Supplement

Periconceptional intake of folic acid among low-risk women in Canada: summary of a workshop aiming to align prenatal folic acid supplement composition with current expert guidelines

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ABSTRACT

The Government of Canada and the Society of Obstetricians and Gynaecologists of Canada both recommend a daily multivitamin supplement containing 400 μg folic acid (FA) for the primary prevention of neural tube defects among low-risk women from before conception and throughout lactation. Prenatal supplements marketed and prescribed in Canada typically exceed the recommended dose, usually providing ≥1000 μg FA/d. This high daily dose, coupled with staple-food FA fortification, has resulted in the observation of very high blood folate concentrations among reproductive-aged women consuming FA-containing supplements. The long-term consequences of high folate status on fetal development are unknown; however, evidence from animal studies and some human epidemiologic data suggest potential adverse consequences. To address this issue, a workshop was convened with the overall goal to identify challenges and solutions to aligning supplemental FA intakes with current evidence-based recommendations. Thirty-eight stakeholders from academia, industry, government, and health professional groups participated. Group discussions facilitated the identification and prioritization of 5 key challenges for which solutions and implementation strategies were proposed. The 5 themes encompassed clarity and harmonization of evidence-based guidelines, reformulation or relabeling of FA-containing supplements, access to FA for all women, knowledge dissemination strategies and education of the public and health care professionals, and attitude change to overcome the perception of "more is better." A combination of the proposed implementation strategies involving all key stakeholders and directed to health care professionals and the public may enable a sustainable change to align FA intake during the periconceptional period with evidence-based recommendations. *Am J Clin Nutr* 2018;108:1357–1368.

Keywords: pregnancy, periconceptional supplementation, folic acid, prenatal supplement, guidelines

INTRODUCTION

Folate is a generic descriptor for a family of compounds that share a pteroylglutamic acid core and whose primary biological role is the transfer of 1-carbon units (1). Pteroylglutamic acid, or folic acid (FA), is the most common form of folate used in dietary supplements and as a fortificant in foods; it is completely oxidized, stable, highly bioavailable, and is seldom found in nature. In contrast, naturally occurring folates are more labile, less bioavailable, typically reduced (e.g., dihydro- or tetrahydrofolate), and frequently carry a carbon group (e.g., methyl, formyl). A significant fraction of naturally occurring folates have a polyglutamate tail which is necessary for cellular retention and affinity to various enzymes in living cells. Folate monoglutamates, but not polyglutamates, are transported across cells. Excellent sources of naturally occurring folate include green leafy vegetables, dark green vegetables (e.g., broccoli and brussel sprouts), and legumes (e.g., beans, chickpeas, lentils). Folate is best known for its role as a cofactor in nucleotide synthesis—necessary for DNA and RNA biosynthesis and repair—and for the remethylation of homocysteine to produce the essential amino acid methionine. Methionine is used for protein synthesis or can be converted to S-adenosylmethionine. S-adenosylmethionine is involved in numerous methylation reactions in the body, including that of DNA and histones, which are required for epigenetic programming early in life (2).

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Abbreviations used: FA, folic acid; MRC, Medical Research Council; NTD, neural tube defect; RBC, red blood cell; RCT, randomized controlled trial; SOGC, Society of Obstetricians and Gynaecologists of Canada; UL, Tolerable Upper Intake Level.

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Internationally, periconceptional supplementation with 400 μg of FA is recommended for the primary prevention of neural tube defects (NTDs), such as spina bifida and anencephaly (1, 3, 4). NTDs occur early in pregnancy, as the neural tube closes within the first 3–4 wk postconception. This recommendation is based on high-level evidence from randomized controlled trials (RCTs) and prospective cohort studies demonstrating an ≤85% reduction in NTD occurrence among women who consume FA supplements before conception and in the first trimester of pregnancy (1, 5–7). Health Canada recommends that women of childbearing age at low risk of having a fetus with an NTD consume a multivitamin supplement containing 400 μg of FA from preconception until the end of lactation (3). Health Canada requires that over-the-counter FA supplements marketed to pregnant women contain ≥400 μg FA (3). Supplements with >1000 μg FA are available by prescription only. The vast majority of prenatal supplements on the Canadian market, however, contain 1000 μg FA (8), preventing health care professionals and women from following public health recommendations. Consequently, high intakes of supplemental FA, coupled with staple food FA fortification, have resulted in very high red blood cell (RBC) folate values among pregnant women and women of reproductive age in Canada (9–12). There is no debate that folate is essential for optimal fetal growth and neural tube closure (13, 14). However, the long-term consequences of high blood folate concentrations on fetal development due to epigenetic programming or other mechanisms are unknown. Given that there is no benefit of a daily intake of FA above the recommended dose, the current FA content of prenatal supplements should be re-evaluated.

With support from a grant from the Canadian Institutes of Health Research, a 1-d workshop was held in Ottawa on 17 November 2017, with the overarching goal to align FA prenatal supplement content in Canada with evidence-based recommendations through constructive discussion among stakeholders from academia, industry, government, and health care professional bodies. The objectives of the workshop were: *1)* to identify challenges and concerns from the supplement industry and health care professionals in aligning recommendations with practice in terms of FA intake of women of childbearing age and pregnant women; and *2)* to identify solutions to overcome the misalignment between the recommendations and the actual FA intake.

STATE OF THE EVIDENCE

The workshop commenced with a series of presentations to provide a foundational understanding of the history of periconceptional FA supplementation, current guidelines, folate status and FA intake of Canadian women, and the benefits and potential risks associated with prenatal FA supplementation. These topics are summarized below.

Recommended dose of FA for primary prevention of NTDs

Historical perspective

FA was synthesized in the early 1940s and Lederle Laboratories manufactured 5000- and 20,000-μg FA tablets in 1945. Vitamin B-12 was identified in 1948 and was generally available for therapeutic use in the early 1950s (15, 16). Deficiencies of either of these vitamins may cause macrocytic (megaloblastic) anemia, which can be effectively treated with FA (15, 16). During the time gap between commercial availability of FA and vitamin B-12, individuals with pernicious anemia were treated with FA alone, which allowed the neurologic damage caused by vitamin B-12 deficiency to progress (1). Pernicious anemia is caused by the absence of intrinsic factor, which is secreted by parietal cells in the stomach and is required for absorption of vitamin B-12 in the small intestine (1).

In 1946, the recommended therapeutic dosages for management of folate deficiency were 5000–20,000 μg/d for adults and 5000–10,000 μg/d for children; these were not changed for 25 y (17). In 1971, the US Food and Drug Administration Drug Efficacy Study workgroup experts recommended that the Food and Drug Association lower the therapeutic dose to 250 and 1000 μg of FA for children and adults, respectively, owing to lack of evidence for greater efficacy at higher doses (18, 19).

In the 1960s, Hibbard and Smithells (20) hypothesized a link between FA and NTDs. Through a series of primarily observational studies conducted mainly in the 1970s and 1980s, it was proposed that >85% of recurrent cases of NTDs might be prevented by periconceptional FA supplementation (21). In order to establish a causal relation between FA intake and NTDs, 2 key RCTs were conducted in the 1980s and 1990s to examine the effect of FA on NTD recurrence and primary prevention (22, 23). These RCTs showed that supplemental FA in the periconceptional period (before conception and for the first trimester) significantly reduced the risk of recurrence (4000 μg FA) or primary occurrence (prenatal multivitamin containing 800 μg FA) of NTDs (22, 23). These data led to the public health recommendation that women should take an FA supplement in the periconceptional period. In Canada and the United States, these data were also used to underpin the implementation of mandatory FA fortification of white flour and other enriched cereal and pasta products (24, 25).

Recommended dose for NTD risk reduction

In the United States, it is recommended that women at high risk of having an NTD-affected pregnancy take 4000 μg FA/d, which is based on the UK Medical Research Council (MRC) Trial (**Table 1**) (5, 23). The MRC Trial was a randomized double-blind prevention trial to determine whether supplementation with FA around the time of conception could prevent NTDs. The dose used in the MRC Trial was selected based on observations from a small nonrandomized trial for the prevention of NTD recurrence (26). It is noteworthy that in that trial, the 4000-μg dose was chosen because that was the dose available in the hospital pharmacy at the time of the study. A dosage of 400 μg FA/d was recommended for women considered to be at low risk of an NTD, based on the knowledge that a prenatal vitamin containing 800 μg FA prevented NTD occurrence (22) and that 4000 μg FA prevented NTD recurrence (MRC), and the pragmatic reality that earlier observational studies associated multivitamins, which usually contained 360–400 μg FA, with reduced occurrence of NTDs (27, 28). In the late 1990s, a population-based community intervention project in China was the first to show that 400 μg FA/d alone (not in the context of a multivitamin) significantly reduced the primary occurrence of NTDs (from 4.8 to 1.0/1000 in northern China and from 1.0 to 0.6/1000 in southern China) (27). The Institute of Medicine published the Dietary Reference

TABLE 1
Recommendations for prenatal FA supplementation in Canada and the United States[1]

		Recommended FA dose and definition of NTD risk groups					
		Low risk		Intermediate/moderate risk		High risk	
Organization	Year	Dose, μg	Definition	Dose, μg	Definition	Dose, μg	Definition
US CDC (5)	1991	—	—	—	—	4000	Women who have had a pregnancy resulting in an infant or fetus with an NTD
US Public Health Service (29)	1992	400	All women of childbearing age in the United States who are capable of becoming pregnant	—	—	—	—
Society of Obstetricians and Gynaecologists of Canada (7, 30–32)	1993	400	Women of childbearing age and low NTD risk planning a pregnancy[2]	1000–4000	No NTD history, but have T1D, epilepsy treatment, first-degree relative with NTD, FA antagonist use	4000	Previous pregnancy with NTD
	2003	400–1000	Women of childbearing age and low NTD risk planning a pregnancy	4000–5000	No NTD history, but have T1D, epilepsy treatment, first-degree relative with NTD, FA antagonist use	4000–5000	Previous pregnancy with NTD
	2007	400–1000	No personal health risks, planned pregnancy, good compliance	5000	Epilepsy, T1D, obesity with BMI $>$ 35 kg/m^2, family history of NTD, high-risk ethnic group (e.g., Sikh); history of poor compliance with medications, variable diet, no consistent birth control, possible teratogenic substance use (alcohol, tobacco, recreational nonprescription drugs)	5000	Previous pregnancy with NTD or other potentially folate-responsive congenital anomaly
	2015	400	Women or male partners with no personal or family history of FA-sensitive birth defects	1000–4000	First or second family history of NTD, personal history of other folate-sensitive congenital anomalies, maternal diabetes, teratogenic medications, maternal GI malabsorption conditions	4000	Personal history of NTD or previous NTD pregnancy in either partner
Health Canada and the Public Health Agency of Canada (6, 33)	1993	—	As early as possible, women planning a pregnancy should consult physician about FA supplements	—	—	—	Previous NTD pregnancy, refer to physician
	1995–2018	400[3]	All women who could become pregnant	—	Refer to health care provider	—	Refer to health care provider

[1]FA, folic acid; GI, gastrointestinal; NTD, neural tube defect; T1D, type 1 diabetes.
[2]Women should consider a minimum of 400 μg FA or the adequate dietary equivalent according to Canada's Food Guide to Healthy Eating.
[3]As part of a multivitamin containing 400 μg FA.

Intakes for folate in 1998, also recommending that women of reproductive age consume 400 μg FA/d from fortified foods or supplements (1).

Folate status, FA intake, and NTD risk

The WHO defined serum and RBC folate cutoffs for classical folate deficiency based on the relation between these biomarkers and hematologic symptoms of anemia and circulating homocysteine (28). For RBC folate, this cutoff is 340 nmol/L. The WHO also endorsed a higher RBC folate concentration cutoff of 906 nmol/L, as originally observed by Daly et al. (34), that has been associated with maximal NTD risk reduction for women of reproductive age (35, 36).

In the United States, where FA is consumed in enriched cereal grain products and ready-to-eat cereals in addition to supplements, intake modelling studies showed that women consuming enriched cereal grain products as their only source of folate had lower RBC folate status and higher predicted NTD prevalence than women consuming additional supplemental sources of FA (36, 37). Further findings have shown that achieving the optimal RBC folate concentration for NTD risk reduction requires a daily intake of ~600 μg dietary folate equivalent (~400 μg FA/d), an intake that is only achieved in women consuming FA-containing supplements in addition to fortified foods (37).

Canadian recommendations for periconceptional FA supplement use for the prevention of NTDs

Health Canada's first recommendation for FA intake in 1993 stated that women should consult their physician about FA

supplements as early as possible when planning a pregnancy (Table 1) (33, 38). It noted that women who have had a previous pregnancy with an NTD are at higher risk of having another NTD-affected pregnancy and should consult their physician. The guideline recommended that all women of childbearing potential follow Canada's Food Guide to Healthy Eating and take care to choose foods higher in folate. Subsequent iterations of the Health Canada recommendation, and later also the Public Health Agency of Canada recommendation, stated that all women who could become pregnant and those who are pregnant should consume a multivitamin supplement containing 400 μg FA and women at higher risk of an NTD-affected pregnancy, such as those with a previous NTD-affected pregnancy, a family history of NTDs, diabetes, or taking an anticonvulsant drug, may require a higher dose and should refer to their physician about an appropriate FA supplement dose (6, 39–41).

The Society of Obstetricians and Gynaecologists of Canada (SOGC)'s first policy statement in 1993 on the use of FA to reduce NTDs categorized women of childbearing age as either low, intermediate, or high NTD risk (Table 1) (7). Low-risk women planning a pregnancy were recommended to consume 400 μg supplemental FA/d. High-risk women (those with a previous pregnancy affected by an NTD) were recommended to consume 4000 μg supplemental FA/d. The doses for low- and high-risk women were based on the doses used in clinical trials and observational studies. Intermediate-risk women, defined as having had no previous NTD history but being at increased risk owing to certain medical conditions or family history (Table 1), were recommended to consume 1000–4000 μg supplemental FA/d. The intermediate-risk category was based on observations that certain medical conditions are associated with higher NTD risk. Multivitamin supplements sold in Canada at the time generally contained 800 μg FA.

The SOGC guidelines for FA supplement use have since undergone 3 revisions, each of which resulted in modifications to the risk category definitions and/or the recommended doses (30–32) (Table 1). They have all recommended consuming an FA-containing supplement, in addition to consuming a healthy folate-rich diet. Importantly, in 2007, the SOGC defined low-risk women as those with no personal health risks, having a planned pregnancy, and with good compliance; the recommended dose of supplemental FA was 400–1000 μg (30). All other women were recommended to consume 5000 μg supplemental FA/d (plus dietary intake) based on an expanded list of risk characteristics including women with obesity, belonging to certain ethnic groups, with a history of poor medication compliance, and with lifestyle issues such as variable diet, inconsistent use of birth control, and possible teratogenic substance use (e.g., alcohol, tobacco, recreational nonprescription drugs). In response to confusion and concern among health care professionals about the 2007 SOGC guideline, Health Canada published a Questions and Answers for Health Professionals document to clarify the approach to identifying women that might benefit from high-dose FA supplementation (42). The current SOGC guideline, published in 2015, narrowed the 2007 risk definitions and eliminated dose ranges for risk groups (31). The daily recommended dose for the low-risk group is 400 μg FA, and the low-risk group includes women when they and their male partners have no personal or family history of an NTD or another FA-sensitive birth defect.

Shifting folate status of Canadians

The folate status of Canadians, including women of reproductive age, has dramatically shifted over the past 50 y. The 1970–1972 Nutrition Canada Survey reported on the nutritional status of 12,795 Canadians from all 10 provinces (43, 44). At that time, 50% of Canadian women of reproductive age had serum folate concentrations that were indicative of either moderate (<12 nmol/L) or high risk (<5 nmol/L) of classical folate deficiency. A number of subsequent provincial surveys and local reports examining the folate status of women of reproductive age over the next 3 decades confirmed these biochemical findings and suggested that most women had intakes below recommendations (45–47). In 1998, the Canadian government mandated that all white-wheat flour and enriched pasta contain 150 μg FA/100 g flour and up to a maximum amount of 270 μg FA/100 g pasta, to increase the folate intakes of reproductive-aged women by 100 μg/d (24). Based on monitoring data of births and pregnancy terminations due to fetal anomalies from 7 of 10 Canadian provinces, mandatory fortification resulted in a 46% reduction in the prevalence of NTDs, from a prefortification rate of 1.58/1000 births to a rate of 0.86/1000 births postfortification (48). The first nationally representative blood folate values after FA fortification of the food supply were available from the 2007–2009 Canadian Health Measures Survey. The data indicated that classical folate deficiency as measured by an RBC folate concentration <305 nmol was virtually nonexistent (12). Among women of reproductive age, ~80% had RBC concentrations considered maximally protective against an NTD (906 nmol/L) (12).

Studies examining the sources of folate in the diet of women postfortification suggest FA-fortified foods are now major contributors to total dietary folate intake (49, 50). However, modelling nationally representative population-based data postfortification from the 2004 Canadian Community Health Survey indicated that the consumption of fortified foods alone does not result in FA intakes above the Tolerable Upper Intake Level (UL) of 1000 μg FA (51). The UL for folate refers to FA, the fully oxidized folate form, only and does not include the intake of naturally occurring dietary folate. The same modelling exercise showed that supplemental FA intakes of 325–500 μg are required by Canadian women aged 19–50 y, in addition to FA intake from fortified foods, to ensure a total intake of 400 μg of FA to meet guidance for reduction of NTDs without exceeding the UL (51).

Approximately 58% of women interviewed for the Canadian Maternity Experiences Survey reported consuming an FA-containing supplement during the 3 mo before conception (52). Whereas guidelines for low-risk women in Canada recommend a daily dose of 400 μg of FA to prevent NTDs, the vast majority of pregnant women report consuming prenatal supplements containing 1000 μg of FA, as reported in 2 Canadian cohorts (50, 53). Nationally representative data on the blood folate concentrations of pregnant women in Canada do not exist. However, recent data from a demographically diverse population from Southern Ontario suggest very high maternal RBC folate concentrations during pregnancy; the geometric mean (95% CI) in early pregnancy was 2417 nmol/L (2362, 2472 nmol/L) (9). Importantly, all women had RBC folate concentrations maximally protective against NTD in early pregnancy (>906 nmol/L). Moreover, cord RBC folate concentrations were high.

Unmetabolized FA was detectable in 97% of women, suggesting that the intake of supplemental FA exceeded the physiologic capacity to reduce and utilize FA in most women. Similarly, a recent Albertan pregnancy cohort noted an upward shift in RBC folate concentrations compared with early reports (10). However, unlike the pregnancy cohort from Southern Ontario, RBC folate concentrations were found to be below the NTD protective cutoff of <906 nmol/L in 24% of Albertan pregnant women in their first trimester (10).

Adverse effects potentially associated with high FA intake

The Institute of Medicine set the UL for FA at 1000 μg/d, based on case reports in the 1940s of precipitation or exacerbation of neurologic damage in vitamin B-12–deficient individuals (1). The UL was intended to be the usual intake level of FA at which no one would exceed the Lowest Observed Adverse Effect Level of 5000 μg.

More recently, concerns have been raised that "high" intakes of FA may have other potential adverse health consequences in addition to those related to vitamin B-12 and the UL. Systematic review of this literature is difficult owing to inconsistent application of the term "high" FA intake and/or status (54). Some potential adverse effects associated with supplemental FA intake explored in the literature include impaired fetal growth, promotion of cancer, an aggravating interaction with vitamin B-12 deficiency, and increased risk of childhood diseases such as asthma and autism. Although there exists a body of literature discussing FA and cancer (e.g., 55–60), the US National Toxicology Program and the UK Scientific Advisory Committee on Nutrition did not identify conclusive evidence on adverse effects of FA in cancer as recently reviewed (61). In the context of this workshop, however, we focused specifically on pregnancy-associated outcomes.

Studies of pregnancy- and child-related outcomes associated with prenatal supplemental FA intake for different periods in pregnancy have been summarized in **Table 2**. Meta-analyses and systematic reviews reported beneficial effects of periconceptional FA supplementation in addition to NTD reduction, including lower risk of small-for-gestational-age and low-birth-weight infants. The reported relations of maternal FA intake with adverse pregnancy and child outcomes are inconsistent and are solely based on observational studies and thus on lower-level evidence. Recent reviews from the United Kingdom and United States failed to identify adverse consequences of higher-dose FA on pregnancy outcomes (62). The interpretation of observational studies of supplemental FA intake is challenging owing to the biases and confounding inherent to associational studies: supplement users can be very different from nonusers in terms of important characteristics that influence health outcomes. Further, there is no agreed-upon definition of a "high" FA intake, and studies apply inconsistent cutoffs for assigning high and low groups. In addition, multivitamins represent the principal determinant of higher folate status and most often also contain vitamin B-12; animal studies can be used to propose mechanisms but their metabolism is not always directly applicable to humans. Overall, the currently available evidence on the effect of high FA intake or status is inconsistent and equivocal.

Although evidence is lacking to confirm a potential dose-dependent adverse effect of FA when supplemented across all trimesters, the "precautionary principle" could be considered in the re-evaluation or confirmation of periconceptional supplementation guidelines. The precautionary principle had its origin in environmental science and aims to anticipate, monitor, and prevent unintended adverse consequences of public health interventions. In the context of prenatal supplementation guidelines, the precautionary principle can be defined as a guide for decision making in the public health context and a policy tool for acknowledging scientific uncertainty by prompting a preventive intervention, call for more research, or both, in light of the existing state of the evidence (81).

CHALLENGES AND SOLUTIONS IN ALIGNING SUPPLEMENTAL FA INTAKE WITH EXPERT GUIDELINES

After the formal presentations, the 38 workshop participants were assigned to 1 of 5 working groups. Equal representation in each group from each stakeholder group (i.e., academia, industry, government, and professional associations) was ensured by random assignment before the workshop. To facilitate open and frank discussion, participants were advised that although they would be identified as a workshop participant, no statement would be attributed to any individual or organization in the workshop proceedings. The working groups first convened to identify challenges in aligning FA intake for women of childbearing age with recommendations to reduce NTD-affected pregnancies in low-risk women. Once these challenges were shared with the larger group and summarized into statements, participants were asked to individually prioritize what they thought were the 5 most important challenges by placing a sticker on ≤5 of the summary statements posted around the room. The smaller working groups were then asked to reconvene to develop potential solutions to the top 5 challenges, which were then shared with the larger group. The last session consisted of a full group discussion focusing on prioritization of the solutions. The top 5 challenges and the proposed solutions are detailed in **Table 3**.

The challenges and solutions were interrelated and general themes emerged. First, there was a perception that the gaps in the literature on the effective FA supplement dose and duration for NTD prevention inherently resulted in different guidelines. Different guidelines have led to confusion among health care professionals and consumers. Second, a prenatal supplement containing the recommended amount of FA for low-risk women is not generally available in the marketplace, hindering health care professionals and women from adhering to the recommendations. Third, there remain barriers in Canada for some women, particularly vulnerable women, in accessing FA-containing supplements and family planning services. Fourth, there was a low level of awareness, even among workshop participants, of the harmonization of the SOGC guideline for women at low NTD risk with that of Health Canada at 400 μg FA in 2015 (31). The SOGC guideline remains a preferred resource among health care professionals, but lack of free access to the guideline constitutes a barrier to its active implementation more broadly by other stakeholders. Finally, when it comes to vitamin and mineral supplements, there seems to be a "more is better" attitude and a low level of awareness that FA intake in high

TABLE 2
Pregnancy and birth health outcomes associated with FA intake[1]

Outcomes, specific outcomes	Study type	FA dose	Timing of FA supplementation	Direction of effect	Ref.
Birth outcomes					
BW, LBW, SGA, preterm	Cochrane review	• No FA • FA supplements (with or without other micronutrients)	• During pregnancy (studies with periconceptional FA supplementation excluded)	No association of FA supplementation with BW or with risk of preterm birth, stillbirths/neonatal deaths, or LBW	(63)
SGA	Meta-analysis, systematic review	• No FA (15% of women) • FA taken (85%) in dosages of either: 400 μg/d (95.5%), 5000 μg/d (3.5%), or other dosage (1%)	• Preconceptional (25.5%) • Postconceptional (74.5%)	Reduced risk of SGA if supplemented preconceptionally SGA <10th centile (adjusted OR: 0.80; 95% CI: 0.71, 0.90; $P < 0.01$) SGA <5th centile (adjusted OR: 0.78; 95% CI: 0.66, 0.91; $P < 0.01$).	(64)
LBW (BW <5th centile)	Meta-analysis, systematic review	• No FA (15% of women) • FA taken (85%) in dosages of either: 400 μg/d (95.5%), 5000 μg/d (3.5%), or other dosage (1%)	• Preconceptional (25.5%) • Postconceptional (74.5%)	Preconception low-dose FA supplement: LBW adjusted OR: 0.75; 95% CI: 0.61, 0.92; $P = 0.006$ Postconception: not significant	(64)
SGA for height, SGA for weight	Population-based multicenter cohort study	• No FA use • FA use ≤1000 μg/d • FA use >1000 μg/d	• Periconceptional (≥1 mo of FA use between 3-mo preconception and end of first trimester)	Increased risk of SGA for height for women with FA use >1000 μg/d	(65)
Embryonic growth	Prospective cohort study	• No FA use • FA use 400 μg/d	• Periconceptional • Postconceptional	No or postconceptional FA use negatively associated with crown-rump-length and embryonic volume	(66)
LBW, SGA	Prospective cohort study	• No FA use • FA use 400 μg/d	• Periconceptional • Preconceptional • Postconceptional	Periconceptional FA intake (until end of first trimester) associated with 20% lower risk of LBW and 10% lower SGA risk	(67)
SGA, LGA	Prospective cohort study	400 μg/d	• Periconceptional only • Periconceptional + second trimester • Periconceptional + third trimester • Periconceptional + second + third trimesters	FA supplement use beyond first trimester (group of periconceptional + second + third trimester FA use) associated with increased risk of LGA compared with FA supplement in periconceptional time only; RR: 1.87; 95% CI: 1.21, 2.87	(68)
Childhood disease outcomes—asthma and allergic diseases					
Asthma	Meta-analysis, systematic review	• No FA use • FA use	• Periconceptional or first trimester • Second + third trimesters • Any trimester/throughout pregnancy	No association between first trimester FA use and risk of asthma; conflicting results for second and third trimester FA use and asthma	(69)
Asthma and allergic disease	Review including 10 prospective cohort studies	Different doses	• Periconceptional • Preconceptional • Postconceptional	Majority of studies support no association of maternal FA intake and development of childhood asthma and allergy; limited evidence on dose-response relation between FA and risk of asthma or allergic diseases	(70)
Asthma, wheezing, dermatitis—allergic diseases	Prospective cohort study	Median (ranges) of FA: • early pregnancy 700 μg/d (43–5500 μg/d) • late pregnancy 300 μg/d (27–5895 μg/d)	• Early pregnancy (<16 weeks of gestation) • Late pregnancy (30–34 weeks of gestation)	FA use in late pregnancy associated with 26% increased risk of asthma at 3.5 y of age, but not at 5.5 y of age; pre- and periconceptional FA use not associated with asthma risk	(71)
Wheeze, asthma, atopic dermatitis, eczema, allergic sensitization	Prospective cohort study	• No FA use • FA use	• Periconceptional/first trimester • Throughout pregnancy • Others (e.g., third trimester only)	No association between FA use during pregnancy and increased risk of developing eczema, atopic dermatitis, allergic sensitization, wheeze, or asthma	(72)
Childhood disease outcomes—autism					
Autism/ASD/ neurodevelopment	Systematic review (22 studies)	Different doses	• Periconceptional • Preconceptional • Postconceptional	Fifteen studies showed beneficial effect, 6 studies reported no significant findings, 1 prospective cohort study reported increased risk of delayed psychomotor development in 7-y-old children of mothers who took >5000 μg/d FA during pregnancy	(73)

(*Continued*)

TABLE 2
(*Continued*)

Outcomes, specific outcomes	Study type	FA dose	Timing of FA supplementation	Direction of effect	Ref.
ASD	Case-control study	• FA use (400 μg/d) • Multivitamin use • FA and/or multivitamin use (with FA 400 μg/d)	• Before pregnancy (i.e., 540–271 d before birth) • During pregnancy (i.e., 270 d before birth up to date of childbirth)	Lower risk of ASD in children of mothers exposed to FA and/or multivitamin supplements before and/or during pregnancy (adjusted RR: 0.27–0.56); no significant risk reduction in offspring of parents with psychiatric condition; no risk reduction if women took vitamin supplements before pregnancy for treatment of vitamin deficiency	(74)
ASD	Case-control study	• No FA (28% of women) • FA 400 μg/d (72%)	• Periconceptional (4 wk before to 8 wk after conception)	Reduced risk of ASD (adjusted OR: 0.61; 95% CI: 0.41, 0.90) in children (mean age 6.4 y) of mothers with periconceptional FA	(75)
ASD	Case-control study	Total FA intake summed based on data including dose, brand, frequency of supplement, and fortified food intake	• 3 mo before pregnancy and throughout each month of pregnancy	Lower risk (OR: 0.62; 95% CI: 0.42, 0.92) of ASD in children of women who took ≥600 μg/d compared with <600 μg/d in first month of pregnancy; decreasing OR with increasing FA intake (0, ≤500, 500–<800, 800–1000, >1000 μg/d)	(76)
Childhood disease outcomes—metabolism, insulin resistance, and obesity					
Obesity/insulin resistance (HOMA-IR)	Systematic review (5 human and 9 animal studies)	In human studies/RCTs: • No FA use • FA 400 μg/d Folate status in observational studies	During pregnancy	Inconsistent findings; animal studies showed overall protective effect of FA on obesity + insulin resistance; human studies reported decreased risk of metabolic syndrome, and higher HOMA-IR with FA supplementation, and no or a positive association between late-pregnancy maternal folate status and HOMA-IR	(77)
HOMA-IR	Cluster RCT	• No FA • FA 400 μg/d • FA 400 μg/d + iron • FA 400 μg/d + iron + zinc • FA 400 μg/d in multimicronutrient supplement	Start of supplementation in early pregnancy	No association between maternal plasma folate concentration and HOMA-IR in 6- to 8-y-old children	(78)
HOMA-IR	Prospective cohort study	500 μg/d	Start of supplementation at 18 weeks of gestation	Higher maternal folate status predicted higher adiposity (fat mass and body fat percentage) and insulin resistance (HOMA-IR) in 6-y-old children; highest HOMA-IR if mothers had high folate and low vitamin B-12 status	(79)
Body composition	Population-based birth cohort study	• No FA use • FA use	During pregnancy: 18 and 32 weeks of gestation	No association between maternal FA supplementation during pregnancy and body composition in 9-y-old children	(80)

[1]ASD, autism spectrum disorder; BW, birthweight; FA, folic acid; LBW, low birthweight; LGA, large-for-gestational-age; RCT, randomized controlled trial; Ref., reference; SGA, small-for-gestational-age.

amounts may not have any added benefit and might even cause harm.

A number of research priorities and activities to facilitate the proposed solutions are described in **Table 4**. At a high level, solutions focused on strategies to increase awareness of the SOGC and Health Canada harmonized guidelines for FA and NTD prevention among low-risk women for both health care professionals and consumers. A refreshed public health campaign was proposed that would use innovative marketing strategies (e.g., front-of-package messaging on or coupons in sanitary products) and online social media targeting all women of childbearing age, not just those planning a pregnancy.

Based on the discussions, workshop participants felt that if health care professionals are going to advise women to take a multivitamin supplement containing 400 μg/d of FA, one will need to be made widely available. Further, ownership by all stakeholders and not deflection of responsibility will be required to move this forward. There was a general appreciation amongst workshop participants that education regarding FA recommendations for the prevention of NTDs and availability of the supplement need to occur in concert, and industry would

TABLE 3
Top 5 challenges and potential solutions identified by workshop participants in aligning FA intake among women with recommendations for primary prevention of NTDs[1]

Themes	Challenges	Solutions and potential implementation strategies
Need for additional evidence on the effective dose and duration to prevent NTDs	Different groups have developed different guidelines, in part due to gaps in the knowledge about the minimally effective dose and duration of supplemental FA for NTD prevention. Gaps are due to the following: - Evidence used for setting initial recommendations was derived from RCTs and observational studies that used the dose of FA in supplements commercially available at the time. - Because FA was traditionally given in a prenatal supplement combined with iron to prevent pregnancy-related anemia, FA was consumed for the entire pregnancy, which has influenced guidelines in regards to the duration of supplement use. - The foundational RCT studies included women not consuming FA-fortified foods, so baseline folate status was likely different than that of the current Canadian and US populations. - The foundational RCT studies supplemented with FA up to 12 wk only, so there is lack of evidence for additional health benefits of FA supplement intake beyond the first trimester. - National surveys show that ~20% of Canadian women of childbearing age do not have RBC folate values that provide maximal reduction of NTD risk (e.g., <906 nmol/L). It is known that the majority of these women are likely not supplement users and may benefit from supplement use, not necessarily a higher FA dose. These women need to be identified and characterized. - Aboriginal and immigrant pregnant women are underrepresented in Canadian studies. - Pregnant women living in remote areas (North or rural) have poor access to fresh fruit and vegetables (i.e., high cost, low availability) and FA-containing supplements. - Women at moderate risk of an NTD-affected pregnancy are ill-defined. - Because of the use of different study designs, each with its own limitations, and the lack of harmonization among analytic folate methods used to assess status across studies, it has proven difficult to consistently integrate and interpret data.	- Commitment from professional groups to have harmonized guidelines based on the best available evidence. - Harmonization of definitions of women at low, moderate, and high risk of an NTD-affected pregnancy. - Recommendations that do not fully align with the available evidence should be acknowledged in guidelines to ensure that recommendations based on judgment are differentiated from those based on a high(er) level of evidence. For example, it is recommended that prenatal supplements containing FA be consumed throughout pregnancy even though FA is required for the neural tube closure in the first trimester.
Supplement content inconsistent with recommendations	Despite the 2015 SOGC and Health Canada/Public Health Agency of Canada aligning their FA recommendations, it can be difficult for women to purchase supplements with the recommended doses due to the following: - Lack of availability of prenatal supplements containing the recommended 400 μg FA. - Health care providers prescribe a 1000-μg prenatal supplement because that is what is generally available in the marketplace, and they are hesitant to recommend something that is not available. - Insurance companies reimburse for prescribed supplements only, so women consume what their health care provider prescribes. - Individual supplement companies are reluctant to reduce the FA dose in their prenatal supplements because it may put them at a competitive disadvantage if they are not comparable with other products. - The 2015 SOGC guidelines maintain a dose range (400–1000 μg) for moderate-risk women so supplement companies are producing products that, in part, still meet the current guidelines. - Reformulation of a supplement is a significant undertaking for industry with associated costs; Canada is a smaller market.	- Education of both health care professionals and consumers on harmonized recommendations of FA to increase demand for products with the recommended dose. These efforts could benefit from the inclusion of women of childbearing age in the development of knowledge translation initiatives. - Reformulation should be encouraged industry-wide to mitigate risk to companies who are the first to align dose with recommendations. - Industry could take a stepwise approach to reformulation to allow sufficient time to transition prenatal vitamins to contain 400 μg FA. - Develop a multivitamin/mineral monograph specific for prenatal supplements that aligns the allowable FA content with the recommended dose of FA. Other nutrients of concern regarding pregnancy would also be included. - Change the maximum allowable over-the-counter dose of FA in supplements to 400 μg, resulting in doses ≥400 μg being available by prescription only. - Allow a label content claim on prenatal supplements indicating that the product contains the recommended dose of FA for NTD risk reduction.

(*Continued*)

TABLE 3
(*Continued*)

Themes	Challenges	Solutions and potential implementation strategies
	- There is a perception among stakeholders that responsibility for supplement formulation belongs to another stakeholder, resulting in inaction regarding reformulation (e.g., industry is reluctant to initiate reformulation in the absence of regulatory requirement changes; health care professionals are unlikely to prescribe a dose that is not already available on the market). - There is some concern that women who have low supplement-use compliance will not benefit from supplement formulations with lower doses.	
Facilitating access to FA-containing supplement during periconception	Despite recommendations to consume an FA-containing supplement in the periconceptional period, many women do not consume the recommended dose (or supplements at all) because they have limited access to them. This can be due to the following: - Cost and access of prenatal supplements for women are variable across municipalities, regions, and provinces, especially for those living in poverty, who are food insecure, or living in remote locations. - Access to health care and family planning is uneven in Canada. - About half of pregnancies in Canada are estimated to be unplanned.	- FA-containing prenatal supplements (recommended dose) and contraception should be made available to all women (e.g., free of charge to those unable to purchase). - Clinicians and policymakers should develop an increased awareness of the social determinants of health that may influence the risk of an unplanned pregnancy, the ability to access FA-containing supplements, and the ability to adhere to FA recommendations.
Knowledge transfer	Whereas many health care professionals are aware of the FA recommendations, many others remain unaware, resulting in lost opportunities for ensuring that women consume the recommended amount of FA. Also, many women themselves are not aware of the recommendations. - The SOGC guidelines are the preferred source of information regarding FA for most health care professionals, but the guidelines are not accessible to everyone (e.g., need to pay for access to guidelines if not a member of SOGC). - There is a lower level of awareness of the new 2015 SOGC guidelines among medical subspecialists (e.g., family physicians, reproductive endocrinologists). - Many women of childbearing age are not aware of the recommendations for FA supplement use during pregnancy. - Vulnerable women such as those who are younger, are of certain ethnicities, or who have lower levels of education/socioeconomic status may be at the highest risk of lower folate status, due in part to food insecurity and low prevalence of supplement intake, and are also the least likely to be aware of FA recommendations.	- More education of the public and health care professionals regarding the recommended FA intake is needed. This could be facilitated by making guidelines more widely available and engaging stakeholders, including consumers, in the development of knowledge transfer activities. - A refreshed public health campaign on FA recommendations should adopt innovative marketing strategies (e.g., front-of-package messaging or coupons on sanitary products; shelf information at the point of purchase) and online social media that target all women of childbearing age, not just those planning a pregnancy. - FA recommendations could be packaged within an overall strategy targeting women about a healthy lifestyle and family planning. - Anticipatory guidance on FA and NTD, family planning, etc., should be routinely provided to all women of childbearing age at "well woman" visits (e.g., preventive care visits; pap exams). - More education of the public and health care professionals regarding the recommended FA intake is needed. This could be facilitated by making the guidelines more widely available and including them in sex education classes in public school and in the curriculum of health care professionals. - Engage with health care professional bodies to promote the recommendations, including those for alternative and complementary medicine providers. - Engage with the Canadian Prenatal Nutrition Program and those on the front lines delivering prenatal support to vulnerable women. Revisit preconception care guidelines to ensure they are aligned and up to date. - Harmonization of definitions of women at low, moderate, and high risk of an NTD-affected pregnancy to facilitate health care professionals in recommending appropriate FA doses to women.
"More is better" attitude	Decades ago, micronutrient deficiencies were common in Canada, and the emphasis had been on ensuring nutrient adequacy in the population. However, this "more is better" attitude persists. - There is a low level of awareness that supplemental vitamin and mineral intake in high amounts may not provide additional benefit and might even cause harm.	- Messaging that "more is *not* always better" in terms of use of vitamin and mineral supplements could be incorporated into knowledge transfer solutions identified above. - It is important that messages should be positive without scaring women; the concept that 400 μg is *sufficient* should be emphasized. - Take the opportunity to have pharmacists serve as "gatekeepers" regarding the appropriate FA dose for low-risk women.

[1]FA, folic acid; NTD, neural tube defect; RBC, red blood cell; RCT, randomized controlled trial; SOGC, Society of Obstetricians and Gynaecologists of Canada.

TABLE 4
Research priorities and other activities to facilitate solutions[1]

Use existing cohorts or nationally representative survey data to:
- Identify the determinants of lower RBC folate status (<906 nmol/L) (e.g., not capable of becoming pregnant, do not consume FA-fortified foods, social/societal barriers to accessing FA supplements, living in remote communities, etc.).
- Identify the determinants of access to and use of prenatal supplements.
- Identify the prevalence of low, moderate, and high-risk women.
- Characterize the determinants of maternal FA intake.
- Investigate other pregnancy outcomes, other than NTDs, associated with maternal FA intake.
- Monitor FA intake and blood folate status of reproductive-aged women in Canada before and after reformulation of supplements.
- Consider other nutrients implicated in NTD risk—e.g., vitamin B-12 (currently in prenatal supplements) and choline (not in prenatal supplements)—and their potential interaction with FA intake. Additional research regarding the adequacy of maternal intake of these vitamins and health outcomes should be encouraged.
Evidence review to address whether there would be unintended consequences of lowering the commonly consumed supplement dose from 1000 μg FA to 400 μg
- e.g., would incidence of other folate-sensitive congenital anomalies change?
Studies of blood folate analytic methods including standard reference material to facilitate comparison across studies and populations
- e.g., using reference material from the National Institute of Standards and Technology.
Analysis of marketing methods to better understand how to reach women before conception
- Focus especially on those not following the FA recommendations to provide strategies to conduct targeted research projects and awareness campaigns.
Improve knowledge transfer and enhance education strategies for both health care professionals and the general public
- Perform a scoping review of knowledge and awareness of the 2015 SOGC recommendations (identify who knows about them and what they know).
- Develop education campaigns in collaboration with pharmacist associations in Canada and support pharmacies' ability to transfer knowledge to women by providing accurate shelf information on FA recommendations.
- Modify medical, nursing, and allied health undergraduate curricula to include the importance of the recommended supplemental FA intake before and during pregnancy.
- Integrate notions of nutrition, biology, and human health in secondary school curricula (e.g., knowledge of FA and NTDs in sex education courses).

[1]FA, folic acid; NTD, neural tube defect; RBC, red blood cell; SOGC, Society of Obstetricians and Gynaecologists of Canada.

require time to make the change. Finally, although the best available evidence in Canada suggests that 80% of women have blood values that are maximally protective against an NTD (12), very little is known about the remaining 20% in terms of who they are and whether they are capable of becoming pregnant, or have access to prenatal supplements and family planning services. An improved understanding of this group of women and how to reach them was identified as a key research priority.

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REFERENCES

1. Institute of Medicine (US). Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington (DC): National Academy of Sciences; 1998.
2. Xu J, Sinclair KD. One-carbon metabolism and epigenetic regulation of embryo development. Reprod Fertil Dev 2015;27(4):667–76.
3. Health Canada. Prenatal nutrition guidelines for health professionals: folate[Internet]. Ottawa, Canada: Government of Canada; 2009. p. 1–8. Report No.: H164–109/2–2009E-PDF. Available from: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/pubs/folate-eng.pdf.
4. World Health Organization. Periconceptional folic acid supplementation to prevent neural tube defects [Internet]. Geneva, Switzerland: WHO—e-Library of Evidence for Nutrition Actions (eLENA); 2017[cited 2018 Jun 19]. Available from: http://www.who.int/elena/titles/folate_periconceptional/en/.
5. Centers for Disease Control (CDC). Use of folic acid for prevention of spina bifida and other neural tube defects—1983–1991. MMWR Morb Mortal Wkly Rep 1991;40(30):513–16.
6. Health Canada. Summary report: national workshop on the primary prevention of neural tube defects. Ottawa, Canada: Government of Canada; 1995.
7. SOGC Genetics Committee. Policy statement: recommendations on the use of FA for the prevention of neural tube defects. J Soc Obstet Gynaecol Can 1993;15:41–6.
8. Health Canada. Licensed Natural Health Products Database (LNHPD) [Internet]. Ottawa, Canada: Government of Canada; 2015, [cited 2018 Jun 19]. http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/lnhpd-bdpsnh-eng.php.
9. Plumptre L, Masih SP, Ly A, Aufreiter S, Sohn K-J, Croxford R, Lausman AY, Berger H, O'Connor DL, Kim YI. High concentrations of folate and unmetabolized folic acid in a cohort of pregnant Canadian women and umbilical cord blood. Am J Clin Nutr 2015;102(4):848–57.
10. Fayyaz F, Wang F, Jacobs RL, O'Connor DL, Bell RC, Field CJ, APrON Study Team. Folate, vitamin B12, and vitamin B6 status of a group of high socioeconomic status women in the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort. Appl Physiol Nutr Metab 2014;39(12):1402–8.
11. Colapinto CK, O'Connor DL, Dubois L, Tremblay MS. Folic acid supplement use is the most significant predictor of folate concentrations in Canadian women of childbearing age. Appl Physiol Nutr Metab 2012;37(2):284–92.
12. Colapinto CK, O'Connor DL, Tremblay MS. Folate status of the population in the Canadian Health Measures Survey. Can Med Assoc J 2011;183(2):E100–6.
13. Furness D, Fenech M, Dekker G, Khong TY, Roberts C, Hague W. Folate, vitamin B12, vitamin B6 and homocysteine: impact on pregnancy outcome. Matern Child Nutr 2013;9(2):155–66.
14. Fekete K, Berti C, Cetin I, Hermoso M, Koletzko BV, Decsi T. Perinatal folate supply: relevance in health outcome parameters. Matern Child Nutr 2010;6(Suppl 2):23–38.
15. Hoffbrand AV, Weir DG. The history of folic acid. Br J Haematol 2001;113(3):579–89.

16. Chanarin I. Historical review: a history of pernicious anaemia. Br J Haematol 2000;111(2):407–15.
17. Wintrobe M. Macrocytosis and macrocytic anemias. Philadelphia, PA: Lea & Febiger; 1974. p. 566–601.
18. The drug efficacy study. N Engl J Med 1969;280(21):1177–9.
19. US Food and Drug Administration (FDA). FA preparations, oral and parenteral for therapeutic use. 1971. p. 6843–4. Report No.: 36.
20. Hibbard E, Smithells R. Folic acid metabolism and human embryopathy. Lancet 1965;1:1254.
21. Grosse SD, Collins JS. Folic acid supplementation and neural tube defect recurrence prevention. Birth Defects Res A Clin Mol Teratol 2007;79(11):737–42.
22. Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 1992;327(26):1832–5.
23. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991;338(8760):131–7.
24. Health Canada. Canada Gazette Part II. Regulatory impact analysis statement. Ottawa, Canada: Bureau of Food Regulatory Affairs; 1998. p. 3029–33. Report No.: SOR/98-550.
25. Food and Drug Administration (FDA). Food standards: amendment of standards of identity for enriched grain products to require addition of folic acid[Internet]. Washington (DC): Department of Health and Human Services; 1996. p. 8781–97. Report No.: 61. Available from: www.gpo.gov/fdsys/pkg/FR-1996-08-05/pdf/96-19803.pdf.
26. Laurence KM, Campbell H. Trial of folate treatment to prevent recurrence of neural tube defect. Br Med J Clin Res Ed 1981;282(6282):2131.
27. Berry RJ, Li Z, Erickson JD, Li S, Moore CA, Wang H, Mulinare J, Zhao P, Wong LY, Gindler J, et al. Prevention of neural-tube defects with folic acid in China. China-U.S. collaborative project for neural tube defect prevention. N Engl J Med 1999;341(20):1485–90.
28. World Health Organization. Serum and red blood cell folate concentrations for assessing folate status in populations[Internet]. Geneva, Switzerland: WHO; 2012. Report No.: WHO/NMH/NHD/EPG/12.1. Available from: http://apps.who.int/iris/bitstream/10665/75584/1/WHO_NMH_NHD_EPG_12.1_eng.pdf.
29. Centers for Disease Control (CDC). Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR Morb Mortal Wkly Rep 1992;41(RR-14):1–7.
30. Wilson RD, Genetics Committee. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can 2007;29(12):1003–13.
31. Wilson RD, Audibert F, Brock J-A, Carroll J, Cartier L, Gagnon A, Johnson JA, Langlois S, Murphy-Kaulbeck LGenetics Committee,, et al., Genetics Committee Pre-conception folic acid and multivitamin supplementation for the primary and secondary prevention of neural tube defects and other folic acid-sensitive congenital anomalies. J Obstet Gynaecol Can 2015;37(6):534–52.
32. Wilson RD, Davies G, Desilets V, Reid GJ, Summers A, Wyatt P, Young D, Genetics Committee and Executive and Council of the Society of Obstetricians and Gynaecologists of Canada. The use of folic acid for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can 2003;25(11):959–73.
33. Health Canada. Folic acid: the vitamin that helps protect against neural tube (birth) defects. Ottawa, Canada: Government of Canada; 1993.
34. Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. Folate levels and neural tube defects. Implications for prevention. JAMA 1995;274(21):1698–702.
35. World Health Organization. Guideline: optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects [Internet]. Geneva, Switzerland: WHO Press; 2015 [cited 2018 Jun 19]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK294192/.
36. Crider KS, Devine O, Hao L, Dowling NF, Li S, Molloy AM, Li Z, Zhu J, Berry RJ. Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. BMJ 2014;349:g4554.
37. Crider KS, Qi YP, Devine O, Tinker SC, Berry RJ. Modeling the impact of folic acid fortification and supplementation on red blood cell folate concentrations and predicted neural tube defect risk in the United States: have we reached optimal prevention? Am J Clin Nutr 2018;107(6):1027–34.
38. McCourt C. Primary prevention of neural tube defects: notice from the HPB. CMAJ 1993;148(9):1451.
39. Health Canada. Folic acid and neural tube defects [Internet]. Ottawa, Canada: Government of Canada; 2018. Available from: https://www.canada.ca/en/public-health/services/pregnancy/folic-acid.html.
40. Van Allen MI, McCourt C, Lee NS. Preconception health: folic acid for the primary prevention of neural tube defects. A resource document for health professionals. Ottawa, Canada: Minister of Public Works and Government Services; 2002. Report No.: H39-607/2002E.
41. Health Canada. Nutrition for a healthy pregnancy: national guidelines for the childbearing years[Internet]. Ottawa, Canada: Government of Canada; 1999. Report No.: H39-459/1999E. Available from: http://publications.gc.ca/site/eng/80452/publication.html.
42. Health Canada. High dose folic acid supplementation - questions and answers for health professionals[Internet]. 2010. Available from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/prenatal-nutrition/high-dose-folic-acid-supplementation.html.
43. Nutrition Canada. Nutrition: a national survey, Ottawa, Ontario, Canada. Bureau of Nutritional Sciences, Health Protection Branch, Department of National Health and Welfare; 1973.
44. Nutrition Committee of the Canadian Paediatric Society. The Nutrition Canada Survey: a review. CMAJ 1976;115(8):775–7.
45. Dolega-Cieszkowski JH, Bobyn JP, Whiting SJ. Dietary intakes of Canadians in the 1990s using population-weighted data derived from the provincial nutrition surveys. Appl Physiol Nutr Metab 2006;31(6):753–8.
46. Green TJ, Allen OB, O'Connor DL. A three-day weighed food record and a semiquantitative food-frequency questionnaire are valid measures for assessing the folate and vitamin B-12 intakes of women aged 16 to 19 years. J Nutr 1998;128(10):1665–71.
47. Keizer SE, Gibson RS, O'Connor DL. Postpartum folic acid supplementation of adolescents: impact on maternal folate and zinc status and milk composition. Am J Clin Nutr 1995;62(2):377–84.
48. De Wals P, Tairou F, Van Allen MI, Uh S-H, Lowry RB, Sibbald B, Evans JA, Van den Hof MC, Zimmer P, Crowley M, et al. Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med 2007;357(2):135–42.
49. Sherwood KL, Houghton LA, Tarasuk V, O'Connor DL. One-third of pregnant and lactating women may not be meeting their folate requirements from diet alone based on mandated levels of folic acid fortification. J Nutr 2006;136(11):2820–6.
50. Masih SP, Plumptre L, Ly A, Berger H, Lausman AY, Croxford R, Kim YI, O'Connor DL. Pregnant Canadian women achieve recommended intakes of one-carbon nutrients through prenatal supplementation but the supplement composition, including choline, requires reconsideration. J Nutr 2015;145(8):1824–34.
51. Shakur YA, Garriguet D, Corey P, O'Connor DL. Folic acid fortification above mandated levels results in a low prevalence of folate inadequacy among Canadians. Am J Clin Nutr 2010;92(4):818–25.
52. Chalmers B, Dzakpasu S, Heaman M, Kaczorowski J. The Canadian Maternity Experiences Survey: an overview of findings. J Obstet Gynaecol Can 2008;30(3):217–28.
53. Gomez MF, Field CJ, Olstad DL, Loehr S, Ramage S, McCargar LJ, APrON Study Team. Use of micronutrient supplements among pregnant women in Alberta: results from the Alberta Pregnancy Outcomes and Nutrition (APrON) cohort. Matern Child Nutr 2013;11(4):497–510.
54. Colapinto CK, O'Connor DL, Dubois L, Tremblay MS. Prevalence and correlates of high red blood cell folate concentrations in the Canadian population using 3 proposed cut-offs. Appl Physiol Nutr Metab 2015;40(10):1025–30.
55. Ciappio ED, Mason JB, Crott JW. Maternal one-carbon nutrient intake and cancer risk in offspring. Nutr Rev 2011;69(10):561–71.
56. Sie KKY, Medline A, van Weel J, Sohn K-J, Choi S-W, Croxford R, Kim YI. Effect of maternal and postweaning folic acid supplementation on colorectal cancer risk in the offspring. Gut 2011;60(12):1687–94.
57. Ly A, Lee H, Chen J, Sie KKY, Renlund R, Medline A, Sohn KJ, Croxford R, Thompson LU, Kim YI. Effect of maternal and postweaning folic acid supplementation on mammary tumor risk in the offspring. Cancer Res 2011;71(3):988–97.

58. Tu H, Dinney CP, Ye Y, Grossman HB, Lerner SP, Wu X. Is folic acid safe for non-muscle-invasive bladder cancer patients? An evidence-based cohort study. Am J Clin Nutr 2018;107(2):208–16.
59. Metayer C, Milne E, Dockerty JD, Clavel J, Pombo-de-Oliveira MS, Wesseling C, Spector LG, Schüz J, Petridou E, Ezzat S, et al. Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a Childhood Leukemia International Consortium study. Epidemiology 2014;25(6):811–22.
60. Milne E, de Klerk NH, van Bockxmeer F, Kees UR, Thompson JR, Baker D, Armstrong BK. Is there a folate-related gene-environment interaction in the etiology of childhood acute lymphoblastic leukemia? Int J Cancer 2006;119(1):229–32.
61. Field MS, Stover PJ. Safety of folic acid. Ann N Y Acad Sci 2018;1414(1):59–71.
62. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FA, Kemper AR, Krist AH, Kurth AE, Landefeld CS, et al. Folic acid supplementation for the prevention of neural tube defects: US preventive services task force recommendation statement. JAMA 2017;317(2):183–9.
63. Lassi ZS, Salam RA, Haider BA, Bhutta ZA. Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. Cochrane Database Syst Rev 2013(3):CD006896.
64. Hodgetts VA, Morris RK, Francis A, Gardosi J, Ismail KM. Effectiveness of folic acid supplementation in pregnancy on reducing the risk of small-for-gestational age neonates: a population study, systematic review and meta-analysis. BJOG 2015;122(4): 478–90.
65. Pastor-Valero M, Navarrete-Muñoz EM, Rebagliato M, Iñiguez C, Murcia M, Marco A, Ballester F, Vioque J. Periconceptional folic acid supplementation and anthropometric measures at birth in a cohort of pregnant women in Valencia, Spain. Br J Nutr 2011;105(9): 1352–60.
66. Van Dijk MR, Borggreven NV, Willemsen SP, Koning AHJ, Steegers-Theunissen RPM, Koster MPH. Maternal lifestyle impairs embryonic growth: the Rotterdam periconception cohort. Reprod Sci 2018;25(6):916–22.
67. Li N, Li Z, Ye R, Liu J, Ren A. Impact of periconceptional folic acid supplementation on low birth weight and small-for-gestational-age infants in China: a large prospective cohort study. J Pediatr 2017;187:105–10.
68. Wang S, Ge X, Zhu B, Xuan Y, Huang K, Rutayisire E, Mao L, Huang S, Yan S, Tao F. Maternal continuing folic acid supplementation after the first trimester of pregnancy increased the risk of large-for-gestational-age birth: a population-based birth cohort study. Nutrients 2016;8(8):E493.
69. Crider KS, Cordero AM, Qi YP, Mulinare J, Dowling NF, Berry RJ. Prenatal folic acid and risk of asthma in children: a systematic review and meta-analysis. Am J Clin Nutr 2013;98(5):1272–81.
70. Brown SB, Reeves KW, Bertone-Johnson ER. Maternal folate exposure in pregnancy and childhood asthma and allergy: a systematic review. Nutr Rev 2014;72(1):55–64.
71. Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. Am J Epidemiol 2009;170(12):1486–93.
72. Magdelijns FJH, Mommers M, Penders J, Smits L, Thijs C. Folic acid use in pregnancy and the development of atopy, asthma, and lung function in childhood. Pediatrics 2011;128(1):e135–44.
73. Gao Y, Sheng C, Xie R-H, Sun W, Asztalos E, Moddemann D, Zwaigenbaum L, Walker M, Wen SW. New perspective on impact of folic acid supplementation during pregnancy on neurodevelopment/autism in the offspring children – a systematic review. PloS One 2016;11(11):e0165626.
74. Levine SZ, Kodesh A, Viktorin A, Smith L, Uher R, Reichenberg A, Sandin S. Association of maternal use of folic acid and multivitamin supplements in the periods before and during pregnancy with the risk of autism spectrum disorder in offspring. JAMA Psychiatry 2018;75(2):176–84.
75. Surén P, Roth C, Bresnahan M, Haugen M, Hornig M, Hirtz D, Lie KK, Lipkin WI, Magnus P, Reichborn-Kjennerud T, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA 2013;309(6):570–7.
76. Schmidt RJ, Tancredi DJ, Ozonoff S, Hansen RL, Hartiala J, Allayee H, Schmidt LC, Tassone F, Hertz-Picciotto I. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr 2012;96(1):80–9.
77. Xie R-H, Liu Y-J, Retnakaran R, MacFarlane AJ, Hamilton J, Smith G, Walker MC, Wen SW. Maternal folate status and obesity/insulin resistance in the offspring: a systematic review. Int J Obes 2016;40(1):1–9.
78. Stewart CP, Christian P, Schulze KJ, Arguello M, LeClerq SC, Khatry SK, West KP, Jr. Low maternal vitamin B-12 status is associated with offspring insulin resistance regardless of antenatal micronutrient supplementation in rural Nepal. J Nutr 2011;141(10):1912–17.
79. Yajnik CS, Deshpande SS, Jackson AA, Refsum H, Rao S, Fisher DJ, Bhat DS, Naik SS, Coyaji KJ, Joglekar CV, et al. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia 2008;51(1):29–38.
80. Lewis SJ, Leary S, Davey Smith G, Ness A. Body composition at age 9 years, maternal folate intake during pregnancy and methyltetrahydrofolate reductase (MTHFR) C677T genotype. Br J Nutr 2009;102(4):493–6.
81. Grandjean P. Implications of the precautionary principle for primary prevention and research. Annu Rev Public Health 2004;25:199–223.