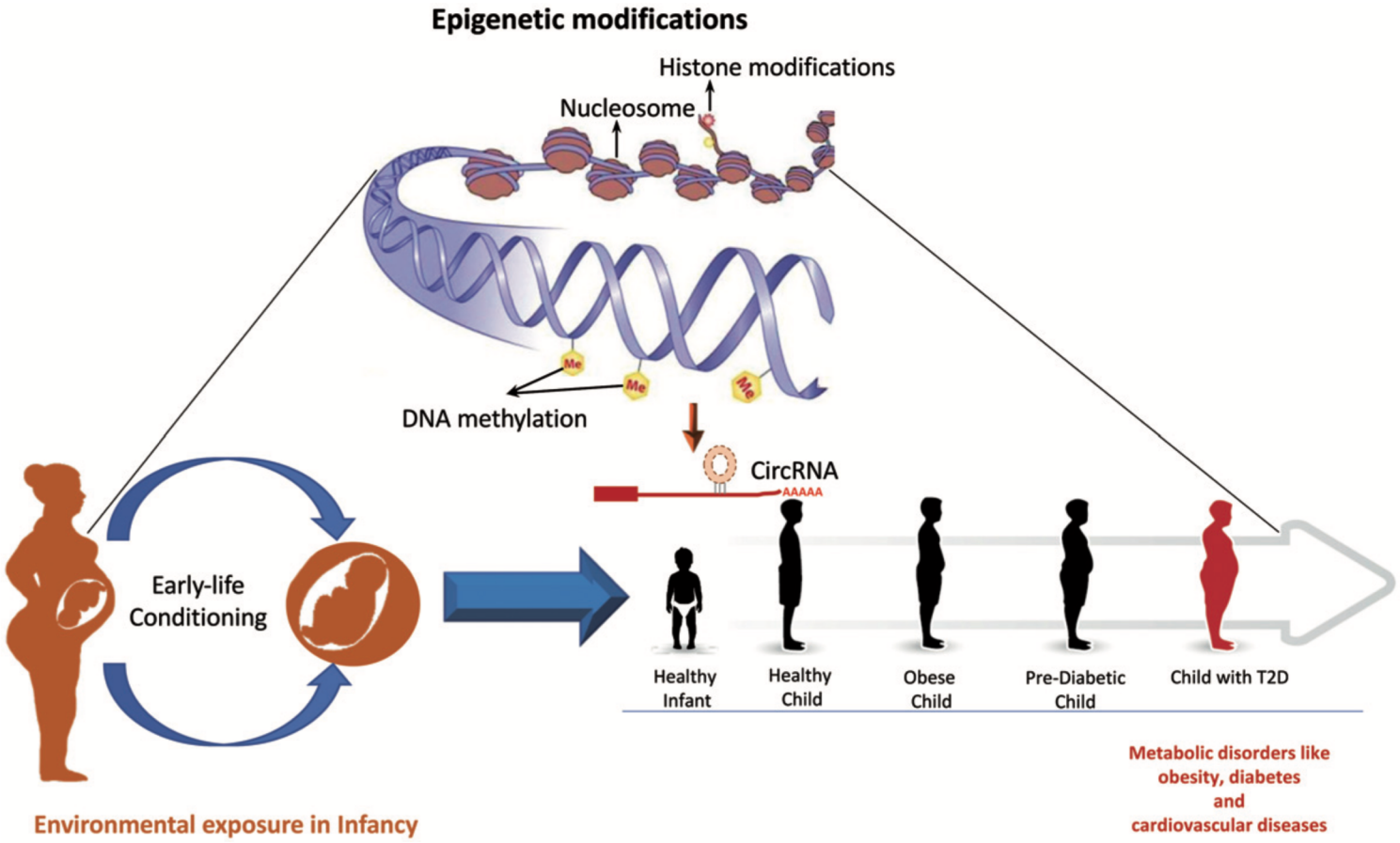


Workshop outcomes and proposed research agenda (in preparation)

QUESTIONS Is there a too much folic acid?

Biological plausibility: Folate = key methyl donor → epigenetic alterations

Folic acid in high doses → 'anti-folate' effect in *in vitro* studies

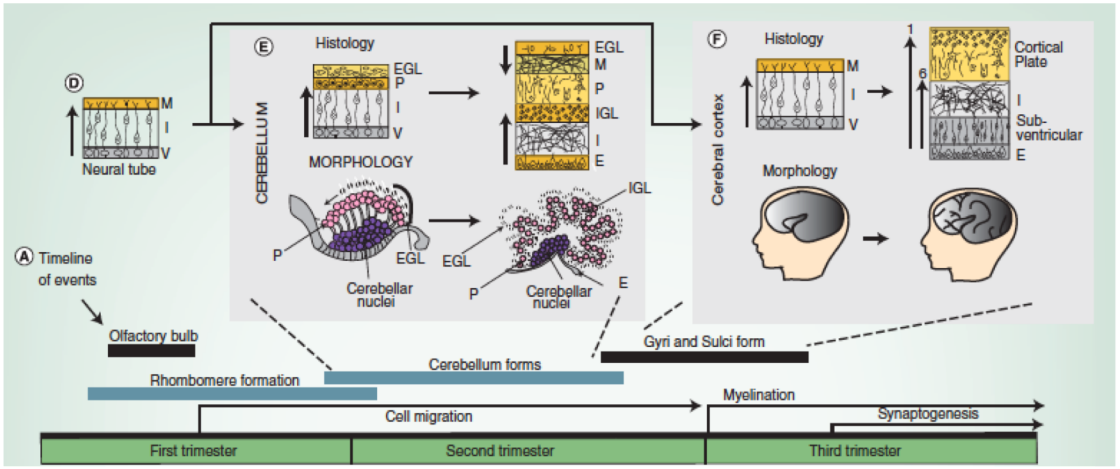


Agarwal et al. 2018 Crit Rev Clin Lab Sci

Is prolonged supplementation beneficial?

Relevant milestones in human brain development

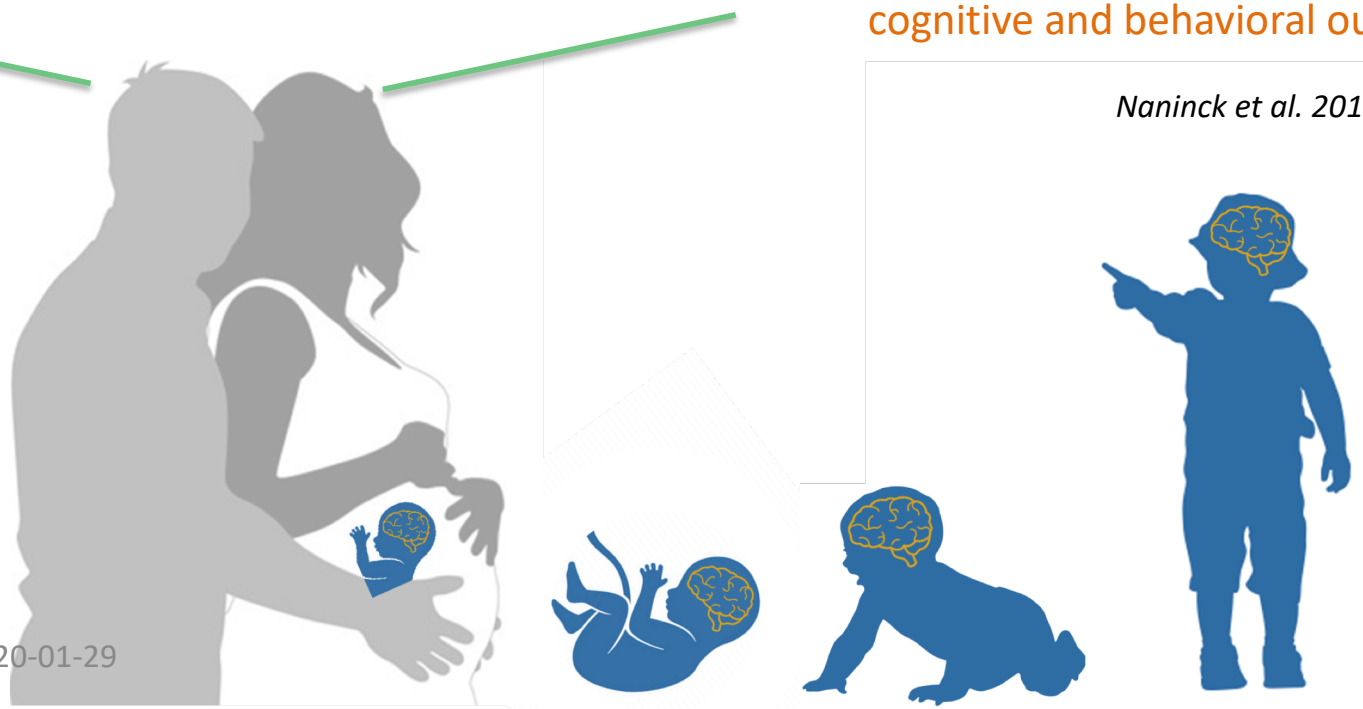
Irwin et al. 2016 Epigenomics



Current state of evidence from observational studies:

positive or *no* association between maternal folate status in early and/or late pregnancy and child cognitive and behavioral outcomes

Naninck et al. 2019 Adv Nutr



Is prolonged supplementation beneficial?

Randomized intervention trials required to test for causal relationship

Nutraceuticals for a Healthy Life (NUHEAL) Study (Germany, Spain, Hungary)

- 2x2 factorial design: 400µg 5-MTHF vs. fish oil vs. placebo
- Second half of pregnancy (n=136)

→ Improved executive function in 8.5y-old children of 5-MTHF supplemented mothers

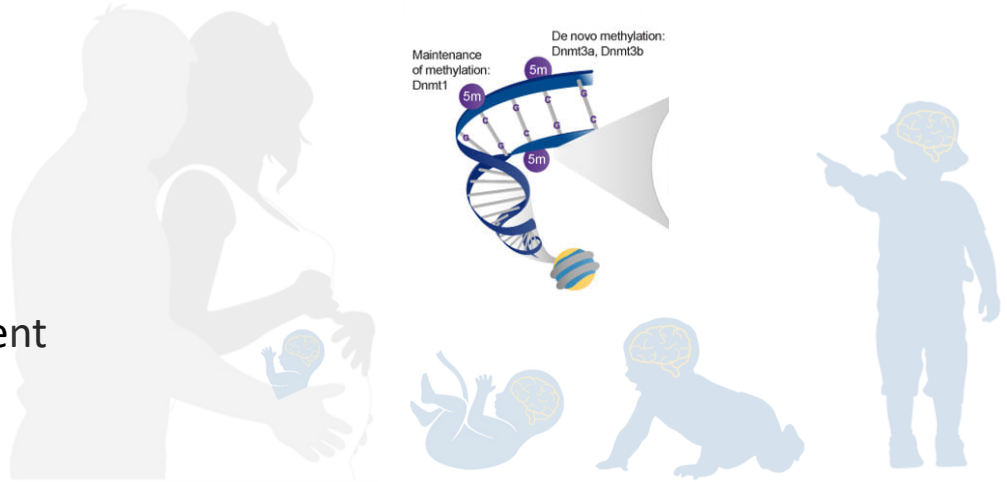
Folic Acid Supplementation in the Second and Third Trimester (FASSTT) Study (Northern Ireland)

- 400µg folic acid versus placebo
- 2nd and 3rd trimester (n=119)

→ 7y-old children of folic acid supplemented mothers:
improved developmental outcomes including verbal reasoning ability

EpiFASSTT Study

- Continued supplementation with 400µg folic acid affected DNA methylation levels in candidate genes, in cord blood
- Significantly lower DNA methylation levels of genes related to brain development



Catena et al. 2016 Am J Clin Nutr; Caffrey et al. 2018 Am J Clin Nutr; McNulty et al. 2019 BMJ Medicine; Irwin et al. 2016 Epigenomics

Summary and emerging questions

Emerging questions since release of recommendations in 1992

1. **Post-fortification era: are supplements still required?**
   Yes, and for all women

2. **Is there a too much of folic acid?**
   Unknown: dose response studies in humans required to define optimal dosage
   Linkage between epigenetic changes and physiologic outcomes to be studied
   Whether effect (if any) is folate form specific unknown

3. **From inadequacy to excess: recommendations and practice in despair**
   Alignment of supplement content with evidence-based recommendation required

Translational outcomes of stakeholder workshop in Canada (Ottawa 2017)

- **Industry (Fall 2018)**:
  Reduction of folic acid dose of most sold prenatal supplement to 600µg/d
- **Health Canada (Fall 2018):** Multi-Vitamin/Mineral Supplements
  Monograph amended to reflect current expert guidelines

Lamers, MacFarlane, O'Connor, Fontaine-Bisson 2018 Am J Clin Nutr

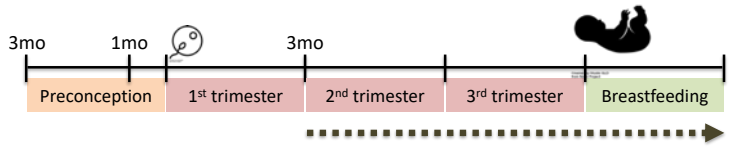
Summary and emerging questions

Emerging questions since release of recommendations in 1992

4. **Reaching all women: need to identify at risk women**
   - Low-income / lower education / unintended pregnancy → **access**
   - 20% of reproductive-aged women: RBC folate below cutoff for optimal NTD prevention, independent of socioeconomic status → **knowledge transfer**
   - Will change in dietary patterns (promotion of plant-based diets, increasing trend to vegetarianism, veganism, and gluten intolerance) alter folic acid intake in young women? → **monitoring**

5. **Do women with *MTHFR* 677C>T genetic variant require more folate/folic acid?**
   - Randomized controlled trials for primary NTD prevention: no genotype data
   - Once RBC folate >906nmol/L, similar NTD risk expected. *Crider et al. 2014*

4. **Is prolonged supplementation beneficial? Trimester-specific dosing effect?**
   - Dose-response studies needed



Vitamin B12 in Pregnancy **Dietary recommendations**

Dietary recommendations (EAR and RDA)

- Women 14-50yrs 2.0 and 2.4µg/d → based on hematological indicators
- Pregnant women **2.2 and 2.6µg/d** → + fetal deposition; absorption increases
- Lactating women **2.3 and 2.8µg/d** → + B12 excreted in human milk 0-6mo

Recommendation for periconceptional supplement use SOGC Wilson et al. 2015

"…taken in a multivitamin including 2.6 µg/day of vitamin B12."

Dietary sources of B12:

animal sourced foods; fermented products;
fortified foods; supplements

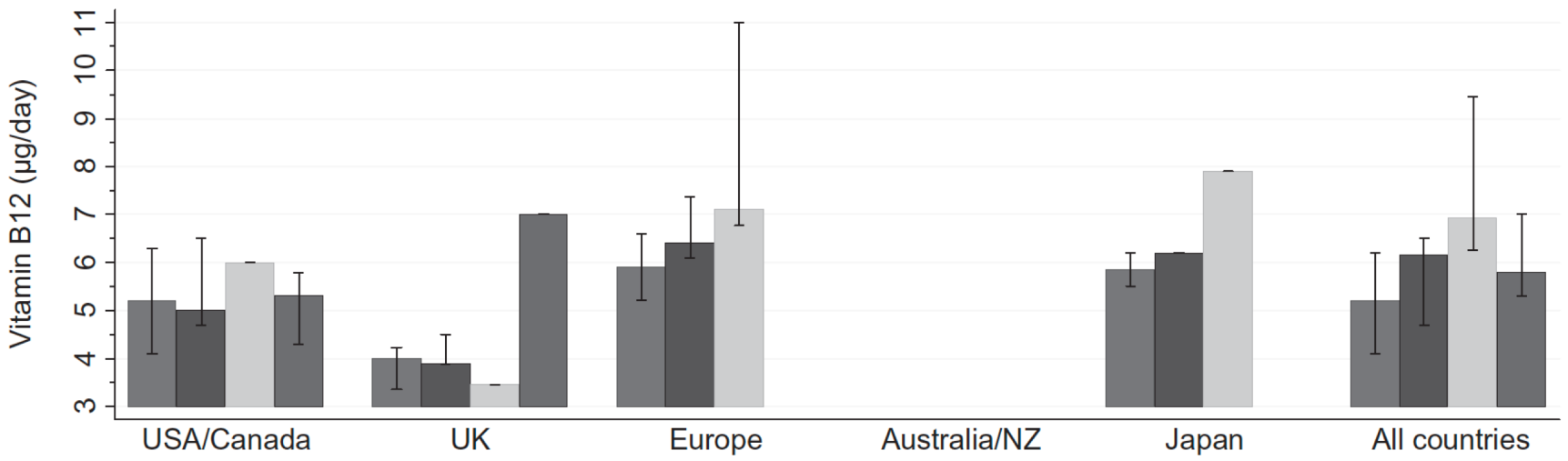
Population groups at risk for inadequate B12 intake

- Vegetarians, vegans, plant-based diets
- Certain ethnic groups, e.g., South Asians
- Low socio-economic status
- Gastrointestinal infections/diseases

B12 STATUS

Vitamin B12 intake <-> Vitamin B12 status

Median dietary vitamin B12 intake during pregnancy by trimester (1st, 2nd, 3rd, multiple)



Blumfield et al. 2013 Nutr Rev

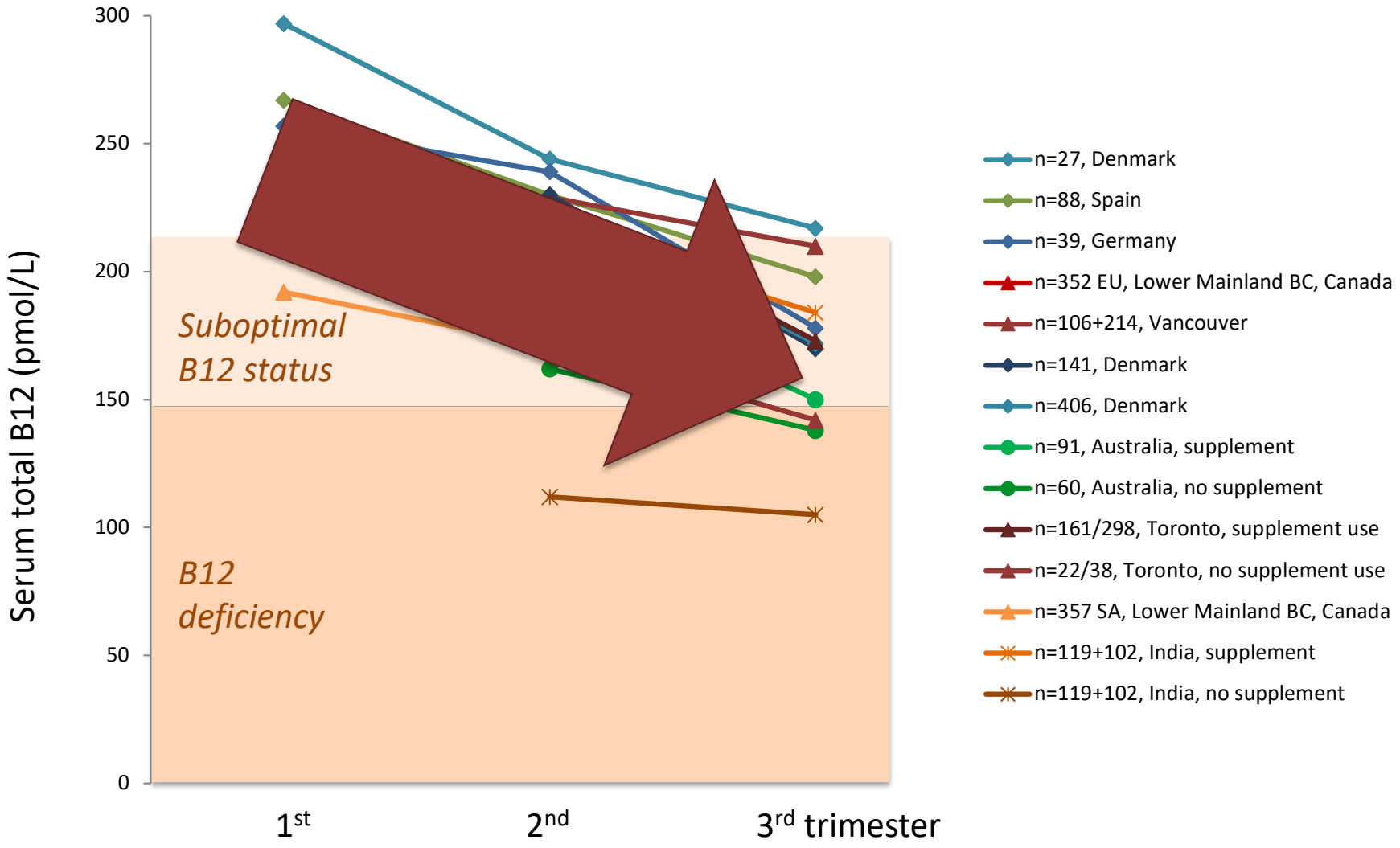
	Early pregnancy	At delivery	Dietary B12 intake (µg/day)
Deficient (tB12 <148pM)	**10%**	**23%**	**5.2 ± 2.0**
Suboptimal (tB12 148-220pM)	**21%**	**35%**	**5.8 ± 2.0**
Adequate (tB12 >220pM)	69%	42%	**6.4 ± 2.1**

100% of women used prenatal vitamins containing B12

Wu et al. 2013 Am J Clin Nutr

B12 STATUS

Physiologic change in B12 biomarker concentration



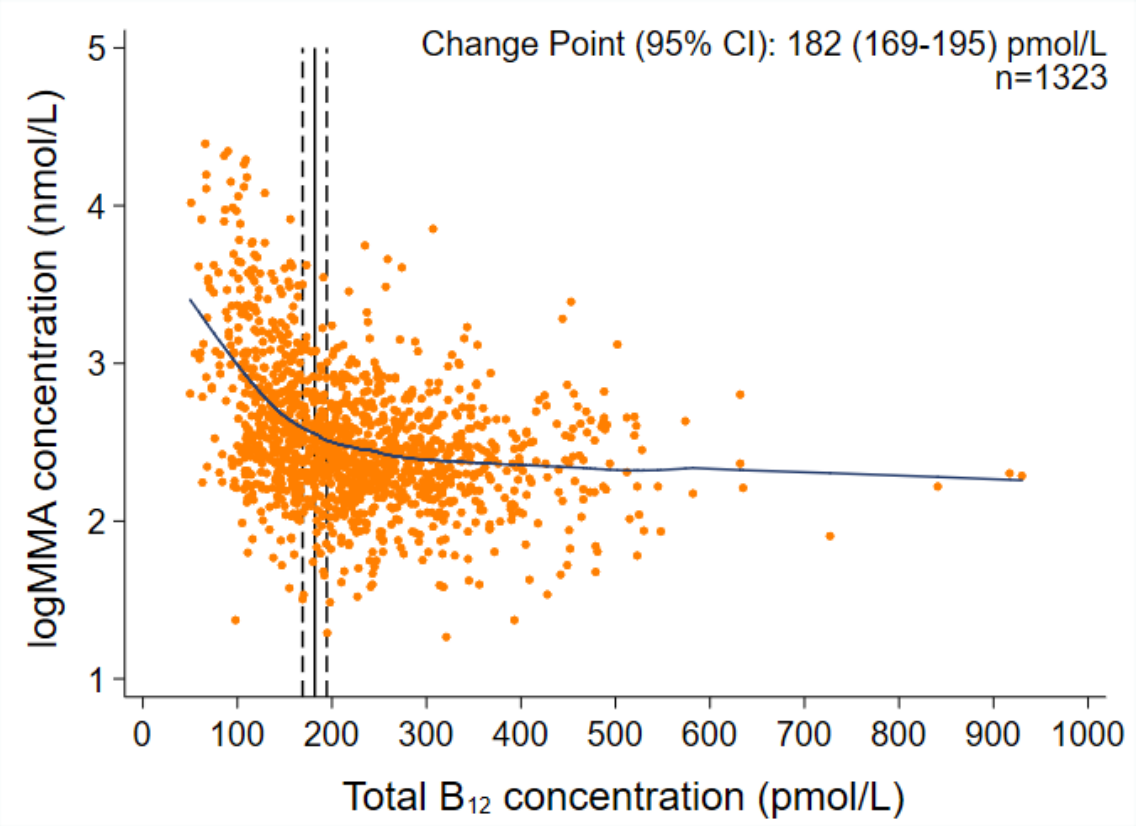
Greibe et al. 2011, Murphy et al. 2007, Koebnick et al. 2002, Schroder et al. 2017, Jeruska-Bielak et al. 2017, Morkbak et a. 2007, Milman et al. 2006, Hure et al. 2012, Duggan et al. 2014

B12 STATUS

How to define adequacy during pregnancy?

Pregnancy-specific cutoffs for vitamin B12 biomarkers are needed.

Retrospective cohort study: 750 pregnant women, 1st and 2nd trimester samples
50% of European and 50% of South Asian ethnicity



At serum total B12 <182 pmol/L: increased probability of impaired intracellular B12 status

No difference between trimesters or ethnicities.

Schroder and Tan et al. 2019 Clin Chem Lab Med

Vitamin B12 in Pregnancy — Perinatal Outcomes

Low birth weight

Rogne et al 2017
Yajnik et al 2005, Muthayya 2006

Intra-uterine growth restriction

Dror et al 2008

Preterm birth

Rogne et al 2017, *Dhobale et al 2012*

Small-for-gestational age

Yajnik et al 2008

Spontaneous abortion

Reznikoff-Etievant et al 2002

Congenital Anomalies

van Rooij et al 2003
Verkleij-Hagoort et al 2006

Neural tube defects

Ray et al 2007
Molloy et al 2009

Lowest NTD risk at serum total B12 >221pM

Molloy et al. 2009

34% of NTDs in Canada due to low B12

Vitamin B12 Suggested role in fetal programming

Maternal folic acid supplementation → **Low B12 status** → **Higher susceptibility to disease outcomes**

RBC folate >1144nM at 28 weeks

Plasma B-12 <160pM at 18 weeks

Insulin resistance
Adiposity in the offspring

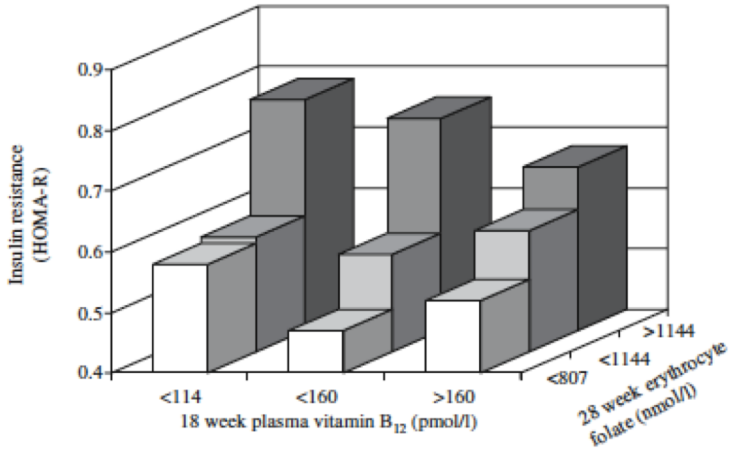


Fig. 2 Insulin resistance (*HOMA-R*) in the children at 6 years in relation to maternal vitamin B_{12} (18 weeks) and erythrocyte folate (28 weeks)

Yajnik et al. 2008, Dwarkanath et al. 2013

Vitamin B12 Suggested role in fetal programming

Maternal folic acid supplementation → **Low B12 status** → **Higher susceptibility to disease outcomes**

RBC folate >1144nM at 28 weeks

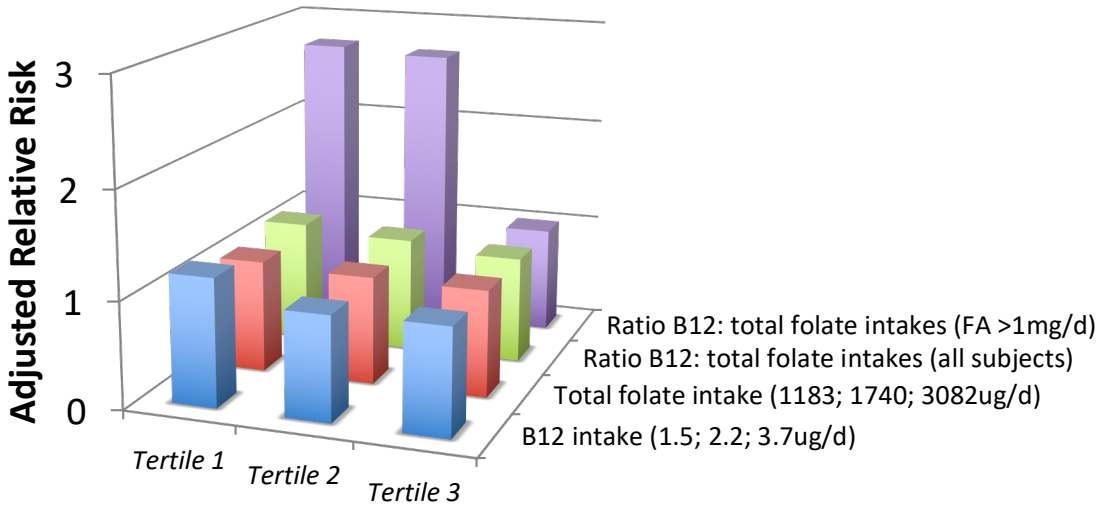
Plasma B-12 <160pM at 18 weeks

Insulin resistance
Adiposity in the offspring

Folic acid intake >1 mg/d in second trimester

Low B12

Intra-uterine growth restriction



Yajnik et al. 2008, Dwarkanath et al. 2013

Vitamin B12

Early adequacy crucial for child development




Development of **fetal B12 stores**

Newborn with **sufficient B12 stores**

B12 status in 12-mo old infant associated with **maternal serum total B12 not breastmilk B12**

B12 status/B12 intake during pregnancy = **strong determinants of neonatal and infant B12 status**

Deegan et al. 2012, Duggan et al. 2015

B12 in Pregnancy

Summary and Research Needs

High prevalence of suboptimal vitamin B12 status in reproductive-aged women

- Maternal B12 = independent NTD risk factor → more NTDs to prevent?
- Dose-dependency trial needed: 400ug folic acid plus different doses of vitamin B12

Dietary requirements met or exceeded by many pregnant women

- Need to identify women at risk (e.g., South Asians, low income status)

Indicators of exposure and outcomes

- Significance of decrease in serum total B12 and holoTC unexplained
- Higher intake showed higher status
- Need for the study of functional outcomes

→ Are the current RDAs too low?

Folate / Folic Acid / B12 – in the context

- Food security
- Socioeconomic status
- Environmental factors
- Maternal health

Genetic factors