Table 1S. Reports of potentially beneficial effects of folic acid fortification

Title	Type of study	Abstract	Comment	Reference
Folic acid and placental pathology	Retrospective population study	Prevalence of placental abruption and/or infarct did not change after fortification in Canada	Compare (Table 3) Norwegian population study on supplement use Nilsen (2008) Am J Epidemiol 167: 867-74	McDonald (2005) Epidemiology 16: 419-20
Improvement in stroke mortality in Canada and the United States, 1990 to 2002	Observational population study	BACKGROUND: In the United States and Canada, folic acid fortification of enriched grain products was fully implemented by 1998. The resulting population-wide reduction in blood homocysteine concentrations might be expected to reduce stroke mortality if high homocysteine levels are an independent risk factor for stroke. METHODS AND RESULTS: In this population-based cohort study with quasi-experimental intervention, we used segmented log-linear regression to evaluate trends in stroke-related mortality before and after folic acid fortification in the United States and Canada and, as a comparison, during the same period in England and Wales, where fortification is not required. Average blood folate concentrations increased and homocysteine concentrations decreased in the United States after fortification. The ongoing decline in stroke mortality observed in the United States between 1990 and 1997 accelerated in 1998 to 2002 in nearly all population strata, with an overall change from -0.3% (95% CI, -0.7 to 0.08) to -2.9 (95% CI, -3.5 to -2.3) per year (P=0.0005). Sensitivity analyses indicate that changes in other major recognized risk factors are unlikely to account for the reduced number of stroke-related deaths in the United States. The fall in stroke mortality in Canada averaged -1.0% (95% CI, -1.4 to -0.6) per year from 1990 to 1997 and accelerated to -5.4% (95% CI, -6.0 to -4.7) per year in 1998 to 2002 (P< or =0.0001). In contrast, the decline in stroke mortality in England and Wales did not change significantly between 1990 and 2002. CONCLUSIONS: The improvement in stroke mortality observed after folic acid fortification in the United States and Canada but not in England and Wales is consistent with the hypothesis that folic acid fortification helps to reduce deaths from stroke.	Important report showing faster decline in deaths from stroke after fortification in USA and Canada	Yang (2006) Circulation 113: 1335-43
Reduction in neural-tube defects after folic acid fortification in Canada	Observational population study	BACKGROUND: In 1998, folic acid fortification of a large variety of cereal products became mandatory in Canada, a country where the prevalence of neural-tube defects was historically higher in the eastern provinces than in the western provinces. We assessed changes in the prevalence of neural-tube defects in Canada before and after food fortification with folic acid was implemented. METHODS: The study population included live births, stillbirths, and terminations of pregnancies because of fetal anomalies	Important finding that effect of fortification was greater the higher the prevalence of NTD	De Wals (2007) N Engl J Med 357: 135-42

		among women residing in seven Canadian provinces from 1993 to 2002. On the basis of published results of testing of red-cell folate levels, the study period was divided into prefortification, partial-fortification, and full-fortification periods. We evaluated the relationship between baseline rates of neural-tube defects in each province and the magnitude of the decrease after fortification was implemented. RESULTS: A total of 2446 subjects with neural-tube defects were recorded among 1.9 million births. The prevalence of neural-tube defects decreased from 1.58 per 1000 births before fortification to 0.86 per 1000 births during the full-fortification period, a 46% reduction (95% confidence interval, 40 to 51). The magnitude of the decrease was proportional to the prefortification baseline rate in each province, and geographical differences almost disappeared after fortification began. The observed reduction in rate was greater for spina bifida (a decrease of 53%) than for anencephaly and encephalocele (decreases of 38% and 31%, respectively). CONCLUSIONS: Food fortification with folic acid was associated with a significant reduction in the rate of neural-tube defects in Canada. The decrease was greatest in areas in which the baseline rate was high.		
Folate and neural tube defects	Review	A protective effect of folate against the development of neural tube defects (NTDs), specifically, anencephaly and spina bifida, is now well recognized, having been established by a chain of clinical research studies over the past half century. This article summarizes the more important of these studies, which have led to the current situation in which all women capable of becoming pregnant are urged to ingest folic acid regularly. The recommended intakes are 4 mg/d for those at high risk (by virtue of a previous NTD pregnancy outcome) and 0.4 mg/d for all others. However, a reduction in NTD births did not follow promulgation of these recommendations, and so folic acid fortification was mandated in the United States and some other countries. Although some controversy remains about the adequacy of fortification levels, the process was followed by significant improvement in folate indexes and a reduction of 25-30% in NTD frequency (about one-half of the proportion of cases assumed to be responsive to folate). The folate-NTD relation represents the only instance in which a congenital malformation can be prevented simply and consistently. Nevertheless, several research gaps remain: identification of the mechanism by which the defect occurs and how folate ameliorates it; characterization of the relative efficacy of food folate, folic acid added to foods, and folic acid by itself; delineation of the dose-response relations of folate and NTD prevention; and more precise quantification of the dose needed to prevent recurrences		Pitkin (2007) Am J Clin Nutr 85: 285S-288S
Reassessing folic acid consumption patterns in the United States (1999	Modelling based on population data	Background: In the United States, folic acid fortification of cereal- grain foods has significantly increased folate status. However, blood folate concentrations have decreased from their postfortification high as a result, in part, of decreasing food fortification concentrations and the popularity of low-	Did not cite Wald 2001!	Quinlivan (2007) Am J Clin Nutr 86:

2004): potential effect on neural tube defects and overexposure to folate		carbohydrate weight-loss diets. Objectives: The objectives of the study were to quantify changes in folate intake after folic acid fortification and to estimate the effect on neural tube defect (NTD) occurrence. Design: Expanding on an earlier model, we used data from 11 intervention studies to determine the relation between chronic folate intervention and changes in steady state serum folate concentrations. With serum folate data from the National Health and Nutrition Examination Survey (NHANES), we used reverse prediction to calculate postfortification changes in daily folate equivalents (DFEs). With the use of NHANES red blood cell folate data and a published equation that related NTD risk to maternal red cell folate concentrations, we calculated NTD risk. Results: Folate intake decreased by (approx)130 microg DFE/d from its postfortification high, primarily as a result of changes seen in women with the highest folate status. This decrease in folate intake was predicted to increase the incidence of NTD by 47%, relative to a predicted 43% postfortification decrease. In addition, the number of women consuming >1 mg bioavailable folate/d decreased. Conclusions: Folate consumption by women of childbearing age in the United States has decreased. However, the decrease in those women with the lowest folate status was disproportionately small. Consequently, the effect on NTD risk should be less than would be seen if a uniform decrease in folate concentrations had occurred. These results reinforce the need to maintain monitoring of the way fortification is implemented.		1773-1779
Spina bifida before and after folic acid fortification	Population survey	BACKGROUND: In 1998, fortification of a large variety of cereal products with folic acid became mandatory in Canada. A multicentric study was carried out to assess the impact of this policy on the frequency of NTDs. The present analysis focused on spina bifida. METHODS: The study population included approximately 2 million livebirths, stillbirths, and terminations of pregnancies because of fetal anomalies among women residing in seven Canadian provinces, from 1993 to 2002. Spina bifida cases were divided according to the upper limit of the defect: upper (cranial, cervical, or thoracic) and lower (lumbar or sacral) defects. Based on published results of red blood cell folate tests, the study period was divided into prefortification, partial fortification, and full fortification periods. RESULTS: A total of 1,286 spina bifida cases were identified: 51% livebirths, 3% stillbirths, and 46% terminations. Prevalence decreased from 0.86/1,000 in the prefortification to 0.40 in the full fortification period, while the proportion of upper defects decreased from 32% to 13%. Following fortification, regional variations in the prevalence and distribution of sites almost disappeared. CONCLUSIONS: Results confirmed the etiologic heterogeneity of spina bifida and the more pronounced effect of folic acid in decreasing the risk of the more severe clinical presentations.	Regional differences were striking. Incidence (per 1000) were: East 1.68 down to 0.41; central 0.98 to 0.53; west 0.53 to 0.26.	De Wals (2008) Birth Defects Res A Clin Mol Teratol 82: 622-6
Trends in the postfortification	Observational, population	BACKGROUND: The prevalence of NTDs in the US declined significantly after mandatory folic acid fortification; however, it is not known if the prevalence of NTDs has continued to decrease in recent years relative to the		Boulet (2008) Birth Defects

prevalence of spina bifida and anencephaly in the United States		period immediately following the fortification mandate. METHODS: Population-based data from 21 birth defects surveillance systems were used to examine trends in the birth prevalence of spina bifida and anencephaly during 1999-2000, 2001-2002, and 2003-2004. Prevalence data were stratified by non-Hispanic White, non-Hispanic Black, and Hispanic race or ethnicity. Prevalence ratios were calculated by dividing the birth prevalences during the later time periods (2001-2002 and 2003-2004) by the birth prevalences during 1999-2000. RESULTS: During 1999-2004, 3,311 cases of spina bifida and 2,116 cases of anencephaly were reported. Hispanic infants had the highest prevalences of NTDs for all years. For all infants, the combined birth prevalences of spina bifida and anencephaly decreased 10% from the 1999-2000 period to the 2003-2004 period. The decline in spina bifida (3%) was not significant; however the decline in anencephaly (20%) was statistically significant. CONCLUSIONS: While the prevalences of spina bifida and anencephaly in the United States have declined since folic acid fortification in the food supply began, these data suggest that reductions in the prevalence of anencephaly continued during 2001-2004 and that racial and ethnic and other disparities remain.		Res A Clin Mol Teratol
NTD prevalences in central California before and after folic acid fortification	Observational, population	BACKGROUND: In many regions, NTD prevalences were already declining prior to folic acid fortification. This study examined whether the declining prefortification (1989-1996) NTD prevalences continued into the postfortification period (1998-2003) in selected California counties. METHODS: This population-based study used vital statistics data and birth defects registry data that were actively ascertained from medical records. The study population included all live births and stillbirths delivered in central California counties from 1989 to 2003. Cases included deliveries with NTDs during the same time period. RESULTS: For all NTDs combined, the slopes indicated that NTD prevalence was decreasing by 7.5 (slope: -7.5; 95% CI: -12.4, -2.5) cases per 100,000 deliveries per year before fortification, whereas NTD prevalence was no longer decreasing after fortification. Comparison of the difference in the two slopes indicated that the postfortification slope exceeded the prefortification slope by 12.6 (95% CI: 2.6, 22.6) cases per 100,000 deliveries per year. CONCLUSIONS: Annual NTD prevalences in central California did not continue to decrease after implementation of folic acid fortification.	Included pregnancy terminations	Chen (2008) Birth Defects Res A Clin Mol Teratol
Did national folic acid fortification reduce socioeconomic and racial disparities in folate status in the US?	Observational, population	BACKGROUND: The purpose of this study is to determine the impact of the 1998 US Food and Drug Administration folic acid fortification policy on disparities in folate status in the United States. METHODS: We use repeated cross-sectional data from the U.S. National Health and Nutrition Examination Surveys (NHANES), a nationally representative sample of over 14 000 participants ages 25 and older. We calculate pre-fortification (1991-94) and post-fortification (1999-2002) absolute differences and relative prevalence ratios of low red blood cell (RBC) folate status (<362.6 nmol), by race/ethnicity and income quartile. We also estimate kernel density plots and		Dowd (2008) Int J Epidemiol 37: 1059-1066

		relative and absolute concentration curves pre- and post-fortification. RESULTS: The excess prevalence of low RBC folate status associated with the lowest income quartile and black race declined by 67% and 48%, respectively, following fortification. Despite these absolute gains, the relative ratio of low folate status increased after fortification for the lowest compared with the highest income groups (from 1.27 to 2.08) and among whites compared with blacks (from 1.64 to 3.75). CONCLUSIONS: The effects of the fortification policy highlight the importance of distinguishing absolute from relative differences when evaluating interventions to reduce health disparities. Targeting of high risk populations is likely needed to eliminate remaining folate disparities.		
Changes in frequencies of select congenital anomalies since the onset of folic acid fortification in a Canadian birth defect registry	Observational, population	OBJECTIVES: Fortification of grain products with folic acid has been shown to significantly reduce the occurrence of neural tube defects (NTDs) in Canada and elsewhere. However, the impact on non-NTD anomalies has not been well studied. METHODS: Using the Alberta Congenital Anomalies Surveillance System (ACASS), we examined changes in occurrence of select congenital anomalies where folic acid supplementation with multivitamins had previously been suggested to have an effect. Anomalies documented in the ACASS 1992-1996 (pre-fortification) were compared to 1999-2003 (post-fortification). RESULTS: A significant decrease in spina bifida (OR 0.51, 95% CI 0.36-0.73) and ostium secundum atrial septal defects (OR 0.80, 95% CI 0.69-0.93) was evident, but there was a significant increase in obstructive defects of the renal pelvisand ureter (OR 1.45, 95% CI 1.24-1.70), abdominal wall defects (OR 1.40, 95% CI 1.04-1.88) and pyloric stenosis (OR 1.49, 95% CI 1.18-1.89). CONCLUSIONS: Consistent with other studies, a 50% reduction in spina bifida was associated with the post-fortification time period. Supporting the possibility that folic acid fortification may play a role in preventing other birth defects, a 20% reduction in atrial septal defects was also associated. The increase in abdominal wall defects, most notably gastroschisis, is likely related to pre-existing increasing trends documented in several regions around the world. The increase in pyloric stenosis and obstructive urinary tract defects was not expected and any causal relationship with folic acid fortification remains unclear. Similar studies by other birth defects surveillance systems in Canada and elsewhere are needed to confirm these trends.		Godwin (2008) Can J Public Health 99: 271-5
National food-fortification program with folic acid in Chile	Observational, population	The Chilean Ministry of Health legislated to add folic acid (2.2 mg/100 g) to wheat flour to reduce the risk of neural tube defects (NTD), beginning in January 2000. This policy resulted in a significant increase in serum and red blood cell folate in women of childbearing age 1 year after fortification. The frequency of NTD was studied in all births, both live and stillbirths, in a prospective hospital-based design including 25% of national births during 1999-2000 (prefortification period) and 2001-2002 (postfortification period). During the prefortification period, there was a total of 120,566 newborns, and the NTD rate was 17.1/10,000 births. During the postfortification period		Hertrampf (2008) Food Nutr Bull 29: S231-7

		(2001-2002) there was a total of 117,704 newborns, and the NTD rate was significantly reduced by 43% to 9.7/10,000 births (RR = 0.57; 95% CI, 0.45 to 0.71). This implies a reduction of 43% in the rate of NTD. The costs per NTD case and infant death averted were 1,200 international dollars (I$) and I$11,000, respectively. The cost per disability-adjusted life year (DALY) averted was I$91, or 0.8% of the country's per capita GDP. On the overall, fortification resulted in net cost savings of I$1.8 million. Fortification of wheat flour with folic acid has proven to be an effective and cost saving strategy for the primary prevention of NTD in a middle-income country in a postepidemiological transition, and in a dramatically short period of time.		
Decline in the prevalence of neural tube defects following folic acid fortification and its cost-benefit in South Africa	Population survey	BACKGROUND: In October 2003 South Africa embarked on a program of folic acid fortification of staple foods. We measured the change in prevalence of NTDs before and after fortification and assessed the cost benefit of this primary health care intervention. METHODS: Since the beginning of 2002 an ecological study was conducted among 12 public hospitals in four provinces of South Africa. NTDs as well as other birth defect rates were reported before and after fortification. Mortality data were also collected from two independent sources. RESULTS: This study shows a significant decline in the prevalence of NTDs following folic acid fortification in South Africa. A decline of 30.5% was observed, from 1.41 to 0.98 per 1,000 births (RR = 0.69; 95% CI: 0.49-0.98; p = .0379). The cost benefit ratio in averting NTDs was 46 to 1. Spina bifida showed a significant decline of 41.6% compared to 10.9% for anencephaly. Additionally, oro-facial clefts showed no significant decline (5.7%). An independent perinatal mortality surveillance system also shows a significant decline (65.9%) in NTD perinatal deaths, and in NTD infant mortality (38.8%). CONCLUSIONS: The decrease in NTD rates postfortification is consistent with decreases observed in other countries that have fortified their food supplies. This is the first time this has been observed in a predominantly African population. The economic benefit flowing from the prevention of NTDs greatly exceeds the costs of implementing folic acid fortification.		Sayed (2008) Birth Defects Res A Clin Mol Teratol 82: 211-6
Will increasing folic acid in fortified grain products further reduce neural tube defects without causing harm? Consideration of the evidence	Review	To reduce neural tube defects (NTDs), the U.S. Food and Drug Administration (FDA) mandated that by January 1998 all enriched grain products should contain 140 mug of folic acid (FA)/100 g of flour. Groups concerned with optimal prevention of NTDs had argued that the level should be 350 mug/100g. However, when it appeared that the debate might delay implementation of any fortification, these groups petitioned the FDA to implement fortification at the originally proposed level of 140 mug/100 g, anticipating that the FDA might consider increasing the level at a later time. Mandated FA fortification (FAF) has now been in place in the United States for 9 y. The impact of this important public health intervention on NTD rates, the possible benefit to other disease conditions, and potential harms have been evaluated. As background for a possible request that the FDA consider increasing FAF, evidence bearing on the question of whether an increase		Johnston (2008) Pediatr Res 63: 1-7

		can further reduce NTD births without causing harm is reviewed here. The published data indicate that it is appropriate that the FDA conduct or commission a balanced analysis of the evidence by scientists who will act on that evidence to decide this important question.		
Efficacy of Canadian folic acid food fortification	Review	No abstract. Reports changes in folate, B12 levels and in NTD incidence after fortification		Ray (2008) Food Nutr Bull 29: S225-30
Public health significance of supplementation or fortification of grain products with folic acid	Review	No abstract. Comments on differences between folic acid and folates		Selhub (2008) Food Nutr Bull 29: S173-6
Prevalence and effects of gene-gene and gene-nutrient interactions on serum folate and serum total homocysteine concentrations in the United States: findings from the third National Health and Nutrition Examination Survey DNA Bank	Population study	BACKGROUND: Abnormalities of folate and homocysteine metabolism are associated with a number of pediatric and adult disorders. Folate intake and genetic polymorphisms encoding folate-metabolizing enzymes influence blood folate and homocysteine concentrations, but the effects and interactions of these factors have not been studied on a population-wide basis. OBJECTIVE: The objective was to assess the prevalence of these genetic polymorphisms and their relation to serum folate and homocysteine concentrations. DESIGN: DNA samples from 6793 participants in the third National Health and Nutrition Examination Survey (NHANES III) during 1991-1994 were genotyped for polymorphisms of genes coding for folate pathway enzymes 5,10-methylenetetrahydrofolate reductase (MTHFR) 677C--T and 1298A--C, methionine synthase reductase (MTRR) 66A--G, and cystathionine-beta-synthase 844ins68. The influence of these genetic variants on serum folate and homocysteine concentrations was analyzed by age, sex, and folate intake in 3 race-ethnicity groups. RESULTS: For all race-ethnicity groups, serum folate and homocysteine concentrations were significantly related to the MTHFR 677C--T genotype but not to the other polymorphisms. Persons with the MTHFR 677 TT genotype had a 22.1% (95% CI: 14.6%, 28.9%) lower serum folate and a 25.7% (95% CI: 18.6%, 33.2%) higher homocysteine concentration than did persons with the CC genotype. Moderate daily folic acid intake (mean: 150 microg/d; 95% CI: 138, 162) significantly reduced the difference in mean homocysteine concentrations between those with the MTHFR 677 CC and TT genotypes. We found a significant interaction between MTHFR 677C--T and MTRR 66A--G on serum homocysteine concentrations among non-Hispanic whites. CONCLUSIONS: The MTHFR 677C--T polymorphism was associated with significant differences in serum folate and homocysteine concentrations in the US population before folic acid fortification. The effect of MTHFR 677C--T on homocysteine concentrations was reduced by moderate daily folic acid intake.	Pre-fortification study showing beneficial effect of 150 microgram folate/day on homocysteine levels in people with MTHFR TT genotype.	Yang (2008) Am J Clin Nutr 88: 232-46
Trends in circulating	Observational population study	Background: The National Health and Nutrition Examination Survey (NHANES) has monitored total homocysteine (tHcy) concentrations in a		Pfeiffer (2008)

concentrations of total homocysteine among US adolescents and adults: findings from the 1991-1994 and 1999-2004 National Health and Nutrition Examination Surveys		nationally-representative sample of the US population since 1991. Until recently, however, data could not be compared across survey periods because of changes in analytical methods and specimen matrices. Such an analysis of these data could supplement current knowledge regarding whether the US folic acid fortification program has modified national plasma tHcy concentrations. Methods: We examined tHcy data in the prefortification NHANES III survey (phase II, 1991-1994) and in 3 postfortification survey periods (1999-2000, 2001-2002, and 2003-2004). We applied method adjustment equations to the survey data based on method comparison studies of separate samples. Persons with chronic kidney disease were excluded from the analyses. Results: Mean plasma tHcy concentrations decreased by 8%, 9%, and 10% for adolescent, adult, and older men and by 6%, 3%, and 13% for women, respectively, from before to after fortification. Concentrations remained unchanged between the first and third postfortification survey periods. Prevalence estimates of increased plasma tHcy concentrations (>13 micromol/L) for older men and women decreased from prefortification (32% and 20%, respectively) to postfortification (14% and 5%, respectively) but remained unchanged thereafter (16% and 14%, respectively [males] and 5% and 9%, respectively [females]). Conclusions: After adjusting for method changes, we quantified a prefortification to postfortification decrease in circulating tHcy concentrations of about 10% in a national sample of the US population. This change is similar to effects seen in intervention trials with folic acid and in smaller observational studies.		Clin Chem 54: 801-813
The scientific basis for eliminating folic acid-preventable spina bifida: a modern miracle from epidemiology	Review	One of the most remarkable successes of epidemiology was the demonstration in the late twentieth century that spina bifida and anencephaly-two of the most common and severe birth defects-are caused primarily by folate deficiency. This article reviews the descriptive epidemiological studies that began when we did not have a clue about etiology. The paper tells the success story of the trials that proved that folic acid would prevent folic-acid-preventable spina bifida. Finally, it will tell how difficult it is to get prevention policy implemented, even when the scientific evidence is compelling. It concludes by noting that the inaction or inappropriate actions of food regulatory bodies in so many countries means that only 10% of folic-acid-preventable spina bifida is actually being prevented--a serious failure of public health policy.	One-sided and passionate!	Oakley (2009) Ann Epidemiol 19: 226-30
A cost-effectiveness analysis of folic acid fortification policy in the United States	Health economics	OBJECTIVE: To quantify the health and economic outcomes associated with changes in folic acid consumption following the fortification of enriched grain products in the USA. DESIGN: Cost-effectiveness analysis. SETTING: Annual burden of disease, quality-adjusted life years (QALY) and costs were projected for four steady-state strategies: no fortification, or fortifying with 140, 350 or 700 microg folic acid per 100 g enriched grain. The analysis considered four health outcomes: neural tube defects (NTD), myocardial infarctions (MI), colon cancers and B12 deficiency maskings. SUBJECTS: The US adult population subgroups defined by age, gender and	Assumptions made were that MI would be reduced by 24% and that colon cancer would be reduced by up to 30%. Neither assumption is likely to be valid	Bentley (2009) Public Health Nutr 12: 455-67

		race/ethnicity, with folate intake distributions from the National Health and Nutrition Examination Surveys (1988-1992 and 1999-2000), and reference sources for disease incidence, utility and economic estimates. RESULTS: The greatest benefits from fortification were predicted in MI prevention, with 16 862 and 88 172 cases averted per year in steady state for the 140 and 700 microg fortification levels, respectively. These projections were between 6261 and 38 805 for colon cancer and 182 and 1423 for NTD, while 15-820 additional B12 cases were predicted. Compared with no fortification, all post-fortification strategies provided QALY gains and cost savings for all subgroups, with predicted population benefits of 266 649 QALY gained and $3.6 billion saved in the long run by changing the fortification level from 140 microg/100 g enriched grain to 700 microg/100 g. CONCLUSIONS: The present study indicates that the health and economic gains of folic acid fortification far outweigh the losses for the US population, and that increasing the level of fortification deserves further consideration to maximise net gains.		
Toward an optimal use of folic acid: an advisory report of the Health Council of the Netherlands	Expert consensus	In this report, benefits (preventing neural tube defects and folate deficiency), risks (masking vitamin B12 deficiency), and uncertain effects (risk of colon cancer) of folic acid supplementation and fortification have been weighted. On the basis of the available evidence, the Health Council of the Netherlands advises the Dutch government to improve the use of folic acid approximately at the time of conception by increased education and the implementation of preconception care. It further recommends considering fortifying staple foods, provided that voluntary fortification of specific foods is banned, as otherwise children are at risk of having an excessively high intake of folic acid. Policy making in relation to fortification should take into account all possible health effects, even if the evidence is not strong.	Similar to English recommendations	Weggemans (2009) Eur J Clin Nutr 63: 1034-6
Update on prevention of folic acid-preventable spina bifida and anencephaly	Review	BACKGROUND: The number of countries fortifying wheat and maize flour with folic acid has increased in the past 2 years. Folic acid prevents most cases of spina bifida and anencephaly by raising serum folate levels among women capable of bearing children, as does encouraging women to consume folic acid supplements prior to pregnancy. METHODS: The progress in preventing these serious birth defects can be measured by tracking the number of countries now fortifying and program coverage in each. Country estimates of the number of pregnancies affected by spina bifida and anencephaly are calculated using a prefortification birth prevalence baseline and estimates of the proportion prevented by wheat and maize flour fortified with folic acid. RESULTS: Current fortification programs are preventing about 22,000, or 9% of the estimated folic acid-preventable spina bifida and anencephaly cases. This represents an annual global decrease of about 6,600 folic acid-preventable spina bifida and anencephaly cases since 2006. CONCLUSIONS: The pace of preventing these serious birth defects can be accelerated if more countries require fortification of both wheat and maize flour and if regulators set fortification levels high enough to	Advocate increasing fortification level so that average intake is 400 mcg per day	Bell (2009) Birth Defects Res A Clin Mol Teratol

		increase a woman's daily average consumption of folic acid to 400 mcg.		
Hemoglobin and hematocrit values are higher and prevalence of anemia is lower in the post-folic acid fortification period than in the pre-folic acid fortification period in US adults	Population survey	BACKGROUND: It is not known whether the improved folate status from mandatory folic acid fortification had any impact on indexes and prevalence of anemias in the United States. OBJECTIVE: We investigated trends in indexes and prevalence of anemia and macrocytosis with a focus on comparison of prefortification data with postfortification data. DESIGN: Hemoglobin, hematocrit, mean corpuscular volume (MCV) and prevalences and likelihood of anemia and macrocytosis were determined for 26,596 adults examined in the National Health and Nutrition Examination Surveys, 1988-2004. RESULTS: From 1988-1994 to 1999-2004, hemoglobin modestly but significantly improved from 15.1 to 15.4 g/dL (approximately 2.0%; P < 0.0001) and from 13.3 to 13.6 g/dL (approximately 2.3%; P < 0.0001) in men and women, respectively. There was a significant increase in MCV from 1988-1994 to 1999-2004 in men (from 90.2 to 90.7; P = 0.0123) and older (>60 y) men (from 91.6 to 92.4; P = 0.0105) and in women (from 90.7 to 91.4; P = 0.0141). Only in women was the prevalence of anemia significantly lower in 1999-2004 than in 1988-1994 (27.9% reduction; P = 0.0005). The odds of having anemia in the postfortification period relative to the prefortification period was 0.64 (95% CI: 0.54, 0.75; P < 0.0001) in women and 0.79 (95% CI: 0.62, 0.99; P < 0.0433) in men. In general, the prevalence of macrocytosis and the odds of having macrocytosis did not change significantly from 1988-1994 to 1999-2004. CONCLUSION: The improvement in hemoglobin and the decreased prevalence of anemia from 1988-1994 to 1999-2004, especially in women, may be attributable to improved folate status, increased vitamin/mineral supplements use, and other unknown causes after the initiation of folic acid fortification. The cause of increased MCV in men, and in older persons of both sexes, warrants further investigation.	But see Morris Morris (2007) Am J Clin Nutr 85: 193-200 who found in a subgroup of elderly with low B12 status that high folate was associated with more anemia.	Ganji (2009) Am J Clin Nutr 89: 363-71
Prevalence of severe congenital heart disease after folic acid fortification of grain products: time trend analysis in Quebec, Canada	Case survey	OBJECTIVE: To investigate whether the 1998 government policy for mandatory fortification of flour and pasta products with folate was followed by a reduction in the prevalence of severe congenital heart defects. DESIGN: Time trend analysis. SETTING: Province of Quebec, Canada. PARTICIPANTS: Infants born in 1990-2005 identified with severe congenital heart defects (tetralogy of Fallot, endocardial cushion defects, univentricular hearts, truncus arteriosus, or transposition complexes) in Quebec administrative databases. METHODS: Data analysed in two time periods (before and after fortification). Birth prevalence measured annually as infants (live and stillbirths) with severe congenital heart defects per 1000 births in Quebec. Changes in the birth prevalence from the period before to the period after fortification were estimated with Poisson regression. RESULTS: Among the 1, 324,440 births in Quebec in 1990-2005 there were 2083 infants born with severe congenital heart defects, corresponding to an average birth prevalence of 1.57/1000 births. Time trend analysis showed no change in the birth prevalence of severe birth defects in the nine years	But see editorial by Gardiner (2009) Bmj 338: b1144	Ionescu-Ittu (2009) Bmj 338: b1673

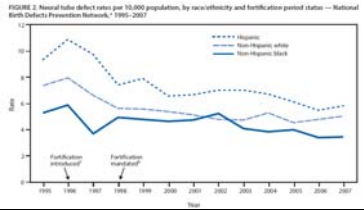
		before fortification (rate ratio 1.01, 95% confidence interval 0.99 to 1.03), while in the seven years after fortification there was a significant 6% decrease per year (0.94, 0.90 to 0.97). CONCLUSIONS: Public health measures to increase folic acid intake were followed by a decrease in the birth prevalence of severe congenital heart defects. These findings support the hypothesis that folic acid has a preventive effect on heart defects.		
Folic acid fortification and congenital heart disease	Editorial	Comments on paper by Ionescu-Ittu, Suggest that some of the apparent decrease in CHD after fortification was due to better ante-natal diganosis	Cautionary tale about changes in diagnosis influencing apparent outcomes	Gardiner et al. (2009) Bmj 338: b1144
Folic acid food fortification prevents inadequate folate intake among preschoolers from Ontario	Cross-sectional population study	OBJECTIVE: Folic acid food fortification has successfully reduced neural tube defect-affected pregnancies across Canada. The effect of this uncontrolled public health intervention on folate intake among Canadian children is, however, unknown. Our objectives were to determine folic acid intake from food fortification and whether fortification promoted adequate folate intakes, and to describe folic acid-fortified food usage among Ontario preschoolers. DESIGN: Cross-sectional data were used from the NutriSTEP validation project with preschoolers recruited using convenience sampling. Mean daily total folate and folic acid intakes were estimated from 3 d food records, which included multivitamin supplement use. Comparisons were made to Dietary Reference Intakes, accounting for and excluding fortificant folic acid, to determine the prevalence of inadequate and excessive intakes. SETTING: Canada. SUBJECTS: Two hundred and fifty-four preschoolers (aged 3-5 years). RESULTS: All participants (130 girls, 124 boys) ate folic acid-fortified foods and 30% (n 76) used folic acid-containing supplements. Mean (SE) fortificant folic acid intake was 83 (2) microg/d, which contributed 30% and 50% to total folate intake for supplement users and non-users, respectively. The prevalence of total folate intakes below the Estimated Average Requirement was <1%; however, excluding fortificant folic acid, the prevalence was 32%, 54% and 47% for 3-, 4- and 5-year-olds, respectively. The overall prevalence of folic acid (fortificant and supplemental) intakes above the Tolerable Upper Intake Level was 2% (7% among supplement users). CONCLUSIONS: Folic acid food fortification promotes dietary folate adequacy and did not appear to result in excessive folic acid intake unless folic acid-containing supplements were consumed.	Weakness is that blood levels were not measured.	Hennessy-Priest (2009) Public Health Nutr 12: 1548-55
Not all cases of neural-tube defect can be prevented by increasing the intake of folic acid	Systematic review	Some countries have introduced mandatory folic acid fortification, whereas others support periconceptional supplementation of women in childbearing age. Several European countries are considering whether to adopt a fortification policy. Projections of the possible beneficial effects of increased folic acid intake assume that the measure will result in a considerable reduction in neural-tube defects (NTD) in the target population. Therefore, the objective of the present study is to evaluate the beneficial effects of different levels of folic acid administration on the prevalence of NTD.	A floor effect was found: folic fortification or supplement use does not reduce NTD prevalence below about 7-8 cases per 10,000. Important critical review of	Heseker (2009) Br J Nutr 102: 173-80

		Countries with mandatory fortification achieved a significant increase in folate intake and a significant decline in the prevalence of NTD. This was also true for supplementation trials. However, the prevalence of NTD at birth declined to approximately five cases at birth per 10 000 births and seven to eight cases at birth or abortion per 10 000 births. This decline was independent of the amount of folic acid administered and apparently reveals a 'floor effect' for folic acid-preventable NTD. This clearly shows that not all cases of NTD are preventable by increasing the folate intake. The relative decline depends on the initial NTD rate. Countries with NTD prevalence close to the observed floor may have much smaller reductions in NTD rates with folic acid fortification. Additionally, potential adverse effects of fortification on other vulnerable population groups have to be seriously considered. Policy decisions concerning national mandatory fortification programmes must take into account realistically projected benefits as well as the evidence of risks to all vulnerable groups.	claims.	
Do dietary patterns in older men influence change in homocysteine through folate fortification? The Normative Aging Study	Prospective cohort study	OBJECTIVE: We aimed to describe the difference in B-vitamin intake and in plasma B-vitamin and homocysteine concentrations before and after folic acid fortification, in relation to dietary patterns. DESIGN: The Normative Aging Study (NAS) is a longitudinal study on ageing. Between 1961 and 1970, 2280 male volunteers aged 21-80 years (mean 42 years) were recruited. Dietary intake data have been collected since 1987 and assessment of plasma B vitamins and homocysteine was added in 1993. SETTING: Boston, Massachusetts, USA. SUBJECTS: In the present study, 354 men who had completed at least one FFQ and one measurement of homocysteine, both before and after the fortification period, were included. RESULTS: Three dietary patterns were identified by cluster analysis: (i) a prudent pattern, with relatively high intakes of fruit, vegetables, low-fat milk and breakfast cereals; (ii) an unhealthy pattern, with high intakes of baked products, sweets and added fats; and (iii) a low fruit and vegetable but relatively high alcohol intake pattern. Dietary intake and plasma concentrations of folate increased significantly ($P < 0.05$) among all dietary patterns after the fortification period. Homocysteine tended to decrease in supplement non-users and in subjects in the high alcohol, low fruit and vegetable dietary pattern (both $P = 0.08$). CONCLUSIONS: After fortification with folic acid, folate intake and plasma folate concentration increased significantly in all dietary patterns. There was a trend towards greatest homocysteine lowering in the high alcohol, low fruit and vegetable group.		Knoops (2009) Public Health Nutr 12: 1760-6
Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States	Case survey	Rates of neural tube defects have decreased since folic acid fortification of the food supply in the United States. The authors' objective was to evaluate the associations between neural tube defects and maternal folic acid intake among pregnancies conceived after fortification. This is a multicenter, case-control study that uses data from the National Birth Defects Prevention Study, 1998-2003. Logistic regression was used to compute crude and adjusted odds ratios between cases and controls assessing maternal	Floor effect evidence	Mosley (2009) Am J Epidemiol 169: 9-17

		periconceptional use of folic acid and intake of dietary folic acid. Among 180 anencephalic cases, 385 spina bifida cases, and 3, 963 controls, 21.1%, 25.2%, and 26.1%, respectively, reported periconceptional use of folic acid supplements. Periconceptional supplement use did not reduce the risk of having a pregnancy affected by a neural tube defect. Maternal intake of dietary folate was not significantly associated with neural tube defects. In this study conducted among pregnancies conceived after mandatory folic acid fortification, the authors found little evidence of an association between neural tube defects and maternal folic acid intake. A possible explanation is that folic acid fortification reduced the occurrence of folic acid-sensitive neural tube defects. Further investigation is warranted to possibly identify women who remain at increased risk of preventable neural tube defects.		
Invited Commentary: Preventing Neural Tube Defects and More via Food Fortification?	Editorial	Many neural tube defects can be prevented if women take folic acid around the time of conception. However, the majority of women do not take folic acid at the critical time, so the US government required that food be fortified with folic acid effective January 1, 1998. Whether the amount being added was sufficient to prevent all folate-related neural tube defects has been hotly debated. Mosley et al. (Am J Epidemiol. 2009;169(1):9-17) found no evidence that folic acid supplement use or dietary folate intake was related to neural tube defects, indicating that fortified food is probably providing sufficient folic acid to prevent folate-related defects. Because data on the effectiveness of fortification in the United States are scarce, this is an important contribution. There is great interest in the other effects of fortification. Folic acid reduces homocysteine levels, and homocysteine has been linked to cardiovascular disease and cancer. On the basis of current evidence, however, it seems unlikely that fortification will reduce cardiovascular disease rates. Its effect on cancer remains unclear. Folic acid may be useful in primary prevention but may also stimulate the growth of existing malignancies or premalignant lesions. Although these issues remain unresolved, Mosley et al. have provided important data to address the primary question: Does fortification prevent folate-related neural tube defects?		Mills (2009) Am J Epidemiol 169: 18-21
Mosley and Hobbs Respond to "Folic Acid Fortification and Neural Tube Defects"	Reply to editorial	No Abstract, Extract: One possible conclusion from our findings, stated both in the Discussion of our article and by Mills and Carter, is that folic acid fortification activities may have reached levels sufficient to prevent most folate-preventable neural tube defects.		Mosley (2009) Am J Epidemiol 169: 22-23
Periconceptional folic acid and multivitamin supplementation for the prevention of neural tube defects and other congenital abnormalities	Review	The pioneering studies of Smithells et al. showed the reduction of recurrent neural-tube defects (NTD) after periconceptional folic acid-containing multivitamin supplementation. The Hungarian Periconceptional Service was established in 1984, and this primary health care system offered a chance to organize a randomized controlled trial to check whether the supplementation of a multivitamin containing 0.8 mg of folic acid during the periconceptional period is appropriate for the reduction of a first occurrence of NTD in the	Useful review of trials on other defects	Czeizel (2009) Birth Defects Res A Clin Mol Teratol 85: 260-8

		family. This found a reduction of approximately 90% of primary NTD. An unexpected finding was a significant reduction in the rate of congenital abnormalities overall: 20.6 per 1000 in the 'multivitamin' group, and 40.6 per 1000 in the 'trace-element-like' placebo group (RR = 0.53, 95% CI: 0.35-0.70). When the 6 cases of NTD were excluded, this difference in the rates of major congenital abnormalities between the two study-groups remained very highly significant ($p < 0.0001$). Cardiovascular malformations and urinary tract defects were particularly affected. These findings were confirmed in the Hungarian cohort-controlled trial and by observational studies in other countries. Two questions remain to be answered. Is folic acid better alone or with multivitamins? What is the optimal dose of folic acid? Overall, the Hungarian experiences of periconceptional care have shown not only primary prevention of several severe congenital abnormalities but also a good cost-benefit balance.		
Prevalence of neural tube defects in Australia prior to mandatory fortification of bread-making flour with folic acid	Observational, population	OBJECTIVE: To establish baseline prevalence of neural tube defects (NTDs) prior to mandatory folic acid fortification in Australia. METHOD: Retrospective population based study. Data from the Australian Congenital Anomalies Monitoring System, for 1998-2005 were used to calculate birth prevalence including live/stillbirths of at least 20 weeks gestation or 400 g birthweight. Total prevalence and trends of NTD including terminations of pregnancy (TOPs) before 20 weeks were established using data from South Australia, Victoria and Western Australia because of the incomplete ascertainment in other states. RESULTS: The birth prevalence of NTDs from 1998-2005, was 5/10,000 births. The total prevalence including TOPs was 13/10,000 births. A 26% declining trend in total prevalence was seen from 1992-2005, but the main decline occurred prior to 1998. Women who were Indigenous, socially disadvantaged, young, living in remote areas and had multiple gestations were more likely to give birth to babies with NTDs. CONCLUSION: The prevalence of NTD has been stable since 1998. Reporting of the birth prevalence alone underestimates the actual prevalence of NTD. IMPLICATIONS: From a public health perspective, future monitoring of NTD following implementation of fortification of bread-making flour with folic acid should include a mixed methods approach; reporting birth prevalence on national data and total prevalence on tri-state data.		Abeywardana (2010) Aust N Z J Public Health 34: 351-5
Wonder vitamin or mass medication? Media and academic representation of folate fortification as a policy problem in Australia and New Zealand	Review	OBJECTIVE: The aim was to examine how representations of the 'problem' of folate fortification as policy strategy to reduce neural tube defects (NTDs) had been produced by examining the underlying discourses in media and health and medical journals. The objectives were to evaluate the various framings of the folate fortification 'problem', and discuss ways in which this policy problem could have been repositioned or reframed. METHODS: All articles found in the Australian and New Zealand print media and in health and medical journals from June 1995 when the first expert report was released to one month after the approval of mandatory fortification in July		Begley (2010) Aust N Z J Public Health 34: 466-71

		2007 were identified using two newspaper indexing databases (Factiva-Dow Jones Interactive & Proquest ANZ NewsStand) and multiple databases including PubMed, Expanded Academic ASAP and Informat (Australian Public Affairs). RESULTS: 176 print media articles and 83 peer-reviewed journal articles identified from the database analysis. Critical discourse analysis of these 259 articles resulted in three main discourses being evident in the representations; the dominance of biomedicine in the process of prioritisation of fortification of the food supply, issues of professional encroachment by nutritionists and the representation of fortification as iatrogenic. CONCLUSION AND IMPLICATIONS: Food fortification as a policy response to nutritional deficiencies has implications for influencing food and nutrition policy implementation. Examining how policy problems are represented in the media and journals can help guide public health policy decisions.		
Fortification of flour with folic acid	Review	BACKGROUND: After randomized, controlled trials established that consumption of folic acid before pregnancy and during the early weeks of gestation reduces the risk of a neural tube defect (NTD)-affected pregnancy, the United States Public Health Service recommended in 1992 that all women capable of becoming pregnant consume 400 microg folic acid daily. In 1998, folic acid fortification of all enriched cereal grain product flour was fully implemented in the United States and Canada. OBJECTIVE: To provide guidance on national fortification of wheat and maize flours to prevent 50 to 70% of the estimated 300,000 NTD-affected pregnancies worldwide. METHODS: An expert workgroup reviewed the latest evidence of effectiveness of folic acid flour fortification and the safety of folic acid. RESULTS: Recent estimates show that in the United States and Canada, the additional intake of about 100 to 150 microg/day of folic acid through food fortification has been effective in reducing the prevalence of NTDs at birth and increasing blood folate concentrations in both countries. Most potential adverse effects associated with folic acid are associated with extra supplement use not mandatory fortification. Fortification of wheat flour has a proven record of prevention in other developed countries. In 2009, 51 countries had regulations written for mandatory wheat flour fortification programs that included folic acid. CONCLUSIONS: NTDs remain an important cause of perinatal mortality and infantile paralysis worldwide. Mandatory fortification of flour with folic acid has proved to be one of the most successful public health interventions in reducing the prevalence of NTD-affected pregnancies. Most developing countries have few, if any, common sources of folic acid, unlike many developed countries, which have folic acid available from ready-to-eat cereals and supplements. Expanding the number of developed and developing countries with folic acid flour fortification has tremendous potential to safely eliminate most folic acid-preventable NTDs.		Berry (2010) Food Nutr Bull 31: S22-35
Folic acid to reduce	Meta-analysis	BACKGROUND: Neural tube defects (NTDs) remain an important,	Fortification gave a mean	Blencowe

neonatal mortality from neural tube disorders		preventable cause of mortality and morbidity. High-income countries have reported large reductions in NTDs associated with folic acid supplementation or fortification. The burden of NTDs in low-income countries and the effectiveness of folic acid fortification/supplementation are unclear. OBJECTIVE: To review the evidence for, and estimate the effect of, folic acid fortification/supplementation on neonatal mortality due to NTDs, especially in low-income countries. METHODS: We conducted systematic reviews, abstracted data meeting inclusion criteria and evaluated evidence quality using adapted Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. Where appropriate, meta-analyses were performed. RESULTS: Meta-analysis of three randomized controlled trials (RCTs) of folic acid supplementation for women with a previous pregnancy with NTD indicates a 70% [95% confidence interval (CI): 35-86] reduction in recurrence (secondary prevention). For NTD primary prevention through folic acid supplementation, combining one RCT with three cohort studies which adjusted for confounding, suggested a reduction of 62% (95% CI: 49-71). A meta-analysis of eight population-based observational studies examining folic acid food fortification gave an estimated reduction in NTD incidence of 46% (95% CI: 37-54). In low-income countries an estimated 29% of neonatal deaths related to visible congenital abnormalities are attributed to NTD. Assuming that fortification reduces the incidence of NTDs, but does not alter severity or case-fatality rates, we estimate that folic acid fortification could prevent 13% of neonatal deaths currently attributed to congenital abnormalities in low-income countries. DISCUSSION: Scale-up of periconceptional supplementation programmes is challenging. Our final effect estimate was therefore based on folic acid fortification data. If folic acid food fortification achieved 100% population coverage the number of NTDs in low-income countries could be approximately halved. CONCLUSION: The evidence supports both folic acid supplementation and fortification as effective in reducing neonatal mortality from NTDs.	reduction in NTD of 46%, supplementation gave a decline of 62%, But see Imdad (2011) BMC Public Health 11 Suppl 3: S4 for more recent meta-analysis	(2010) Int J Epidemiol 39 Suppl 1: i110-i121
CDC Grand Rounds: additional opportunities to prevent neural tube defects with folic acid fortification	Review	No abstract. Useful data. See Fig. 2 		Cordero (2010) MMWR 59: 980-984
Folic acid flour fortification: impact on the frequencies of 52 congenital anomaly	Observational, population	The aim of the present investigation was to search for a reduction in birth prevalence estimates of 52 selected types of congenital anomalies, associated with folic acid fortification programs in Chile, Argentina, and Brazil. The material included 3,347,559 total births in 77 hospitals of the		Lopez-Camelo (2010) Am J Med Genet A

types in three South American countries		three countries during the 1982-2007 period: 596,704 births (17 hospitals) in Chile, 1,643,341 (41 hospitals) in Argentina, and 1,107,514 (19 hospitals) in Brazil. We compared pre- and post-fortification rates within each hospital and the resulting Prevalence Rate Ratios (PRRs) were pooled by country. Statistically significant reductions in birth prevalence estimates after fortification were observed for neural tube defects (NTDs), septal heart defects, transverse limb deficiencies, and subluxation of the hip. However, only the reduction of NTDs appeared to be associated with folic acid fortification and not due to other factors, because of its consistency among the three countries, as well as with previously published reports, and its strong statistical significance. Among the NTDs, the maximum prevalence reduction was observed for isolated cephalic (cervical-thoracic) spina bifida, followed by caudal (lumbo-sacral) spina bifida, anencephaly, and cephalocele. This observation suggests etiologic and pathogenetic heterogeneity among different levels of spina bifida, as well as among different NTD subtypes. We concluded that food fortification with folic acid prevents NTDs but not other types of congenital anomalies.		152A: 2444-58
New Zealand should have mandatory fortification of bread with folic acid: yes	Opinion	No abstract	Rather emotional, with sweeping statements	Marks (2010) J Prim Health Care 2: 74-6
New Zealand should have mandatory fortification of bread with folic acid: no	Opinion	No abstract. Extract: "Despite some benefits, folic acid fortification of the food supply is likely, overall, to be deleterious to the health of New Zealanders."	Estimates benefits and harm in numbers of people affected, with assumptions.	Potter (2010) J Prim Health Care 2: 76-8
Maximizing the impact of flour fortification to improve vitamin and mineral nutrition in populations	Expert review: Second WHO Technical Workshop on Wheat Flour Fortification	No abstract. Extract: "Raising blood folate to the higher concentrations associated with maximum NTD risk reduction requires that women consume folic acid from supplements and/or fortified foods in addition to a healthy diet containing natural folate. Mandatory folic acid fortification of cereals and flours has been proven to be a low-cost and highly effective public health strategy in various countries. Although concerns about potential negative health consequences associated with folic acid fortification have arisen since 2004, the general view from this Workshop is that most of the questions raised in recent literature on folic acid probably result from conditions where study participants received high doses of folic acid in supplements not at levels typically found in fortified foods. Furthermore, it was agreed that when flour is fortified with appropriate levels of folic acid, based on appropriate estimates of per capita consumption of "fortifiable" flour, the intervention does not appear to pose a public health risk."		Serdula (2010) Food Nutr Bull 31: S86-93
Efficacy of flour fortification with folic acid in women of childbearing	Population study	Background: Flour fortification with folic acid is one of the main strategies for improving folate status in women of childbearing age. No interventional trial on the efficacy of folic acid fortification has been conducted so far in Iran. Objectives: To study the effects of flour fortification with folic acid on any	B12 measured but not reported	Abdollahi (2011) Ann Nutr Metab 58:

age in Iran		reduction in neural tube defects (NTDs) and folate status of women of childbearing age. Methods: In a longitudinal hospital-based study, 13,361 postpartum women were studied after admission for childbirth before and after fortification. In addition, two cross-sectional surveys were conducted before (2006) and after flour fortification (2008). The cluster sampling method was used and 580 women, 15-49 years old, were studied as a representative sample of Golestan province in the north of Iran. Fasting blood samples were collected to measure serum vitamin B12, folate and plasma homocysteine. Sociodemographic data, health characteristics and dietary intake were determined. Results: The mean daily intakes of folate from natural food before and after flour fortification were 198.3 and 200.8 mug/day, respectively. The total folate intake increased significantly from 198.3 to 413.7 mug/day after fortification ($p < 0.001$). Folate intake increased by an average of 226 mug/day from fortified bread. The mean serum folate level increased from 13.6 to 18.1 nmol/l; folate deficiency decreased from 14.3 to 2.3% ($p < 0.001$). The incidence rate of NTDs declined by 31% ($p < 0.01$) in the post-fortification period (2.19 per 1,000 births; December 2007 to December 2008) compared to the pre-fortification period (3.16 per 1,000 births; September 2006 to July 2007). Conclusions: Implementation of mandatory flour fortification with folic acid can lead to a significant increase in serum folate and a significant decrease in NTDs.		188-96
Folic acid intake and spina bifida in the era of dietary folic acid fortification	Population study	BACKGROUND: The US Food and Drug Administration mandated that enriched grain products be fortified with folic acid by 1998. We evaluated whether intake of folic acid from supplements and diet was associated with a reduction in spina bifida in the setting of folic acid fortification. METHODS:: Data were collected as part of the Slone Birth Defects Study from 1998 to 2008. Mothers of infants with and without birth defects were interviewed within 6 months of delivery about pregnancy exposures, including details of diet and vitamin intake. Dietary natural folate and synthetic folic acid from fortification were combined into a single, weighted measure-dietary folate equivalent. Periconceptional folic acid supplementation and dietary folate consumption were compared between 205 mothers of spina bifida cases and 6357 mothers of nonmalformed controls. Relative risks of a spina bifida-affected birth were estimated with odds ratios (ORs) and 95% confidence intervals (CIs). RESULTS:: Spina bifida was not associated with regular folic acid supplementation (>/=4 days per week) either around the time of conception (adjusted OR = 1.1 [95% CI = 0.74-1.7]) or initiated in early pregnancy (0.79 [0.54-1.2]). After adjustment for confounders, a 13% reduced odds of spina bifida was estimated for each 100-mug increase in daily dietary folate equivalent consumed. CONCLUSIONS:: In the setting of folic acid fortification of grains, our data suggest that folic acid supplementation does not appear to offer further benefit for reducing risk of spina bifida. Rather, the folate-associated benefit on spina bifida risk was found with increasing amounts of dietary folic acid consumed, regardless of folic acid supplementation level.	Floor effect. Note that although terminations were included, ascertainment of these was 'not routine'., Similar result to that of Mosley et al. (2009) Am J Epidemiol 169: 9-17	Ahrens (2011) Epidemiology

The impact of mandatory fortification of flour with folic acid on the blood folate levels of an Australian population	Population study	OBJECTIVE: To determine the impact that mandatory fortification with folic acid of wheat flour used in breadmaking has had on the blood folate levels of an Australian population since it was introduced in September 2009. DESIGN, SETTING AND PATIENTS: A retrospective analysis of serum and red blood cell (RBC) folate levels of 20 592 blood samples collected between April 2007 and April 2010 from a wide variety of inpatients and outpatients and analysed in a large public hospital diagnostic pathology laboratory. MAIN OUTCOME MEASURES: Prevalences of low levels of serum and RBC folate and monthly mean levels before and after introduction of mandatory fortification. RESULTS: Between April 2009 and April 2010, there was a 77% reduction in the prevalence of low serum folate levels (from 9.3% to 2.1%) in all samples tested and an 85% reduction in the prevalence of low RBC folate levels (from 3.4% to 0.5%). In April 2010, the prevalence of low RBC folate levels for females of childbearing age was 0.16% for all samples. There was a 31% increase in mean serum folate level (from 17.7 nmol/L to 23.1 nmol/L; $t = 9.3$, $P < 0.01$), and a 22% increase in mean RBC folate level (from 881 nmol/L to 1071 nmol/L). The greatest increment in mean serum folate levels occurred in September 2009, the month that mandatory fortification was introduced, although there was evidence of a gradual change during the preceding months. CONCLUSION: The introduction of mandatory fortification with folic acid has significantly reduced the prevalence of folate deficiency in Australia, including in women of childbearing age.	Don't define what 'low levels' are! Note that serum folate levels after fortification are lower (23.1 nmol/L) than in NZ before fortification (29.1)	Brown (2011) Med J Aust 194: 65-7
Fortification of corn masa flour with folic acid in the United States	Review	Food fortification is an effective public health tool for addressing micronutrient deficiencies. The mandatory fortification of enriched cereal grains (e.g., wheat flour) with folic acid, which began in the United States in 1998, is an example of a successful intervention that significantly reduced the rate of neural tube defects (NTDs). However, despite the drop in NTD rates across all racial/ethnic groups after fortification, Hispanics continue to have the highest rates of this condition. One possible way to reduce this disparity is to fortify corn masa flour to increase the overall intake of folic acid in Hispanic women. We present the available evidence in favor of this approach, address possible safety issues, and outline next steps in the fortification of corn masa flour with folic acid in the United States		Fleischman (2011) Am J Public Health 101: 1360-4
The mandatory fortification of staple foods with folic acid: a current controversy in Germany	Review	The mandatory fortification of staple foods with folic acid to prevent neural tube defects (NTDs) began in the USA in 1998. Since then, more than 50 countries around the world have followed suit. METHODS: Selective literature review including national study results. RESULTS AND DISCUSSION: Women of child-bearing age need sufficient body stores of folate before conception to prevent folate-sensitive NTDs, which make up 20% to 60% of all NTDs. Merely recommending folic acid supplementation before conception has been found to be an unsuitable strategy. Ingestion of folate-fortified food markedly increases folate intake, generally by about 50% of the recommended daily total intake. In Germany at present, debate		Herrmann (2011) Dtsch Arztebl Int 108: 249-54

		surrounds the issue whether folate intake should be raised by mandatory folate supplementation, which will affect the entire population. Folate deficiency is associated with a higher risk of cancer and other diseases; on the other hand, there is concern that very high folic acid intake might promote the growth of pre-neoplastic lesions. There are no consistent study findings to support the latter hypothesis and the evidence for it is derived from research in animals whose folate metabolism differs from that in humans. About 800 pregnancies with NTD are diagnosed each year in Germany; in most cases, the pregnancy is terminated after positive prenatal screening. The incidence of NTDs in Germany is estimated at 12.36 per 10 000 births (a mean figure derived from registry data in Mainz and Saxony-Anhalt) and is thus much higher than the mean incidence across Europe, 7.88 per 10 000 births (EUROCAT data for 2004-2008). Mandatory folic acid fortification should be adopted, as it is a highly effective and inexpensive way to prevent NTDs.		
Folic Acid in obstetric practice: a review	Review and tutorial	Folic acid is one of the B complex vitamins and is now recognized as a major component of the periconceptional care of women in the reproductive age group. Deficiency of folic acid can lead to neural tube defects in the fetus and megaloblastic anemia in the mother. Due to its lower bioavailability from natural foods, many countries have adopted mandatory folic acid food fortification programs. Although these programs have been a public health triumph in reducing the burden of neural tube defects, there have been growing concerns about the role played by folic acid supplementation in the rising colon cancer rates over the past decade. The majority of the evidence available to date is reassuring, and until further long-term population as well as laboratory studies are completed, folic acid will continue to play a vital role in early pregnancy care. It is important for healthcare professionals to be aware of the recent evidence that has accumulated, suggesting higher folic acid requirements in certain groups of women and offer correct advice on the use of folic acid supplements. This review looks at some of the existing evidence on folic acid supplementation and summarizes the recommendations on the use of folic acid supplements by obstetricians, family physicians, and others providing prenatal care. Target Audience: Obstetricians and Gynecologists, Family physicians Learning Objectives: After completing this CME activity, physicians should be better able to evaluate the need for folic acid supplementation in various patient groups to lower the risk of neural tube defects due to folate deficiency; recommend common, natural and fortified food sources rich in folic acid; and distinguish the effects of folate deficiency in the mother and fetus		Talaulikar (2011) Obstet Gynecol Surv 66: 240-7
Potential reduction in neural tube defects associated with use of Metafolin-fortified oral	Mathematical model	OBJECTIVE: The objective of the study was to estimate the potential reduction of neural tube defects (NTDs) through the use of Metafolin-fortified oral contraceptives (OCs) in the United States. STUDY DESIGN: A population-based decision analytic model was developed to estimate the benefits of increased red blood cell (RBC) folate levels through the use of	An alternative approach to fortification	Taylor (2011) Am J Obstet Gynecol

contraceptives in the United States		Metafolin-fortified OCs on NTD risk during pregnancy. We modeled women who began the year taking Metafolin-fortified or traditional OCs. Folate levels were derived from the National Health and Nutrition Examination Survey and clinical trial data. NTD risk was estimated by applying a published risk equation to respective RBC folate levels. RESULTS: The number of predicted NTD cases declined by 23.7% to 31.4%, depending on median baseline folate levels in women taking a fortified OC compared with taking a traditional OC. CONCLUSION: Metafolin-fortified OCs have the potential to reduce the number of folate-dependent NTDs among current and recent OC users		
Policy statement on folic acid and neural tube defects	Update on policy statement by American College of Genetics	1. All women capable of becoming pregnant should strive for intake of 400 _g (0.4 mg) of folic acid daily, in the form of a supplement, multivitamin, consumption of fortified foods, or a combination of the above. This is particularly important before conception and throughout the first trimester of pregnancy. 2. Women who have had a previous NTD-affected pregnancy, who are themselves affected, have a first- or second-degree relative with a NTD, or who have diabetes mellitus type 1 may be advised to take 4 mg of folic acid commencing 3 months before conception and continuing throughout the first trimester. However, they should seek genetic counseling to determine their occurrence or recurrence risks, pregnancy management, and the appropriate folic acid intake for them. 3. There should be increased public health efforts to increase awareness of the role of folic acid in reducing the incidence of NTDs. 4. Studies have produced conflicting or inconclusive results about the risks and benefits of increasing fortification of foods with folic acid or other foods; therefore, there is no evidence to support such fortification. We do recommend that additional study be done to better determine the risks and benefits for the entire population.	Advise against increasing folic acid levels further by fortification	Toriello (2011) Genet Med 13: 593-6
The effect of folic acid, protein energy and multiple micronutrient supplements in pregnancy on stillbirths	Meta-analysis	BACKGROUND: Pregnancy is a state of increased requirement of macro- and micronutrients, and malnourishment or inadequate dietary intake before and during pregnancy, can lead to adverse perinatal outcomes including stillbirths. Many nutritional interventions have been proposed during pregnancy according to the nutritional status of the mother and baseline risk factors for different gestational disorders. In this paper, we have reviewed three nutritional interventions including peri-conceptional folic acid supplementation, balanced protein energy supplementation and multiple micronutrients supplementation during pregnancy. This paper is a part of a series to estimate the effect of interventions on stillbirths for input to Live Saved Tool (LiST) model. METHODS: We systematically reviewed all published literature to identify studies evaluating effectiveness of peri-conceptional folic acid supplementation in reducing neural tube defects (NTD), related stillbirths and balanced protein energy and multiple micronutrients supplementation during pregnancy in reducing all-cause	Useful up-to-date review on effect of fortification on NTD. Meta-analysis gives a reduction of 41%. Supplements reduce by 62% (primary incidence) or by 70% (recurrence). “It is important to note that the effect of folic acid on incidence of NTDs and related stillbirths will be	Imdad et al. (2011) BMC Public Health 11 Suppl 3: S4

		stillbirths. The primary outcome was stillbirths. Meta-analyses were generated where data were available from more than one study. Recommendations were made for the Lives Saved Tool (LiST) model based on rules developed by the Child Health Epidemiology Reference Group (CHERG). RESULTS: There were 18 studies that addressed peri-conceptional folic acid supplementation for prevention of neural tube defects (NTDs). Out of these, 7 studies addressed folic acid supplementation while 11 studies evaluated effect of folic acid fortification. Pooled results from 11 fortification studies showed that it reduces primary incidence of NTDs by 41 % [Relative risk (RR) 0.59; 95 % confidence interval (CI) 0.52-0.68]. This estimate has been recommended for inclusion in the LiST as proxy for reduction in stillbirths. Pooled results from three studies considered to be of low quality and suggest that balanced protein energy supplementation during pregnancy could lead to a reduction of 45% in stillbirths [RR 0.55, 95 % CI 0.31-0.97]. While promising, the intervention needs more effectiveness studies before inclusion in any programs. Pooled results from 13 studies evaluating role of multiple micronutrients supplementation during pregnancy showed no significant effect in reducing stillbirths [RR = 0.98; 95% CI: 0.88 - 1.10] or perinatal mortality [RR = 1.07; 95% CI: 0.92 - 1.25; random model]. No recommendations have been made for this intervention for inclusion in the LiST model. CONCLUSIONS: Peri-conceptional folic acid supplementation reduces stillbirths due to NTDs by approximately 41%, a point estimate recommended for inclusion in LiST.	different in different countries. The amount of protective effect will depend on baseline NTDs incidence rate, folate deficiency in child bearing women, genetic susceptibility and existing system for screening and termination of affected pregnancies.”	
Commentary: A brief history of folic acid in the prevention of neural tube defects	Comment	No abstract. Extract: The MRC Vitamin Study showed that about 80% of neural tube defects could be prevented by taking 4mg folic acid immediately before pregnancy. Subsequent work8 showed that this achieved a greater degree of protection than with 0.4mg (400 mg) indicating that all women planning a pregnancy should take a 4mg pill daily (or the more readily available 5 mg), not 0.4mg as currently recommended. This would mean recommending the same dose for women in general as for women who have already had a neural tube defect pregnancy, for whom 4mg is already the standard dose.		Wald (2011) Int J Epidemiol 40: 1154-1156
Folic acid fortification - its history, effect, concerns, and future directions	Review	Periconceptional intake of folic acid is known to reduce a woman’s risk of having an infant affected by a neural tube birth defect (NTD). National programs to mandate fortification of food with folic acid have reduced the prevalence of NTDs worldwide. Uncertainty surrounding possible unintended consequences has led to concerns about higher folic acid intake and food fortification programs. This uncertainty emphasizes the need to continually monitor fortification programs for accurate measures of their effect and the ability to address concerns as they arise. This review highlights the history, effect, concerns, and future directions of folic acid food fortification programs.		Crider (2011) Nutrients 3: 370-384

Table 2S. Reports of potentially harmful effects of folic acid fortification

Title	Type of study	Abstract	Interpretation	Reference
Preliminary evidence shows that folic acid fortification of the food supply is associated with higher methotrexate dosing in patients with rheumatoid arthritis	Observational, Clinic	BACKGROUND: Fortification of the diet with folate has been used in the United States since 1997 to prevent neural tube defects in newborn babies. However, an increase in dietary folate intake could theoretically reduce the effectiveness of the anti-folate medication, methotrexate (MTX) in treating rheumatoid arthritis (RA) and other inflammatory diseases. OBJECTIVE: To investigate whether dietary fortification with folic acid interferes with MTX function in patients with RA. METHODS: We computed MTX dose per patient per year for the years 1988 to 1999 and plotted these against time, comparing the overall mean MTX dose before and after 1997, when dietary fortification with folic acid was instituted in the USA. Thirty-six subjects met eligibility criteria. RESULTS: Mean annual MTX dose was stable between 1988 and 1996 (12.4 +/- 4.0mg), but then rose linearly from 1997 to 1999 (16.6 +/- 5.1 mg, $p < 0.001$). CONCLUSIONS: This preliminary study suggests that folic acid supplementation may contribute to higher MTX dosing in patients with RA.		Arabelovic (2007) J Am Coll Nutr 26: 453-5
A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis	Population study	Nationwide fortification of enriched uncooked cereal grains with folic acid began in the United States and Canada in 1996 and 1997, respectively, and became mandatory in 1998. The rationale was to reduce the number of births complicated by neural tube defects. Concurrently, the United States and Canada experienced abrupt reversals of the downward trend in colorectal cancer (CRC) incidence that the two countries had enjoyed in the preceding decade: absolute rates of CRC began to increase in 1996 (United States) and 1998 (Canada), peaked in 1998 (United States) and 2000 (Canada), and have continued to exceed the pre-1996/1997 trends by 4 to 6 additional cases per 100,000 individuals. In each country, the increase in CRC incidence from the prefortification trend falls significantly outside of the downward linear fit based on nonparametric 95% confidence intervals. The statistically significant increase in rates is also evident when the data for each country are analyzed separately for men and women. Changes in the rate of colorectal endoscopic procedures do not seem to account for this increase in CRC incidence. These observations alone do not prove causality but are consistent with the known effects of folate on existing neoplasms, as shown in both preclinical and clinical studies. We therefore hypothesize that the institution of folic acid fortification may have been wholly or partly responsible for the observed increase in CRC rates in the mid-1990s. Further work is needed to definitively establish the nature of this relationship. In the meantime, deliberations about the institution or enhancement of		Mason (2007) Cancer Epidemiol Biomarkers Prev 16: 1325-9

		fortification programs should be undertaken with these considerations in mind.		
Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification	Population study	Historic reports on the treatment of pernicious anemia with folic acid suggest that high-level folic acid fortification delays the diagnosis of or exacerbates the effects of vitamin B-12 deficiency, which affects many seniors. This idea is controversial, however, because observational data are few and inconclusive. Furthermore, experimental investigation is unethical. OBJECTIVE: We examined the relations between serum folate and vitamin B-12 status relative to anemia, macrocytosis, and cognitive impairment (ie, Digit Symbol-Coding score < 34) in senior participants in the 1999-2002 US National Health and Nutrition Examination Survey. DESIGN: The subjects had normal serum creatinine concentrations and reported no history of stroke, alcoholism, recent anemia therapy, or diseases of the liver, thyroid, or coronary arteries (n = 1459). We defined low vitamin B-12 status as a serum vitamin B-12 concentration < 148 pmol/L or a serum methylmalonic acid concentration > 210 nmol/L-the maximum of the reference range for serum vitamin B-12-replete participants with normal creatinine. RESULTS: After control for demographic characteristics, cancer, smoking, alcohol intake, serum ferritin, and serum creatinine, low versus normal vitamin B-12 status was associated with anemia [odds ratio (OR): 2.7; 95% CI: 1.7, 4.2], macrocytosis (OR: 1.8; 95% CI: 1.01, 3.3), and cognitive impairment (OR: 2.5; 95% CI: 1.6, 3.8). In the group with a low vitamin B-12 status, serum folate > 59 nmol/L (80th percentile), as opposed to < or = 59 nmol/L, was associated with anemia (OR: 3.1; 95% CI: 1.5, 6.6) and cognitive impairment (OR: 2.6; 95% CI: 1.1, 6.1). In the normal vitamin B-12 group, ORs relating high versus normal serum folate to these outcomes were < 1.0 (P(interaction) < 0.05), but significantly < 1.0 only for cognitive impairment (0.4; 95% CI: 0.2, 0.9). CONCLUSION: In seniors with low vitamin B-12 status, high serum folate was associated with anemia and cognitive impairment. When vitamin B-12 status was normal, however, high serum folate was associated with protection against cognitive impairment.		Morris (2007) Am J Clin Nutr 85: 193-200
Folic acid fortification: the good, the bad, and the puzzle of vitamin B-12	Editorial	Comment on paper by Morris		Smith (2007) Am J Clin Nutr 85: 3-5
In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations	Observational, population	In a recent study of older participants (>60 years) in the 1999-2002 National Health and Nutrition Examination Survey (NHANES), we showed that a combination of high serum folate and low vitamin B12 status was associated with higher prevalence of cognitive impairment and anemia than other combinations of vitamin B12 and folate status. In the present study, we sought to determine the joint influence of serum folate and vitamin B12 concentrations on two functional indicators of vitamin B12 status, total homocysteine (tHcy) and methylmalonic acid (MMA), among adult participants in phase 2 of the NHANES III (19911994) and the NHANES 19992002. Exclusion of subjects who were <20 years old, were pregnant,		Selhub (2007) PNAS 104: 19995-20000

		had evidence of kidney or liver dysfunction, or reported a history of alcohol abuse or recent anemia therapy left 4,940 NHANES III participants and 5,473 NHANES 19992002 participants for the study. Multivariate analyses controlled for demographic factors, smoking, alcohol use, body mass index, self-reported diabetes diagnosis, and serum concentrations of creatinine and alanine aminotransferase revealed significant interactions between serum folate and serum vitamin B12 in relation to circulating concentrations of both metabolites. In subjects with serum vitamin B12 >148 pmol/liter (L), concentrations of both metabolites decreased significantly as serum folate increased. In subjects with lower serum vitamin B12, however, metabolite concentrations increased as serum folate increased starting at approx 20 nmol/L. These results suggest a worsening of vitamin B12's enzymatic functions as folate status increases in people who are vitamin B12-deficient.		
Proportion of individuals with low serum vitamin B-12 concentrations without macrocytosis is higher in the post folic acid fortification period than in the pre folic acid fortification period	Retrospective cross-sectional population study	Background: Large intakes of folic acid may delay the diagnosis of vitamin B-12 deficiency, which could lead to irreversible neuropathy. Objective: The objective of this study was to determine whether the proportion of individuals with low serum vitamin B-12 without macrocytosis (undiagnosed vitamin B12 deficiency) has increased in the postfolic acid fortification period. Design: Individuals aged ≥19 y with low serum vitamin B12 (<258 pmol/L) and mean corpuscular volume (MCV) measured between 1995 and 2004 were identified from medical records. The proportion and odds ratios of individuals with low serum vitamin B-12 without macrocytosis by sex, race, and age according to prefortification (n = 86), perifortification (n = 138), and postfortification (n = 409) periods were determined. Results: MCV was significantly lower in the postfortification period (88.6 fL) than in the prefortification (94.4 fL; P < 0.001) and perifortification (90.6 fL; P = 0.007) periods. The proportion of subjects with low serum vitamin B-12 without macrocytosis was significantly higher in the postfortification ({approx}87%) and perifortification ({approx}85%) periods than in the prefortification period ({approx}70%; P < 0.001). In a sex-, race-, and age-adjusted analysis, the odds ratio for having low serum vitamin B-12 without macrocytosis was 3.0 (95% CI: 1.7, 5.2) in the postfortification period relative to the prefortification period. Conclusions: Subjects with low serum vitamin B12 were likely to be without macrocytosis in the postfortification period. MCV should not be used as a marker for vitamin B12 insufficiency. It is possible that folic acid fortification may have led to a correction of macrocytosis associated with vitamin B12 insufficiency.		Wyckoff (2007) Am J Clin Nutr 86: 1187-1192
Folate and vitamin B12: friendly or enemy nutrients for the elderly	Review	In the UK vitamin B12 deficiency occurs in approximately 20% of adults aged >65 years. This incidence is significantly higher than that among the general population. The reported incidence invariably depends on the criteria of deficiency used, and in fact estimates rise to 24% and 46% among free-living and institutionalised elderly respectively when methylmalonic acid is used as a marker of vitamin B12 status. The incidence of, and the criteria for diagnosis of, deficiency have drawn much attention recently in the wake of	Their conclusion: “As long as there still remains a lack of a reliable clinical test for the diagnosis of true vitamin B12 deficiency, any fortification programme	Cuskelly (2007) Proc Nutr Soc 66: 548-58

		the implementation of folic acid fortification of flour in the USA. This fortification strategy has proved to be extremely successful in increasing folic acid intakes pre-conceptually and thereby reducing the incidence of neural-tube defects among babies born in the USA since 1998. However, in successfully delivering additional folic acid to pregnant women fortification also increases the consumption of folic acid of everyone who consumes products containing flour, including the elderly. It is argued that consuming additional folic acid (as 'synthetic' pteroylglutamic acid) from fortified foods increases the risk of 'masking' megaloblastic anaemia caused by vitamin B12 deficiency. Thus, a number of issues arise for discussion. Are clinicians forced to rely on megaloblastic anaemia as the only sign of possible vitamin B12 deficiency? Is serum vitamin B12 alone adequate to confirm vitamin B12 deficiency or should other diagnostic markers be used routinely in clinical practice? Is the level of intake of folic acid among the elderly (post-fortification) likely to be so high as to cure or 'mask' the anaemia associated with vitamin B12 deficiency?	should be accompanied by appropriate systems to ensure that the elderly at risk of vitamin B12 deficiency are identified. As concluded by Scientific Advisory Committee for Nutrition, the issue of overage needs to be given careful consideration."	
Folic acid fortification: is masking of vitamin B-12 deficiency what we should really worry about?	Editorial	No abstract. Discuss Wyckoff and Morris papers. Conclusion: In conclusion, it is uncertain to what extent the masking of vitamin B-12 deficiency by folic acid is indeed a worry. Doctor's delay appears to be a nonissue if appropriate markers of vitamin B-12 are measured, but patient's delay should be considered. Considering the ongoing discussion of what the best markers and cutoff values for vitamin B-12 deficiency are, it is also hard to say how many people would be at risk. Other possible negative effects of folic acid fortification should be further investigated and thoroughly evaluated. Cofortification with vitamin B-12 may solve some, but not all, of the possible adverse effects.	Idea of co-fortification with B12 discussed	Brouwer (2007) Am J Clin Nutr 86: 897-898
Folate and vitamin B12 status in relation to cognitive impairment and anaemia in the setting of voluntary fortification in the UK	Population study	Concerns about risks for older people with vitamin B12 deficiency have delayed the introduction of mandatory folic acid fortification in the UK. We examined the risks of anaemia and cognitive impairment in older people with low B12 and high folate status in the setting of voluntary fortification in the UK. Data were obtained from two cross-sectional studies (n 2403) conducted in Oxford city and Banbury in 1995 and 2003, respectively. Associations (OR and 95 % CI) of cognitive impairment and of anaemia with low B12 status (holotranscobalamin 30 nmol/l or >60 nmol/l) were estimated after adjustment for age, sex, smoking and study. Mean serum folate levels increased from 15.8 (sd 14.7) nmol/l in 1995 to 31.1 (sd 26.2) nmol/l in 2003. Serum folate levels were greater than 30 nmol/l in 9 % and greater than 60 nmol/l in 5 %. The association of cognitive impairment with low B12 status was unaffected by high v. low folate status (>30 nmol/l) (OR 1.50 (95 % CI 0.91, 2.46) v. 1.45 (95 % CI 1.19, 1.76)), respectively. The associations of cognitive impairment with low B12 status were also similar using the higher cut-off point of 60 nmol/l for folate status ((OR 2.46; 95 % CI 0.90, 6.71) v. (1.56; 95 % CI 1.30, 1.88)). There was no evidence of modification by high folate status of the associations of low B12 with anaemia or cognitive	Claims not to confirm Morris 2007 Morris et al. (2007) Am J Clin Nutr 85: 193-200 but number of subjects (17) with folate > 60 nmol/L was insufficient for the OR of 2.46 to reach significance. Also, used an insensitive measure of cognition: MMSE.	Clarke (2008) Br J Nutr 100: 1054-9

		impairment in the setting of voluntary fortification, but periodic surveys are needed to monitor fortification		
Circulating folic acid in plasma: relation to folic acid fortification	Population	BACKGROUND: The implementation of folic acid fortification in the United States has resulted in unprecedented amounts of this synthetic form of folate in the American diet. Folic acid in circulation may be a useful measure of physiologic exposure to synthetic folic acid, and there is a potential for elevated concentrations after fortification and the possibility of adverse effects. OBJECTIVE: We assessed the effect of folic acid fortification on circulating concentrations of folic acid and 5-methyltetrahydrofolate in the Framingham Offspring Cohort. DESIGN: This is a cross-sectional study that used plasma samples from fasting subjects before and after fortification. Samples were measured for folate distribution with the use of an affinity-HPLC method with electrochemical detection. RESULTS: Among nonsupplement users, the median concentration of folic acid in plasma increased from 0.25 to 0.50 nmol/L (P < 0.001) after fortification, and among supplement users the median increased from 0.54 to 0.68 nmol/L (P = 0.001). Among nonsupplement users, the prevalence of high circulating folic acid (>/=85th percentile) increased from 9.4% to 19.1% (P = 0.002) after fortification. Among supplement users, the prevalence of high circulating folic acid increased from 15.9% to 24.3% (P = 0.02). Folic acid intake and total plasma folate were positively and significantly related to high circulating folic acid after adjustment for potential confounding factors (P for trend < 0.001). CONCLUSIONS: Folic acid fortification has resulted in increased exposure to circulating folic acid. The biochemical and physiologic consequences of this are unknown, but these findings highlight the need to understand the effects of chronic exposure to circulating folic acid.	See also Kalmbach (2008) J Nutr 138: 2323-7 in Table 5 who found an interaction with a polymorphism in gene for DHFR: those with the polymorphism showed greater prevalence of high circulation folic acid	Kalmbach (2008) Am J Clin Nutr 88: 763-8
Folate and clefts of the lip and palate--a U.K.-based case-control study: Part II: Biochemical and genetic analysis	Observational, population	OBJECTIVE: To investigate associations between nonsyndromic oral clefts and biochemical measures of folate status and the MTHFR C677T variant in the United Kingdom, where there has been no folic acid fortification program. METHOD: Dietary details were obtained from the mothers of 112 cases of cleft lip with or without cleft palate (CL+/-P), 78 cleft palate only (CP) cases, and 248 unaffected infants. Infant and parental MTHFR C677T genotype was determined. Red blood cell (RBC) and serum folate and homocysteine levels were assessed in 12-month postpartum blood samples from a subset of mothers. The data were analyzed by logistic and log-linear regression methods. RESULTS: There was an inverse association between CL+/-P and maternal MTHFR CT (odds ratio [OR] = 0.5, 95% confidence interval [CI] = 0.31-0.95) and TT (OR = 0.6, 95% CI = 0.21-1.50) genotypes, with similar risk estimates for CP. There was no clear association with infant MTHFR genotype. Higher levels of maternal postpartum RBC and serum folate were associated with a lower risk for CL+/-P and an increased risk for CP. Higher levels of serum homocysteine were associated with a slightly increased risk for both CL+/-P and CP. CONCLUSION: While the inverse relation between the mother's having the MTHFR C677T variant and both CL+/-P and CP		Little (2008) Cleft Palate Craniofac J 45: 428-38

		suggests perturbation of maternal folate metabolism is of etiological importance, contrasting relations between maternal postpartum levels of RBC and serum folate by type of cleft are difficult to explain.		
Correspondence: will increasing folic acid in fortified grain products further reduce neural tube defects without causing harm?	Letter regarding Johnston's review	No Abstract: Authors point out that high folate levels found after fortification were associated with increased anemia and cognitive deficit in those with low B12 status. Johnston's reply points out that those with very high folate after fortification were also taking supplements	Importance of sub-population studies to reveal potentially harmful effects	Morris (2008) Pediatr Res 63: 450; author reply 450-1
Mandatory fortification with folic acid in the United States is associated with increased expression of DNA methyltransferase-1 in the cervix	Retrospective patient survey	Objective The objective of this study was to evaluate whether mandatory fortification of grain products with folic acid in the United States is associated with changes in DNA methyltransferase-1 (Dnmt-1) expression in cells involved in cervical carcinogenesis.Methods Archived specimens of cervical intraepithelial neoplasia (CIN) diagnosed before (1990-1992) and after (2000-2002) mandatory folic acid fortification were used to examine the expression of Dnmt-1 in specific lesions involved in cervical carcinogenesis by immunohistochemistry. The total number of lesions examined was 101 in the prefortification period and 96 in the postfortification period. Immunohistochemical staining for Dnmt-1, its assessment, and data entry were blinded with regard to the fortification status.Results Age- and race-adjusted mean percentage of cells positive for Dnmt-1 or the Dnmt-1 score was significantly higher in all lesion types (i.e., normal cervical epithelium, reactive cervical epithelium, metaplastic cervical epithelium, CIN, or carcinoma in situ) detected in the postfortification period compared with the prefortification period ($P < 0.05$, all comparisons). The degree of Dnmt-1 was significantly higher ($P < 0.0001$) in CIN >=2 lesions compared with CIN <=1 lesions, regardless of the fortification group.Conclusion These results suggest that mandatory fortification with folic acid in the United States seems to have resulted in a change in the degree of expression of Dnmt-1 in cells involved in cervical carcinogenesis. Because the approach we have taken to demonstrate these differences have limitations inherent to a study of this nature and this is the first study to report a folate fortification associated change in Dnmt-1, validating these results in other study populations and/or with other techniques of assessing Dnmt-1 will increase the scientific credibility of these findings.		Piyathilake (2008) Nutrition 24: 94-99
Has enhanced folate status during pregnancy altered natural selection and possibly Autism prevalence? A closer look at a possible link	Hypothesis	The inverse association between maternal folate status and incidence of infants born with neural tube defects (NTD's) was recognized over twenty years ago and led the US health agencies in the early 1990s to recommend that women of childbearing age consume 400mug of folic acid each day. The FDA followed by mandating that certain foods be fortified with folic acid and this has resulted in a significant enhancement of maternal folate status to levels that are often difficult to otherwise achieve naturally. At least one study indicates that this has decreased the incidence of NTD's. However,	Highly speculative. Depends on evidence for change in frequency of T allele of MTHFR after fortification, which is very weak.	Rogers (2008) Med Hypotheses 71: 406-10

		this same time period directly coincides with what many feel is the apparent beginning and continuous increase in the prevalence of Autism and related Autism Spectrum Disorders (ASD's) in the US. Are these similar time frames of changes in maternal folate status and possible Autism prevalence a random event or has improved maternal (and fetal) folate status during pregnancy played a role? It is not only plausible but highly likely. A particular polymorphic form to a key enzyme required to activate folate for methylation in neurodevelopment, 5-methylenetetrahydrofolate reductase (MTHFR), demonstrates reduced activity under low or normal folate levels but normal activity under conditions of higher folate nutritional status. A consequence of the presence of the polymorphic form of this enzyme during normal or reduced folate status are higher plasma homocysteine levels than noncarriers and the combination of these factors have been shown in several studies to result in an increase rate of miscarriage via thrombotic events. However, the incidence of hyperhomocysteinemia in the presence of the polymorphism is reduced under the common condition of enhanced folate status and thereby masks the latent adverse effects of the presence of this enzyme form during pregnancy. Of great importance is that this polymorphism, although common in the normal population, is found in significantly higher frequency in Autisic individuals. It is hypothesized here that the enhancement of maternal folate status before and during pregnancy in the last 15 years has altered natural selection by increasing survival rates during pregnancy of infants possessing the MTHFR C677T polymorphism, via reduction in hyperhomocysteinemia associated with this genotype and thereby miscarriage rates. This also points directly to an increased rate of births of infants with higher postnatal requirements for folic acid needed for normal methylation during this critical neurodevelopmental period. If these numbers have increased then so have the absolute number of infants that after birth fail to maintain the higher folate status experienced in utero thus leading to an increased number of cases of developmental disorders such as Autism. Detection of the C677T polymorphism as well as other methionine cycle enzymes related to folate metabolism and methylation at birth as part of newborn screening programs could determine which newborns need be monitored and maintained on diets or supplements that ensure adequate folate status during this critical postnatal neurodevelopment period.		
Is folic acid good for everyone?	Review	Fortification of food with folic acid to reduce the number of neural tube defects was introduced 10 y ago in North America. Many countries are considering whether to adopt this policy. When fortification is introduced, several hundred thousand people are exposed to an increased intake of folic acid for each neural tube defect pregnancy that is prevented. Are the benefits to the few outweighed by possible harm to some of the many exposed? In animals, a folic acid-rich diet can influence DNA and histone methylation, which leads to phenotypic changes in subsequent generations. In humans, increased folic acid intake leads to elevated blood		Smith (2008) Am J Clin Nutr 87: 517-33

		concentrations of naturally occurring folates and of unmetabolized folic acid. High blood concentrations of folic acid may be related to decreased natural killer cell cytotoxicity, and high folate status may reduce the response to antifolate drugs used against malaria, rheumatoid arthritis, psoriasis, and cancer. In the elderly, a combination of high folate levels and low vitamin B-12 status may be associated with an increased risk of cognitive impairment and anemia and, in pregnant women, with an increased risk of insulin resistance and obesity in their children. Folate has a dual effect on cancer, protecting against cancer initiation but facilitating progression and growth of preneoplastic cells and subclinical cancers, which are common in the population. Thus, a high folic acid intake may be harmful for some people. Nations considering fortification should be cautious and stimulate further research to identify the effects, good and bad, caused by a high intake of folic acid from fortified food or dietary supplements. Only then can authorities develop the right strategies for the population as a whole.		
Folic acid supplementation and cancer risk: point	Review	No Abstract, Extract: What can we conclude about the effect of folic acid fortification and supplementation on cancer risk? From the discussion above, it seems that folic acid fortification and periconceptional supplementation may reduce the risk of certain childhood cancers in the offspring (40-42). Furthermore, folic acid supplementation may prevent the development of cancers in normal tissues (9, 21, 22, 24-29). However, folic acid supplementation and fortification may promote the progression of already existing preneoplastic and neoplastic lesions (9, 19, 21-23, 39, 66, 68). However, the threshold level above which folic acid supplementation may exert the tumor promoting effect on preneopalstic and neoplastic lesions as well as dose-response of such a effect associated with folic acid supplementation have not been clearly established in humans nor can they be extrapolated from animal studies because inherent differences in folate absorption and metabolism between humans and rodents. Furthermore, it is unclear whether the potential tumor-promoting effect is limited to folic acid, the synthetic form of folate, and is generalizable to naturally occurring folate present in foods		Kim (2008) Cancer Epidemiol Biomarkers Prev 17: 2220-5
Folate and cancer prevention--where to next? Counterpoint	Review	No abstract. Extract: In summary, the recently completed Aspirin/Folate Polyp Prevention Trial has added an important chapter to the story of folate and cancer: the results raise concerns about the use of folic acid in older individuals who may harbor cancer precursors, as well as cancer patients. The exposure of the public to synthetic folic acid is high, particularly among consumers of supplements and fortified health foods. Thus, it is critical that we continue research on the effects of folate on carcinogenesis in the context of our knowledge of cancer biology. A dual role of folate in carcinogenesis is the most likely explanation for the somewhat contradictory research findings		Ulrich (2008) Cancer Epidemiol Biomarkers Prev 17: 2226-30

		from epidemiology and the cancer prevention trial. Yet, we still need better quantitative experimental data on the growth-promoting effects of folate in carcinogenesis of the colon and other tissues to clarify the potential of adverse effects of folate at varied doses. A research agenda on folate and cancer should aim to fill gaps in understanding the biological mechanisms (especially effects of folate status on epigenetics) and cancer etiology (dose response, genetic variability, and noncolon cancers). Yet, particularly important from a public health perspective are studies on the effects of high or excessive folate intakes in patients with cancer precursors or cancer, and the effects of these high intakes on their prognosis. In the absence of these important data to inform our decision making, what should be the current public health recommendations? First, as a safeguard, clinicians should inquire about the use of supplements among cancer patients and caution them against high intakes of folic acid from supplements, particularly when their nutritional intake in general is adequate or good. Second, countries that are currently considering mandatory fortification with folic acid (such as Australia and several European countries) may be best advised to defer decisions until more is known about the potential cancer-promoting effects of added folic acid.		
Shall we put the world on folate?	Editorial	No abstract.	Cautionary. Points out that if mandatory fortification is introduced, most women will reach the required level of folate without supplements and that supplement use may take some people over the safe limit.	Osterhues (2009) Lancet 374: 959-61
Folic acid fortification: a double-edged sword	Review	PURPOSE OF REVIEW: To examine the impact of folic acid fortification, including its use as a functional food component, on human health. RECENT FINDINGS: There is a consensus view that folic acid supplementation has numerous health benefits, many of which are significant in their impact. However, emerging evidence suggests that increased population exposure to folic acid may also have a negative impact with respect to certain developmental and degenerative disorders. As examples, presently much attention is focused on the role of folic acid fortification augmenting colon cancer risk, whereas earlier in the life cycle, the vitamin may additionally influence insulin resistance. Without question, conditions that are influenced by folic acid are both diverse and many - from concerns relating to cognitive decline, breast cancer and vascular disease through to preconceptional issues where maternal folate levels might conceivably alter the phenotype of offspring via epimutations. SUMMARY: The highly complex and critical	Thorough review which also points out interactions with folate pathway genes	Lucock (2009) Curr Opin Clin Nutr Metab Care

		biological importance of folic acid-related molecular nutrition makes it a difficult micronutrient to deploy as a simple intervention at a population level - it has far too many biochemical spheres of influence to predict effects in a generalized way. Additionally, several gene variants and other nutrients are interactive factors. It is, therefore, hardly surprising that the scientific community does not have a true consensus view on whether mandatory fortification is appropriate as a population measure. This latter point not withstanding, any ultimate decisions on fortification should be well rooted in scientific fact rather than political expediency.		
Metabolic evidence of vitamin B12 deficiency, including high homocysteine and methylmalonic acid and low holotranscobalamin, is more pronounced in older adults with elevated plasma folate	Observational, population	Background: Analysis of data from NHANES indicates that in older adults exposed to folic acid fortification, the combination of low serum B12 and elevated folate is associated with higher homocysteine and methylmalonic acid concentrations and higher odds ratios for cognitive impairment and anemia than the combination of low B12 and non-elevated folate. These findings await confirmation in other populations. Objective: The purpose was to compare metabolic indicators of B12 status, cognitive function, and depressive symptoms among elderly Latinos with elevated and non-elevated plasma folate. Design: Cross-sectional data were analyzed on 1535 subjects (age ≥60y) from the Sacramento Area Latino Study on Aging. Subjects were divided into four groups based on plasma B12 (< or ≥148 pmol/L) and folate (≤ or >45.3 nmol/L). Homocysteine, methylmalonic acid, holotranscobalamin (holoTC), holoTC/B12 ratio, and modified mini-mental state examination (3MSE), delayed recall, and depressive symptom scores were compared among the groups. Results: Homocysteine and methylmalonic acid were highest and holoTC and holoTC/B12 ratio were lowest in individuals with low B12 and elevated folate (n=22) compared with all other groups (p≤0.003). No differences in 3MSE, delayed recall, and depressive symptom scores were observed between the low B12/elevated folate group and the other groups. Conclusion: Low B12 is associated with more pronounced metabolic evidence of B12 deficiency when folate is elevated than when folate is not elevated. These data should be considered when assessing the potential costs, risks, and benefits of folic acid and B12 fortification programs.		Miller (2009) Am J Clin Nutr 90: 1586-1592
Folate-vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency	Review	Previous reports on pernicious anemia treatment suggested that high folic acid intake adversely influences the natural history of vitamin B-12 deficiency, which affects many elderly individuals. However, experimental investigation of this hypothesis is unethical, and the few existing observational data are inconclusive. With the use of data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES), we evaluated the interaction between high serum folate and low vitamin B-12 status [ie, plasma vitamin B-12 < 148 pmol/L or methylmalonic acid (MMA) > 210 nmol/L] with respect to anemia and cognitive impairment. With subjects having both plasma folate </= 59 nmol/L and normal vitamin B-12 status as		Selhub (2009) Am J Clin Nutr 89: 702S-706S

		the referent category, odds ratios for the prevalence of anemia compared with normal hemoglobin concentration and impaired compared with unimpaired cognitive function were 2.1 (95% CI: 1.1, 3.7) and 1.7 (95% CI: 1.01, 2.9), respectively, for those with low vitamin B-12 status but normal serum folate and 4.9 (95% CI: 2.3, 10.6) and 5.0 (95% CI: 2.7, 9.5), respectively, for those with low vitamin B-12 status and plasma folate >59 nmol/L. Among subjects with low vitamin B-12 status, mean circulating vitamin B-12 was 228 pmol/L for the normal-folate subgroup and 354 pmol/L for the high-folate subgroup. We subsequently showed increases in circulating homocysteine and MMA concentrations with increasing serum folate among NHANES participants with serum vitamin B-12 < 148 pmol/L, whereas the opposite trends occurred among subjects with serum vitamin B-12 >/= 148 pmol/L. These interactions, which were not seen in NHANES III before fortification, imply that, in vitamin B-12 deficiency, high folate status is associated with impaired activity of the 2 vitamin B12-dependent enzymes, methionine synthase and MMA-coenzyme A mutase.		
Colon cancer in Chile before and after the start of the flour fortification program with folic acid	Observational, population	BACKGROUND: Folate depletion is associated with an increased risk of colorectal carcinogenesis. A temporal association between folic acid fortification of enriched cereal grains and an increase in the incidence of colorectal cancer in the USA and Canada has, however, been recently reported. AIM: To compare the rates of hospital discharges owing to colon cancer in Chile before and after the start of the mandatory flour fortification program with 220 microg of synthetic folic acid/100 g of wheat flour. METHODS: Cancer and cardiovascular hospital discharge rates were compared using rate ratios between two study periods, 1992-1996, before folic acid fortification and 2001-2004, after the flour fortification with folic acid was established in the country. Standard errors of the log rate ratio to derive confidence intervals, and to test the null hypothesis of no difference, were calculated. RESULTS: The highest rate ratio between the two periods was for colon cancer in the group aged 45-64 years (rate ratio: 2.6, confidence interval: 99% 2.93-2.58) and in the 65-79 years (rate ratio: 2.9, confidence interval: 99% 3.25-2.86). CONCLUSION: Our data provide new evidence that a folate fortification program could be associated with an additional risk of colon cancer.		Hirsch (2009) Eur J Gastroenterol Hepatol 21: 436-9
Persistent circulating unmetabolised folic acid in a setting of liberal voluntary folic acid fortification. Implications for further mandatory fortification?	Observational, clinical	BACKGROUND: Ireland is an example of a country that has extensive voluntary fortification with folic acid. After a public consultation process, in 2006, the Food Safety Authority in Ireland FSAI 1 recommended mandatory fortification. However due to safety considerations this decision is now on hold. Before mandatory fortification goes ahead, existing levels of unmetabolised folic acid and their anticipated increase after fortification needs investigation because of the potential of folic acid to mask pernicious anaemia and possibly accelerate the growth of existing cancers. The aim of this study was to examine the levels of circulatory unmetabolised folic acid in Irish adults (both fasted and un-fasted) and new-born infants (fasted) before		Sweeney (2009) BMC Public Health 9: 295

		the proposed implementation of mandatory folic acid fortification. A secondary aim was to predict the increase in circulatory unmetabolised folic acid levels after fortification. METHODS: Study 1. Setting: Irish Blood Transfusion Service (IBTS). Whole blood samples were collected from blood donors (n=50) attending for routine blood donation sessions (representing the general population). Subjects were not fasted prior to sampling. Study 2. Setting: Coombe Women's and Infant's University Hospital, Dublin. Whole blood samples were collected by venipuncture from mothers (n=20), and from their infant's umbilical-cords (n=20) immediately after caesarean section. All women had been fasted for at least 8 hours prior to the surgery. A questionnaire on habitual and recent dietary intakes of folic acid was administered by an interviewer to all subjects. The data collection period was February to April 2006. Serum samples were analysed for plasma folate, plasma folic acid and red cell folate. RESULTS: Blood Donor Group: Circulatory unmetabolised folic acid was present in 18 out of 20 mothers (fasted) (CI: 68.3%-99.8%) comprising 1.31% of total plasma folate, 17 out of 20 babies (fasted) (CI: 62.1%-96.8%), and 49 out of 50 blood donors (unfasted) (CI: 88.0%-99.9%), comprising 2.25% of total plasma folate, CONCLUSION: While the levels of circulatory unmetabolised folic acid reported are low, it is persistently present in women immediately after caesarean section who were fasting indicating that there would be a constant/habitual exposure of existing tumours to folic acid, with the potential for accelerated growth. Mandatory fortification might exacerbate this. This has implications for those with responsibility for drafting legislating in this area.		
Unmetabolized folic acid and total folate concentrations in breast milk are unaffected by low-dose folate supplements	Observational and trial	Background: Many lactating women in North America are exposed to high synthetic folic acid intakes because of food fortification and vitamin supplement use. Few data exist on the potential long-term effect of high folic acid intakes on milk folate concentrations, whereas no data are available on the effect of supplemental [6S]-5-methyltetrahydrofolate ([6S]-5-methylTHF). Objective: The aim of the present study was to investigate the effect of 3 treatments (placebo, folic acid, and [6S]-5-methylTHF) on milk folate and folate-binding protein (FBP) concentrations and to determine whether unmetabolized folic acid is present in milk. Design: In this 16-wk randomized, placebo-controlled intervention, 69 lactating women were randomly assigned to receive [6S]-5-methylTHF (416 {micro}g/d, 906 nmol/d) or a placebo, or were assigned to receive folic acid (400 {micro}g/d, 906 nmol/d) within 1 wk postpartum. Total milk folate, FBP, and unmetabolized folic acid concentrations were measured at 16 wk. Results: Unmetabolized folic acid was detected in 96% of milk samples tested representing {approx}8% of total milk folate concentrations. Total milk folate, FBP, and the proportion of unmetabolized milk folic acid did not differ between treatments; however, FBP concentrations were significantly lower than those published before mandatory folic acid fortification of the food supply. Conclusion: Maternal intake of synthetic folic acid leads to the		Houghton (2009) Am J Clin Nutr 89: 216-220

		appearance of unmetabolized folic acid in milk and, seemingly, a down-regulation of milk FBP synthesis. The impact of these changes on the bioavailability of folate in infants requires further exploration.		
Metabolic evidence of vitamin B12 deficiency, including high homocysteine and methylmalonic acid and low holotranscobalamin, is more pronounced in older adults with elevated plasma folate	Population study	Background: Analysis of data from NHANES indicates that in older adults exposed to folic acid fortification, the combination of low serum B12 and elevated folate is associated with higher homocysteine and methylmalonic acid concentrations and higher odds ratios for cognitive impairment and anemia than the combination of low B12 and non-elevated folate. These findings await confirmation in other populations. Objective: The purpose was to compare metabolic indicators of B12 status, cognitive function, and depressive symptoms among elderly Latinos with elevated and non-elevated plasma folate. Design: Cross-sectional data were analyzed on 1535 subjects (age ≥60y) from the Sacramento Area Latino Study on Aging. Subjects were divided into four groups based on plasma B12 (< or ≥148 pmol/L) and folate (≤ or >45.3 nmol/L). Homocysteine, methylmalonic acid, holotranscobalamin (holoTC), holoTC/B12 ratio, and modified mini-mental state examination (3MSE), delayed recall, and depressive symptom scores were compared among the groups. Results: Homocysteine and methylmalonic acid were highest and holoTC and holoTC/B12 ratio were lowest in individuals with low B12 and elevated folate (n=22) compared with all other groups (p≤0.003). No differences in 3MSE, delayed recall, and depressive symptom scores were observed between the low B12/elevated folate group and the other groups. Conclusion: Low B12 is associated with more pronounced metabolic evidence of B12 deficiency when folate is elevated than when folate is not elevated. These data should be considered when assessing the potential costs, risks, and benefits of folic acid and B12 fortification programs.		Miller et al. (2009) Am J Clin Nutr 90: 1586-1592
Lower risk of cervical intraepithelial neoplasia in women with high plasma folate and sufficient vitamin B12 in the post-folic acid fortification era	Population study	The purpose of this study was to determine the influence of plasma folate and vitamin B12 concentrations on cervical cancer risk in the U.S. after the folic acid fortification era. The study included 376 premenopausal women of childbearing age who tested positive for infections with high-risk (HR) human papillomaviruses (HPVs) and were diagnosed with cervical intraepithelial neoplasia (CIN) grade 2 or higher (CIN 2+, cases) or <or=CIN 1 (noncases). CIN 2+ (yes/no) was the dependent variable in logistic regression models that specified plasma folate concentrations combined with plasma B12 concentrations as the independent predictors of primary interest, adjusting for age, race, education, smoking, parity, number of life-time male sexual partners, use of contraceptives, waist circumference, physical activity, healthy eating index, and circulating concentrations of vitamins A, C, tocopherol, and total carotene. Women with supraphysiologic concentrations of plasma folate (>19.8 ng/mL) who also had sufficient plasma vitamin B12 (>or=200.6 pg/mL) had 70% lower odds of being diagnosed with CIN 2+ (P = 0.04) when compared with women with plasma folate of <or=19.8 ng/mL and	Subgroup again (B12)	Piyathilake (2009) Cancer Prev Res (Phila) 2: 658-64

		plasma vitamin B12 of <200.6 pg/mL. Our results do not corroborate the concern that supraphysiologic plasma folate concentrations seen in the post-U.S. folic acid fortification era increase the risk of CIN in premenopausal women of childbearing age. In fact, higher folate is associated with significantly lower risk of CIN, especially when vitamin B12 is sufficient, demonstrating the importance of vitamin B12 in the high-folate environment created by the folic acid fortification program.		
Mandatory fortification with folic acid in the United States appears to have adverse effects on histone methylation in women with pre-cancer but not in women free of pre-cancer	Retrospective histology	OBJECTIVE: To evaluate whether mandatory fortification of grain products with folic acid in the US is associated with changes in histone methylation in cells involved in cervical carcinogenesis. METHODS: Cervical specimens obtained before (1990 to 1992) and after mandatory folic acid fortification (2000 to 2002) were used to examine the degree of histone methylation (H3 Lys-9) by immunohistochemistry. 91 women (51 before and 40 after fortification) were diagnosed with cervical intraepithelial neoplasia (CIN) grade 3 or carcinoma in situ (CIS) and sections utilized in the study also contained normal, reactive or metaplastic cervical epithelium, CIN 1 or CIN 2. 64 women (34 before and 30 after fortification) were free of CIN and these sections contained only normal or reactive cervical epithelium. Immunohistochemical staining for H3 Lys-9, its assessment in different cell or lesion types and data entry were blinded for fortification status. For each cell type or lesion category we used PROC MIXED in SAS with the specimen identifier as a random effect and the robust variance estimator to estimate age- and race-adjusted intensity score for H3 Lys-9 in the pre- and post-fortification periods. RESULTS: Degree of H3 Lys-9 methylation was significantly higher (P < 0.0001) in >/=CIN 2 lesions (CIN 2, CIN 3 and CIS) than in </=CIN 1 lesions (CIN 1, normal, reactive and metaplastic), in both pre- and post-fortification CIN 3/CIS specimens. Age- and race-adjusted mean H3 Lys-9 score was significantly higher in all cell or lesion types in CIN 3/CIS specimens obtained in the post-fortification period compared to pre-fortification period (P < 0.05, all comparisons). In contrast, in specimens obtained from women free of CIN, Lys-9 methylation in normal/reactive cervical epithelium was significantly lower in post-fortification specimens than in pre-fortification specimens (P = 0.03). CONCLUSIONS: Higher levels of Lys-9 methylation in >/=CIN 2 compared to </=CIN 1 lesions suggest that higher Lys-9 methylation is associated with progression of lower grade CIN to higher grade CIN. Higher Lys-9 methylation in cervical tissues of women diagnosed with CIN 3 in the post-fortification period than in pre-fortification period suggest that fortification may adversely affect histone methylation in already initiated cells. Lower Lys-9 methylation in normal/reactive cervical cells of women free of CIN in the post-fortification period than pre-fortification on the other hand suggests that fortification is likely to protect against	Needs confirmation.	Piyathilake (2010) Int J Womens Health 1: 131-7

		initiation of carcinogenic process in the cervix. These results suggest that mandatory fortification with folic acid in the US seems to have different effects on cancer depending on the stage of carcinogenesis. Because this is the first study to report folic acid fortification-associated differences in histone methylation and because of the limitations inherent to the approach we have taken to demonstrate these differences, validation of the results in other study populations or with other techniques for assessing histone methylation is necessary.		
Folic acid nutrition: what about the little children?	Letter	Points out very high folate levels in young children after fortification in USA: "After mandatory fortification, young children (age 4–11 y) also showed high folate concentrations: in the National Health and Nutrition Examination Survey (NHANES) 1999–2000, 42% had serum folate concentrations .45 nmol/L, although this proportion declined to 19% in the survey carried out in 2003–2004 (5). The Quinlivan formula was obtained for adults so it cannot easily be applied here, but it is likely that many children are today consuming more than the Institute of Medicine's UL for children of 300–400 microg/d. These recent articles (1, 2) do not examine the sources of folic acid in children, and so we have no idea whether these high concentrations are related to flour fortification (ie, through amount of flour products consumed by the child), to the child's choice of RTE cereal, or to use of supplements."	See detailed studies on children in USA by Bailey (2010) Am J Clin Nutr 92: 353-358 and by Yeung (2011) Am J Clin Nutr 93: 172-85 (Table 4)	Smith (2010) Am J Clin Nutr 91: 1408-9; author reply 1409
Antioxidant and DNA methylation-related nutrients and risk of distal colorectal cancer	Case-control study	OBJECTIVE: To investigate the relationship between antioxidant nutrients (vitamins C and E, beta-carotene, selenium) and DNA methylation-related nutrients (folate, vitamins B6 and B12) and distal colorectal cancer risk in whites and African Americans and to examine intakes from food only versus total (food plus dietary supplements) intakes. METHODS: Data are from the North Carolina Colon Cancer Study-Phase II, a case-control study of 945 distal colorectal cancer (including sigmoid, rectosigmoid, and rectum) cases and 959 controls. In-person interviews captured usual dietary intake and various covariates. Multivariate logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI). RESULTS: High intakes of each antioxidant and DNA methylation-related nutrient were significantly associated with lower risk in whites. In African Americans, the highest category of selenium from food only had a marginally significant inverse association with distal colorectal cancer risk (Q4 vs. Q1 OR: 0.55, 95% CI 0.29-1.02). Supplements did not provide additional risk reduction beyond intakes from food. CONCLUSIONS: Our findings provide evidence that antioxidant and DNA methylation-related nutrients may lower the risk of distal colorectal cancer in whites, and selenium may lower risk in African Americans. Optimal micronutrient intakes from food alone may be more beneficial than supplementation.		Williams (2010) Cancer Causes Control 21: 1171-81
Increase in the prevalence of the MTHFR 677 TT polymorphism in women	Population study	Background/Objectives: Folate has been recognized to ensure reproductive health and there is a growing body of epidemiological evidence suggesting that the methylenetetrahydrofolate reductase (MTHFR) 677T allele and	Compare Haggerty study Ref needed	Agodi (2011) Eur J Clin Nutr

born since 1959: potential implications for folate requirements		reduced dietary folate may increase the risk of cervical cancer. The main focus of our survey was to investigate the distribution of the MTHFR C677T polymorphism in relation to women's year of birth and to assess their folate intake and folic acid supplementation. Subjects/Methods: During a 6-months period, 307 healthy women of childbearing age in Catania, Italy, were enrolled in the cross-sectional study. Folate intake was estimated by a semiquantitative food frequency questionnaire and DNA extracted from blood samples for MTHFR C677T genotyping. Results: A TT genotype frequency of 20.5% with an increase in the prevalence of the TT genotype in the cohort of women born since 1959 was shown. The prevalence of inadequate folate intake was 51.5%, significantly higher in non-pregnant women (83.4%) than in pregnant ones (12.3%) with a decrease during the three trimesters of pregnancy (from 25.7 to 5.0%; P=0.013). The use of folic acid supplements improved during the three trimester of pregnancy (from 71.4 to 95.0%; P=0.001). Conclusions: Healthy young women may have higher folate needs due to increasing prevalence of the T allele and reduced folate intake compared with older groups. However, clinicians should be cautious when recommending supplements to women in late pregnancy due to the possible implications in the pregnancy outcome		
Pediatric cancer rates after universal folic acid flour fortification in Ontario	Prospective population	Following the introduction of mandatory Canadian folic acid flour fortification in mid-1997, the incidence of selected childhood cancers that declined in Ontario prior to and subsequent to this public policy initiative was examined. A population-based cohort study of all incident cases of childhood malignancy in Ontario between the years 1985 and 2006 was conducted. Participants were identified from a database provided by the Pediatric Oncology Group of Ontario and included children 0 to 4 years of age and 5 to 9 years of age who were diagnosed with cancer. Among children aged 0 to 4 years, the incidence rate of Wilms' tumor declined from 1.94 to 1.43 per 100 000 (incidence rate ratio 0.74, 95% confidence interval, 0.57-0.95). No significant change was seen in the prefortification vs postfortification time periods for acute lymphoblastic leukemia, brain cancers, or embryonal cancers among the 0- to 4-year or 5- to 9-year age groups. There was an approximately 30% reduction in risk of Wilms' tumor following introduction of the initiative. This corroborates a recent case-control study from Germany. These data may also provide some reassurance that universal flour fortification does not heighten the risk of pediatric cancer		Grupp (2011) J Clin Pharmacol 51: 60-65
Folate fortification and survival of children with acute lymphoblastic leukemia	Observational population	Background: The antifolate drug methotrexate is a mainstay of treatment for children diagnosed with acute lymphoblastic leukemia (ALL). There have been concerns regarding the impact of folate fortification on the efficacy of methotrexate therapy and hence treatment outcomes of ALL. OBJECTIVE: The objective of this study was to evaluate whether folate fortification has been associated with a higher incidence of adverse outcomes in children with ALL. METHODS: In a retrospective, population-based study, using data from the Pediatric Oncology Group of Ontario (POGO), Ontario, Canada,		Kennedy (2011) Paediatr Drugs 13: 193-6

		and the WHO, we examined yearly and population-adjusted mortality rates in Canada, the US, and several European countries. RESULTS: Our analysis demonstrates that there has been a decreasing trend in ALL mortality numbers and rates between 1999 and 2005 in the US and Canada, in a similar degree to those in European countries where folate fortification is not implemented. CONCLUSION: These data suggest that folate fortification does not appear to have caused an increase in therapeutic failures in children with ALL.		
Do high blood folate concentrations exacerbate metabolic abnormalities in people with low vitamin B-12 status?	Population study	BACKGROUND: In elderly individuals with low serum vitamin B-12, those who have high serum folate have been reported to have greater abnormalities in the following biomarkers for vitamin B-12 deficiency: low hemoglobin and elevated total homocysteine (tHcy) and methylmalonic acid (MMA). This suggests that folate exacerbates vitamin B-12-related metabolic abnormalities. OBJECTIVE: We determined whether high serum folate in individuals with low serum vitamin B-12 increases the deleterious effects of low vitamin B-12 on biomarkers of vitamin B-12 cellular function. DESIGN: In this cross-sectional study, 2507 university students provided data on medical history and exposure to folic acid and vitamin B-12 supplements. Blood was collected to measure serum and red cell folate (RCF), hemoglobin, plasma tHcy, and MMA, holotranscobalamin, and ferritin in serum. RESULTS: In subjects with low vitamin B-12 concentrations (<148 pmol/L), those who had high folate concentrations (>30 nmol/L; group 1) did not show greater abnormalities in vitamin B-12 cellular function in any area than did those with lower folate concentrations (</=30 nmol/L; group 2). Group 1 had significantly higher holotranscobalamin and RCF, significantly lower tHcy, and nonsignificantly lower (P = 0.057) MMA concentrations than did group 2. The groups did not differ significantly in hemoglobin or ferritin. Compared with group 2, group 1 had significantly higher mean intakes of folic acid and vitamin B-12 from supplements and fortified food. CONCLUSIONS: In this young adult population, high folate concentrations did not exacerbate the biochemical abnormalities related to vitamin B-12 deficiency. These results provide reassurance that folic acid in fortified foods and supplements does not interfere with vitamin B-12 metabolism at the cellular level in a healthy population.	Claim not to agree with Morris Morris et al. (2007) Am J Clin Nutr 85: 193-200 or MillerMiller et al. (2009) Am J Clin Nutr 90: 1586-1592 BUT they defined high serum folate as above 30, while Morris used 59 and Miller used 45.	Mills (2011) Am J Clin Nutr

Table 3S. Reports of potentially beneficial effects of folic acid supplementation

Title	Type of study	Abstract	Comment	Reference
Maternal folate supplementation in pregnancy and protection against acute lymphoblastic leukaemia in childhood: a case-control study	Retrospective case-control study	BACKGROUND: Acute lymphoblastic leukaemia is the most common childhood cancer in more-developed countries but it has few recognised risk factors or preventive measures. We aimed to determine and assess the risk factors associated with this disease. METHODS: From 1984 to 1992, we investigated known and suspected risk factors for common acute lymphoblastic leukaemia diagnosed in a population-based case-control study of children aged 0-14 years in Western Australia. 83 children in the study group came from the sole referral centre for paediatric cancer in the state and 166 controls matched for age and sex were recruited through a postal survey of people randomly selected from the state electoral roll. We interviewed mothers of 83 study and 166 control children (82% and 74%, respectively, of those eligible). Fathers completed a self-administered questionnaire. FINDINGS: We recorded a protective association between iron or folate supplementation in pregnancy and risk of common acute lymphoblastic leukaemia in the child (odds ratio 0.37 [95% CI 0.21-0.65]; p=0.001). For iron alone, the odds ratio was 0.75 (0.37-1.51); only one mother took folate without iron. Further analyses of folate use with or without iron (0.40; 0.21-0.73) showed that the protective effect varies little by time of first use of supplements or for how long they were taken. The association was not weakened by adjustment for potentially confounding variables. INTERPRETATION: Our results, though unexpected, suggest that folate supplementation in pregnancy reduces the risk of common acute lymphoblastic leukaemia in the child.	Bias possible due to retrospective questionnaire. Doses of folic acid not known; always combined with iron but iron alone seemed ineffective	Thompson (2001) Lancet 358: 1935-40
Folate for depressive disorders: systematic review and meta-analysis of randomized controlled trials	Meta-analysis	The objective of this review was to determine the effectiveness, adverse effects and acceptability of folate in the treatment of depression. Electronic databases (Cochrane Controlled Trials Register and the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register) and reference lists were searched, and authors, experts and pharmaceutical companies contacted to identify randomized controlled trials that compared treatment with folic acid or 5'-methyltetrahydrofolic acid to an alternative treatment, for patients with a diagnosis of depressive disorder. Three randomized trials (247 participants) were included. Two studies assessed the use of folate in addition to other treatment, and found that adding folate reduced Hamilton Depression Rating Scale (HDRS) scores on average by a further 2.65 points [95% confidence interval (CI) 0.38-4.93]. Fewer patients treated with folate experienced a reduction in their HDRS score of less than 50% at 10 weeks (relative risk 0.47, 95% CI 0.24-0.92). The remaining study found no statistically significant difference when folate alone was compared with trazodone. The identified trials did not find evidence of any problems with the acceptability or safety of folate. The limited available evidence suggests folate may have a potential role as a supplement to other treatment for depression. It is currently unclear if this is the case both for people with normal folate levels, and for those with folate deficiency.	Suggestive evidence, but more trials needed	Taylor (2004) J Psychopharmacol 18: 251-6

Prenatal multivitamin supplementation and rates of congenital anomalies: a meta-analysis	Meta-analysis	BACKGROUND: The use of folic acid-fortified multivitamin supplements has long been associated with decreasing the risk of neural tube defects. Several studies have also proposed the effectiveness of these supplements in preventing other birth defects; however, such effects have never been systematically examined. OBJECTIVE: We conducted a systematic review and meta-analysis to evaluate the protective effect of folic acid-fortified multivitamin supplements on other congenital anomalies. METHODS: We searched Medline, PubMed, EMBASE, Toxline, Healthstar, and Cochrane databases for studies describing the outcome of pregnancies in women using multivitamin supplements that were published in all languages from January 1966 to July 2005. The references from all collected articles were reviewed for additional articles. Two independent reviewers who were blinded to the source and identity of the articles extracted data based on predetermined inclusion and exclusion criteria. Using a random effects model, rates of congenital anomalies in babies born to women who were taking multivitamin supplements were compared with rates in the offspring of controls who were not. RESULTS: From the initial search, 92 studies were identified; 41 of these met the inclusion criteria. Use of multivitamin supplements provided consistent protection against neural tube defects (random effects odds ratio[OR] 0.67, 95% confidence intervals [95% CI] 0.58-0.77 in case control studies; OR 0.52, 95% CI 0.39-0.69 in cohort and randomized controlled studies), cardiovascular defects (OR 0.78, 95% CI 0.67-0.92 in case control studies; OR 0.61, 95% CI 0.40-0.92 in cohort and randomized controlled studies), and limb defects (OR 0.48, 95% CI 0.30-0.76 in case control studies; OR 0.57, 95% CI 0.38-0.85 in cohort and randomized controlled studies). For cleft palate, case control studies showed OR 0.76 (95% CI 0.62-0.93), and cohort and randomized controlled studies showed OR 0.42 (95% CI 0.06-2.84); for oral cleft with or without cleft palate, case control studies showed OR 0.63 (95% CI 0.54-0.73), and cohort and randomized controlled studies showed OR 0.58 (95% CI 0.28-1.19); for urinary tract anomalies, case control studies showed OR 0.48 (95% CI 0.30-0.76), and cohort and randomized controlled studies showed OR 0.68 (95% CI 0.35-1.31); and for congenital hydrocephalus case control studies showed OR 0.37 (95% CI 0.24-0.56), and cohort and randomized controlled studies showed OR 1.54 (95% CI 0.53-4.50). No effects were shown in preventing Down syndrome, pyloric stenosis, undescended testis, or hypospadias. Conclusion: Maternal consumption of folic acid-containing prenatal multivitamins is associated with decreased risk for several congenital anomalies, not only neural tube defects. These data have major public health implications, because until now fortification of only folic acid has been encouraged. This approach should be reconsidered	Careful study but cannot conclude that effect is due to folic acid since most of the studies included other vitamins	Goh (2006) J Obstet Gynaecol Can 28: 680-9
Folate and neural tube defects	Review, mainly of trials	A protective effect of folate against the development of neural tube defects (NTDs), specifically, anencephaly and spina bifida, is now well recognized, having been established by a chain of clinical research studies over the past half century. This article summarizes the more important of these studies, which have led to the current situation in which all women capable of becoming pregnant are urged to ingest folic acid regularly. The recommended intakes are 4 mg/d for those at high risk (by virtue of a previous NTD pregnancy outcome) and 0.4 mg/d for all		Pitkin (2007) Am J Clin Nutr 85: 285S-288S

		others. However, a reduction in NTD births did not follow promulgation of these recommendations, and so folic acid fortification was mandated in the United States and some other countries. Although some controversy remains about the adequacy of fortification levels, the process was followed by significant improvement in folate indexes and a reduction of 25-30% in NTD frequency (about one-half of the proportion of cases assumed to be responsive to folate). The folate-NTD relation represents the only instance in which a congenital malformation can be prevented simply and consistently. Nevertheless, several research gaps remain: identification of the mechanism by which the defect occurs and how folate ameliorates it; characterization of the relative efficacy of food folate, folic acid added to foods, and folic acid by itself; delineation of the dose-response relations of folate and NTD prevention; and more precise quantification of the dose needed to prevent recurrences. States in text page 287S: 'The proportion of NTDs that can be prevented by periconceptional folic acid has not been established, but the general assumption is that it is probably in the area of 50–60%.'		
Efficacy of folic acid supplementation in stroke prevention: a meta-analysis	Meta-analysis	Background The efficacy of treatments that lower homocysteine concentrations in reducing the risk of cardiovascular disease remains controversial. Our aim was to do a meta-analysis of relevant randomised trials to assess the efficacy of folic acid supplementation in the prevention of stroke. Methods We collected data from eight randomised trials of folic acid that had stroke reported as one of the endpoints. Relative risk (RR) was used as a measure of the effect of folic acid supplementation on the risk of stroke with a random effect model. The analysis was further stratified by factors that could affect the treatment effects. Findings Folic acid supplementation significantly reduced the risk of stroke by 18% (RR 0.82, 95% CI 0.68-1.00; p=0.045). In the stratified analyses, a greater beneficial effect was seen in those trials with a treatment duration of more than 36 months (0.71, 0.57-0.87; p=0.001), a decrease in the concentration of homocysteine of more than 20% (0.77, 0.63-0.94; p=0.012), no fortification or partly fortified grain (0.75, 0.62-0.91; p=0.003), and no history of stroke (0.75, 0.62-0.90; p=0.002). In the corresponding comparison groups, the estimated RRs were attenuated and insignificant. Interpretation Our findings indicate that folic acid supplementation can effectively reduce the risk of stroke in primary prevention.		Wang (2007) Lancet 369: 1876-1882
Relation of higher folate intake to lower risk of Alzheimer disease in the elderly	Cohort study	BACKGROUND: Higher intake of folate and vitamins B6 (pyridoxine hydrochloride) and B12 (cyanocobalamin) may decrease the risk of Alzheimer disease (AD) through the lowering of homocysteine levels. OBJECTIVE: To relate intake of folate and vitamins B6 and B12 to AD risk. DESIGN AND PATIENTS: We followed up 965 persons 65 years or older without dementia at baseline for a mean +/- SD period of 6.1 +/- 3.3 person-years after the administration of a semiquantitative food frequency questionnaire. Total, dietary, and supplement intake of folate and vitamins B6 and B12 and kilocalorie intake were estimated from the questionnaire responses. We related energy-adjusted intake of folate and vitamins B6 and B12 to incident AD using the Cox proportional hazards regression model. MAIN OUTCOME MEASURE: Incident AD. RESULTS: We		Luchsinger (2007) Arch Neurol 64: 86-92

		found 192 cases of incident AD. The highest quartile of total folate intake was related to a lower risk of AD (hazard ratio, 0.5; 95% confidence interval, 0.3-0.9; P=.02 for trend) after adjustment for age, sex, education, ethnic group, the epsilon4 allele of apolipoprotein E, diabetes mellitus, hypertension, current smoking, heart disease, stroke, and vitamin B6 and B12 levels. Vitamin B6 and B12 levels were not related to the risk of AD. CONCLUSIONS: Higher folate intake may decrease the risk of AD independent of other risk factors and levels of vitamins B6 and B12. These results require confirmation with clinical trials.		
Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial	Clinical trial	BACKGROUND: Low folate and raised homocysteine concentrations in blood are associated with poor cognitive performance in the general population. As part of the FACIT trial to assess the effect of folic acid on markers of atherosclerosis in men and women aged 50-70 years with raised plasma total homocysteine and normal serum vitamin B12 at screening, we report here the findings for the secondary endpoint: the effect of folic acid supplementation on cognitive performance. METHODS: Our randomised, double blind, placebo controlled study took place between November, 1999, and December, 2004, in the Netherlands. We randomly assigned 818 participants 800 mug daily oral folic acid or placebo for 3 years. The effect on cognitive performance was measured as the difference between the two groups in the 3-year change in performance for memory, sensorimotor speed, complex speed, information processing speed, and word fluency. Analysis was by intention-to-treat. This trial is registered with clinicaltrials.gov with trial number NCT00110604. FINDINGS: Serum folate concentrations increased by 576% (95% CI 539 to 614) and plasma total homocysteine concentrations decreased by 26% (24 to 28) in participants taking folic acid compared with those taking placebo. The 3-year change in memory (difference in Z scores 0.132, 95% CI 0.032 to 0.233), information processing speed (0.087, 0.016 to 0.158) and sensorimotor speed (0.064, -0.001 to 0.129) were significantly better in the folic acid group than in the placebo group. INTERPRETATION: Folic acid supplementation for 3 years significantly improved domains of cognitive function that tend to decline with age.	Confirmed by De Jager et al for subjects with Mild Cognitive Impairment de Jager (2011) Int J Geriatr Psychiatry (on-line ahead of publication):	Durga (2007) Lancet 369: 208-16
Effects of folic acid supplementation on hearing in older adults: a randomized, controlled trial	Clinical trial	BACKGROUND: Age-related hearing loss is a common chronic condition of elderly persons. Low folate status has been associated with poor hearing. OBJECTIVE: To determine whether folic acid supplementation slows age-related hearing loss. DESIGN: Double-blind, randomized, placebo-controlled trial conducted from September 2000 to December 2004. SETTING: The Netherlands. PARTICIPANTS: 728 older men and women recruited from municipal and blood bank registries with plasma total homocysteine concentrations 13 micromol/L or greater serum and vitamin B12 concentrations 200 pmol/L or greater at screening, and no middle ear dysfunction, unilateral hearing loss, or pathologic ear conditions unrelated to aging. INTERVENTION: Daily oral folic acid (800 microg) or placebo supplementation for 3 years. MEASUREMENTS: 3-year change in hearing thresholds, assessed as the average of the pure-tone air conduction thresholds of both ears of the low (0.5-kHz, 1-kHz, and 2-kHz) and high (4-kHz, 6-kHz, and 8-kHz) frequencies. RESULTS: Initial median hearing thresholds were		Durga (2007) Ann Intern Med 146: 1-9

		11.7 dB (interquartile range, 7.5 to 17.5 dB) for low frequencies and 34.2 dB (interquartile range, 22.5 to 50.0 dB) for high frequencies. Sixteen participants (2%) were lost to follow-up. After 3 years, thresholds of the low frequencies increased by 1.0 dB (95% CI, 0.6 to 1.4 dB) in the folic acid group and by 1.7 dB (CI, 1.3 to 2.1 dB) in the placebo group (difference, -0.7 dB [CI, -1.2 to -0.1 dB]; P = 0.020). Folic acid supplementation did not affect the decline in hearing high frequencies. LIMITATIONS: The strict criterion for participation on the basis of serum homocysteine concentrations limits extrapolation to the general population. Folic acid fortification of food was prohibited in the Netherlands during the study, so baseline folate levels in participants were about half of those found in the U.S. population. CONCLUSIONS: Folic acid supplementation slowed the decline in hearing of the speech frequencies associated with aging in a population from a country without folic acid fortification of food. The effect requires confirmation, especially in populations from countries with folic acid fortification programs.		
Vitamin and mineral supplements in pregnancy and the risk of childhood acute lymphoblastic leukaemia: a case-control study	Population study and meta-analysis	BACKGROUND: An earlier case-control study from Western Australia reported a protective effect of maternal folic acid supplementation during pregnancy on the risk of childhood acute lymphoblastic leukaemia (ALL). The present study tested that association. METHODS: A national case-control study was conducted in New Zealand. The mothers of 97 children with ALL and of 303 controls were asked about vitamin and mineral supplements taken during pregnancy. RESULTS: There was no association between reported folate intake during pregnancy and childhood ALL (adjusted odds ratio (OR) 1.1, 95% confidence interval (CI) 0.5-2.7). Combining our results with the study from Western Australia and another study from Quebec in a meta-analysis gave a summary OR of 0.9 (95% CI 0.8-1.1). CONCLUSION: Our own study, of similar size to the Australian study, does not support the hypothesis of a protective effect of folate on childhood ALL. Neither do the findings of the meta-analysis.	Relatively small study; no power estimates reported. Meta-analysis a bit more convincing	Dockerty (2007) BMC Public Health 7: 136
Folate intake, markers of folate status and oral clefts: is the evidence converging?	Meta-analysis	BACKGROUND: The ability of folic acid in the periconceptional period to prevent the occurrence of neural tube defects has stimulated tremendous interest in its effects on other health outcomes. Its possible effect on oral clefts has generated considerable debate. The purpose of this systematic review and meta-analysis was to assemble evidence on the role of folate in the aetiology of cleft lip with or without cleft palate (CL/P) and cleft palate only (CPO). METHODS: Medline, PubMed, Embase, Science Citation Index and the HuGE Published Literature Database were searched to February 2007 for articles related to oral clefts and multivitamin use, dietary folate, folic acid fortification, biochemical markers of folate status and polymorphisms in 5,10-methylenetetrahydrofolate reductase (MTHFR) and other genes involved in folate metabolism. Random effects meta-analysis was conducted when appropriate. RESULTS: Maternal multivitamin use was inversely associated with CL/P [odds ratio (OR) 0.75, 95% CI 0.65-0.88, based on 5717 cases and 59 784 controls] but to a lesser extent CPO (OR 0.88, 95% CI 0.76-1.01, 2586 cases and 59 684 controls). The volume of evidence on dietary folate, fortification and biochemical and genetic measures of folate status is substantially less; in aggregate, the evidence suggests that no association		Johnson (2008) Int J Epidemiol 37: 1041-58

		exists but there is substantial heterogeneity between studies. CONCLUSIONS: The evidence is not converging and there is no strong evidence for an association between oral clefts and folic acid intake alone. Multivitamin use in early pregnancy, however, may protect against oral clefts, especially CL/P although this association may be confounded by other lifestyle factors associated with multivitamin use.		
Folic acid and multivitamin supplement use and risk of placental abruption: A population-based registry study	Large observational population register study	The authors investigated a possible association of supplemental folic acid and multivitamin use with placental abruption by using data on 280,127 singleton deliveries recorded in 1999-2004 in the population-based Medical Birth Registry of Norway. Odds ratios, adjusted for maternal age, marital status, parity, smoking, pregestational diabetes, and chronic hypertension, were estimated with generalized estimating equations for logistic regression models. Use of folic acid and/or multivitamin supplements before or any time during pregnancy was reported for 36.4% of the abruptions (0.38% of deliveries) and 44.4% of the nonabruptions. Compared with no use, any supplement use was associated with a 26% risk reduction of placental abruption (adjusted odds ratio = 0.74, 95% confidence interval: 0.65, 0.84). Women who had taken folic acid alone had an adjusted odds ratio of 0.81 (95% confidence interval: 0.68, 0.98) for abruption, whereas multivitamin users had an adjusted odds ratio of 0.72 (95% confidence interval: 0.57, 0.91), relative to supplement nonusers. The strongest risk reduction was found for those who had taken both folic acid and multivitamin supplements (adjusted odds ratio = 0.68, 95% confidence interval: 0.56, 0.83). These data suggest that folic acid and other vitamin supplementation during pregnancy may be associated with reduced risk of placental abruption.	Careful and convincing population study. Data on folic acid use collected during final hospitalization, but cannot exclude residual confounding. But Canadian population study after fortification did not find any effect McDonald (2005) Epidemiology 16: 419-20	Nilsen (2008) Am J Epidemiol 167: 867-74
Folic acid supplementation for the prevention of neural tube defects: an update of the evidence for the U.S. Preventive Services Task Force	Review	BACKGROUND: Neural tube defects (NTDs) are among the most common birth defects in the United States. In 1996, the U.S. Preventive Services Task Force (USPSTF) recommended that all women planning a pregnancy or capable of conception take a supplement containing folic acid to reduce the risk for NTDs. PURPOSE: To search for new evidence published since 1996 on the benefits and harms of folic acid supplementation for women of childbearing age to prevent neural tube defects in offspring, to inform an updated USPSTF recommendation. DATA SOURCES: MEDLINE and Cochrane Central Register of Controlled Trials searches from January 1995 through December 2008, recent systematic reviews, reference lists of retrieved articles, and expert suggestions. STUDY SELECTION: English-language randomized, controlled trials; cohort studies; case-control studies; systematic reviews; and meta-analyses were selected if they provided information on the benefits and harms of folic acid supplementation in women of childbearing age to reduce NTDs in offspring. DATA EXTRACTION: All studies were reviewed, abstracted, and rated for quality by using predefined USPSTF criteria. DATA SYNTHESIS: Four observational studies reported benefit of reduction of risk for NTDs associated with folic acid-containing supplements. Differences in study type and methods prevent the calculation of a summary of the reduction in risk. The one included study on harms reported that the association of twinning with folic acid intake disappeared after adjustment for in		Wolff (2009) Ann Intern Med 150: 632-9

		vitro fertilization and underreporting of folic acid intake. LIMITATIONS: The evidence on dose was limited. No evidence was found on the potential harm of masking vitamin B12 deficiency in women of childbearing age. The search focused on the association of NTDs with supplementation only and therefore does not provide a comprehensive review of the effects of folic acid on all possible outcomes or of the effects of dietary intake of folic acid. CONCLUSION: New observational evidence supports previous evidence from a randomized, controlled trial that folic acid-containing supplements reduce the risk for NTD-affected pregnancies. The association of folic acid use with twin gestation may be confounded by fertility interventions.		
Neural tube defects in Australia: trends in encephaloceles and other neural tube defects before and after promotion of folic acid supplementation and voluntary food fortification	Population survey	BACKGROUND: Use of periconceptional folic acid supplementation has been promoted in Western Australia since late 1992, and voluntary fortification of some foods with folic acid has been permitted in Australia since 1996. Reduced rates of neural tube defects (NTDs) have been observed since 1995. Aboriginal infants have a higher rate of NTDs, but no fall in rates has been documented. Encephaloceles have not been examined separately. METHODS: Data on anencephaly, spina bifida, and encephalocele were obtained from the Western Australian Birth Defects Registry. The prevalence ratio for each type of NTD was calculated, comparing 1993 to 1995 (promotion of supplements, no fortification) and 1996 to 2006 (promotion of supplements and voluntary fortification) with 1980 to 1992 (no promotion or fortification). RESULTS: From 1996 to 2006, there was a 32% reduction in anencephaly, 23% in spina bifida, and 34% in encephalocele compared with 1980 to 1992. There were no differences seen from 1993 to 1995 compared with 1980 to 1992. For Aboriginal infants, the rates were higher than for non-Aboriginal infants, for each type of NTD. The prevalence ratios, comparing 1996 to 2006 with 1980 to 1995, were 0.70 (CI, 0.61-0.79) for non-Aboriginal infants and 0.90 (CI, 0.61-1.32) for Aboriginal infants. CONCLUSIONS: Overall, the rates of encephalocele, anencephaly, and spina bifida have fallen to a similar extent in association with promotion of folic acid supplements and voluntary fortification. No such falls were seen for Aboriginal infants. These data will provide a useful baseline against which to monitor the effects of mandatory fortification on NTDs when it is introduced in Australia in September 2009.	The publicity campaign seemed to work	Bower (2009) Birth Defects Res A Clin Mol Teratol 85: 269-73
Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial	Clinical Trial	BACKGROUND AND PURPOSE: Elevated total homocysteine is associated with a higher risk of cerebrovascular disease. It is not known whether lowering homocysteine impacts on stroke risk, both in terms of severity and ischemic vs hemorrhagic stroke subtypes. Our aim was to determine whether vitamin therapy reduces the risk of ischemic and hemorrhagic stroke, as well as stroke-related disability. METHODS: We analyzed stroke outcomes among participants of the Heart Outcomes Prevention Evaluation 2 (HOPE 2) trial that randomized 5522 adults with known cardiovascular disease to a daily combination of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12, or matching placebo, for 5 years. RESULTS: Among 5522 participants, stroke occurred in 258 (4.7%) individuals during a mean of 5 years of follow-up. The geometric mean homocysteine concentration decreased by 2.2 micromol/L in the vitamin therapy	Consistent with population study of Yang Yang (2006) Circulation 113: 1335-43	Saposnik (2009) Stroke 40: 1365-72

		group and increased by 0.80 micromol/L in the placebo group. The incidence rate of stroke was 0.88 per 100 person-years in the vitamin therapy group and 1.15 per 100 person-years in the placebo group (hazard ratio [HR], 0.75; 95% CI, 0.59-0.97). Vitamin therapy also reduced the risk of nonfatal stroke (HR, 0.72; 95% CI, 0.54-0.95) but did not impact on neurological deficit at 24 hours (P=0.45) or functional dependence at discharge or at 7 days (OR, 0.95; 95% CI, 0.57-1.56). In subgroup analysis, patients aged younger than 69 years, from regions without folic acid food fortification, with higher baseline cholesterol and homocysteine levels, and those not receiving antiplatelet or lipid-lowering drugs at enrollment had a larger treatment benefit. CONCLUSIONS: Lowering of homocysteine with folic acid and vitamins B6 and B12 did reduce the risk of overall stroke, but not stroke severity or disability.		
Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: the Women's Antioxidant and Folic Acid Cardiovascular Study	Clinical trial	BACKGROUND: Observational epidemiologic studies indicate a direct association between homocysteine concentration in the blood and the risk of age-related macular degeneration (AMD), but randomized trial data to examine the effect of therapy to lower homocysteine levels in AMD are lacking. Our objective was to examine the incidence of AMD in a trial of combined folic acid, pyridoxine hydrochloride (vitamin B6), and cyanocobalamin (vitamin B12) therapy. METHODS: We conducted a randomized, double-blind, placebo-controlled trial including 5442 female health care professionals 40 years or older with preexisting cardiovascular disease or 3 or more cardiovascular disease risk factors. A total of 5205 of these women did not have a diagnosis of AMD at baseline and were included in this analysis. Participants were randomly assigned to receive a combination of folic acid (2.5 mg/d), pyridoxine hydrochloride (50 mg/d), and cyanocobalamin (1 mg/d) or placebo. Our main outcome measures included total AMD, defined as a self-report documented by medical record evidence of an initial diagnosis after randomization, and visually significant AMD, defined as confirmed incident AMD with visual acuity of 20/30 or worse attributable to this condition. RESULTS: After an average of 7.3 years of treatment and follow-up, there were 55 cases of AMD in the combination treatment group and 82 in the placebo group (relative risk, 0.66; 95% confidence interval, 0.47-0.93 [P = .02]). For visually significant AMD, there were 26 cases in the combination treatment group and 44 in the placebo group (relative risk, 0.59; 95% confidence interval, 0.36-0.95 [P = .03]). CONCLUSIONS: These randomized trial data from a large cohort of women at high risk of cardiovascular disease indicate that daily supplementation with folic acid, pyridoxine, and cyanocobalamin may reduce the risk of AMD.	Positive outcome	Christen (2009) Arch Intern Med 169: 335-41
Preconceptional folate supplementation and the risk of spontaneous preterm birth: a cohort study	Cohort study	BACKGROUND: Low plasma folate concentrations in pregnancy are associated with preterm birth. Here we show an association between preconceptional folate supplementation and the risk of spontaneous preterm birth. METHODS AND FINDINGS: In a cohort of 34,480 low-risk singleton pregnancies enrolled in a study of aneuploidy risk, preconceptional folate supplementation was prospectively recorded in the first trimester of pregnancy. Duration of pregnancy was estimated based on first trimester ultrasound examination. Natural length of pregnancy was defined as gestational age at delivery in pregnancies with no		Bukowski (2009) PLoS Med 6: e1000061

		medical or obstetrical complications that may have constituted an indication for delivery. Spontaneous preterm birth was defined as duration of pregnancy between 20 and 37 wk without those complications. The association between preconceptional folate supplementation and the risk of spontaneous preterm birth was evaluated using survival analysis. Comparing to no supplementation, preconceptional folate supplementation for 1 y or longer was associated with a 70% decrease in the risk of spontaneous preterm delivery between 20 and 28 wk (41 [0.27%] versus 4 [0.04%] spontaneous preterm births, respectively; HR 0.22, 95% confidence interval [CI] 0.08-0.61, p = 0.004) and a 50% decrease in the risk of spontaneous preterm delivery between 28 and 32 wk (58 [0.38%] versus 12 [0.18%] preterm birth, respectively; HR 0.45, 95% CI 0.24-0.83, p = 0.010). Adjustment for maternal characteristics age, race, body mass index, education, marital status, smoking, parity, and history of prior preterm birth did not have a material effect on the association between folate supplementation for 1 y or longer and spontaneous preterm birth between 20 and 28, and 28 to 32 wk (adjusted HR 0.31, 95% CI 0.11-0.90, p = 0.031 and 0.53, 0.28-0.99, p = 0.046, respectively). Preconceptional folate supplementation was not significantly associated with the risk of spontaneous preterm birth beyond 32 wk. The association between shorter duration (<1 y) of preconceptional folate supplementation and the risk of spontaneous preterm birth was not significant after adjustment for maternal characteristics. However, the risk of spontaneous preterm birth decreased with the duration of preconceptional folate supplementation (test for trend of survivor functions, p = 0.01) and was the lowest in women who used folate supplementation for 1 y or longer. There was also no significant association with other complications of pregnancy studied after adjustment for maternal characteristics. CONCLUSIONS: Preconceptional folate supplementation is associated with a 50%-70% reduction in the incidence of early spontaneous preterm birth. The risk of early spontaneous preterm birth is inversely proportional to the duration of preconceptional folate supplementation. Preconceptional folate supplementation was specifically related to early spontaneous preterm birth and not associated with other complications of pregnancy.		
Folic acid supplementation and spontaneous preterm birth: adding grist to the mill?	Editorial	Comment on Bukowski paper	Balanced review. Need for a trial	Callaway (2009) PLoS Med 6: e1000077
Periconception folic acid supplementation, fetal growth and the risks of low birth weight and preterm birth: the Generation R Study	Observational population	Countries worldwide, including the Netherlands, recommend that women planning pregnancy use a folic acid supplement during the periconception period. Some countries even fortify staple foods with folic acid. These recommendations mainly focus on the prevention of neural tube defects, despite increasing evidence that folic acid may also influence birth weight. We examined whether periconception folic acid supplementation affects fetal growth and the risks of low birth weight, small for gestational age (SGA) and preterm birth, in the Generation R Study in		Timmermans (2009) Br J Nutr 102: 777-85

		Rotterdam, the Netherlands. Main outcome measures were fetal growth measured in mid- and late pregnancy by ultrasound, birth weight, SGA and preterm birth in relation to periconception folic supplementation (0.4-0.5 mg). Data on 6353 pregnancies were available. Periconception folic acid supplementation was positively associated with fetal growth. Preconception folic acid supplementation was associated with 68 g higher birth weight (95 % CI 37.2, 99.0) and 13 g higher placental weight (95 % CI 1.1, 25.5), compared to no folic acid supplementation. In these analyses parity significantly modified the effect estimates. Start of folic acid supplementation after pregnancy confirmation was associated with a reduced risk of low birth weight (OR 0.61, 95 % CI 0.40, 0.94). Similarly, reduced risks for low birth weight and SGA were observed for women who started supplementation preconceptionally, compared to those who did not use folic acid (OR 0.43, 95 % CI 0.28, 0.69 and OR 0.40, 95 % CI 0.22, 0.72). In conclusion, periconception folic acid supplementation is associated with increased fetal growth resulting in higher placental and birth weight, and decreased risks of low birth weight and SGA.		
Periconceptional folic acid and multivitamin supplementation for the prevention of neural tube defects and other congenital abnormalities	Review	The pioneering studies of Smithells et al. showed the reduction of recurrent neural-tube defects (NTD) after periconceptional folic acid-containing multivitamin supplementation. The Hungarian Periconceptional Service was established in 1984, and this primary health care system offered a chance to organize a randomized controlled trial to check whether the supplementation of a multivitamin containing 0.8 mg of folic acid during the periconceptional period is appropriate for the reduction of a first occurrence of NTD in the family. This found a reduction of approximately 90% of primary NTD. An unexpected finding was a significant reduction in the rate of congenital abnormalities overall: 20.6 per 1000 in the 'multivitamin' group, and 40.6 per 1000 in the 'trace-element-like' placebo group (RR = 0.53, 95% CI: 0.35-0.70). When the 6 cases of NTD were excluded, this difference in the rates of major congenital abnormalities between the two study-groups remained very highly significant ($p < 0.0001$). Cardiovascular malformations and urinary tract defects were particularly affected. These findings were confirmed in the Hungarian cohort-controlled trial and by observational studies in other countries. Two questions remain to be answered. Is folic acid better alone or with multivitamins? What is the optimal dose of folic acid? Overall, the Hungarian experiences of periconceptional care have shown not only primary prevention of several severe congenital abnormalities but also a good cost-benefit balance.	Useful review of trials on other defects	Czeizel (2009) Birth Defects Res A Clin Mol Teratol 85: 260-8
Maternal use of folic acid supplements during pregnancy and four-year-old neurodevelopment in a population-based birth cohort	Observational cohort study	The use of folic acid supplements during very early pregnancy is recommended in order to reduce the incidence of neural tube defects. Little is known about the possible benefits of folic acid on child neurodevelopment. A total of 420 children (87% of those eligible) from a birth cohort had complete data for final analyses at age 4 years. Information about folic acid and other over-the-counter dietary supplements was obtained prospectively using interviewer-administered questionnaires at the end of the first trimester of pregnancy. Psychological outcomes were assessed by two psychologists and teachers 4 years later. Low		Julvez (2009) Paediatr Perinat Epidemiol 23: 199-206

		maternal socio-economic status, smoking, high parity and short duration of breast feeding were associated with lower prevalence of folic acid supplement use. Verbal (b = 3.98, SE = 1.69), motor (b = 4.54, SE = 1.66) and verbal-executive function (b = 3.97, SE = 1.68) scores, social competence (b = 3.97, SE = 1.61) and inattention symptom [OR = 0.46; 95% CI 0.22, 0.95] scores were associated with reported folic acid use. Reported folic acid supplement use during pregnancy was associated with improved neurodevelopment in children after adjusting for a number of sociodemographic and behavioural factors.		
Maternal MTHFR 677C>T genotype and dietary intake of folate and vitamin B(12): their impact on child neurodevelopment	Observational study	Using the Bayley test, the mental and psychomotor development in a cohort of 253 children were evaluated. Maternal dietary intake of vitamin B(12) and folate was assessed from a semiquantitative questionnaire administered during the first trimester of pregnancy. Maternal genotypes of MTHFR (677C>T and 1298A>C), were ascertained by PCR-RFLP. The 677T and 1298C variant alleles were present in 59% and 10% of participants, respectively. A dietary deficiency of vitamin B(12) was negatively associated with mental development (beta = -1.6; 95% CI = -2.8 to -0.3). In contrast, dietary intake of folate (< 400 mg/day) reduced the mental development index only among children of mothers who were carriers of the TT genotype (beta = -1.8; 95% CI = -3.6 to -0.04; P for interaction = 0.07). Vitamin B(12) and folate supplementation during pregnancy could have a favorable impact on the mental development of children during their first year of life, mainly in populations that are genetically susceptible.		del Rio Garcia (2009) Nutr Neurosci 12: 13-20
Possible association of folic acid supplementation during pregnancy with reduction of preterm birth: a population-based study	Retrospective population study	OBJECTIVE: Periconceptional folic acid or multivitamin supplementation is recommended for prospective pregnant women to prevent neural-tube defects. The question is whether it is worth continuing these supplementations after the first trimester of pregnancy or not. Thus the possible fetal growth promoting and/or preterm birth reducing effect of vitamin supplements in the second and mainly in the third trimester was studied. STUDY DESIGN: Comparison of birth outcomes of singletons born to primiparous pregnant women with prospectively and medically recorded vitamin supplement in the population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA), 1980-1996 contained 6293, 169, and 311 primiparae with folic acid alone, multivitamins and folic acid+multivitamin supplementation, respectively, and their data were compared to the data of 7319 pregnant women without folic acid and folic acid-containing multivitamin supplementation as reference. RESULTS: Mean gestational age was 0.3 week longer and mean birth weight was by 37 g higher in the group of folic acid alone, than in the reference group (39.2 weeks; 3216 g). The rate of preterm births (7.6%) was significantly lower compared with the reference sample (11.8%), but the rate of low birth weight newborns did not show significant reduction. Folic acid alone in the third trimester associated with 0.6 week longer gestational age and a more significant reduction in the rate of preterm births (4.8%). CONCLUSIONS: Minor increase in mean birth weight after high dose of folic acid supplementation during pregnancy would not be expected to result in too large babies; however, the significant reduction in the rate of preterm births may have great public health benefit	Folic acid late in pregnancy may be beneficial	Czeizel (2010) Eur J Obstet Gynecol Reprod Biol 148: 135-40

Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring	Observational cohort study	BACKGROUND: Maternal nutrition during pregnancy has been linked with fetal brain development and psychopathology in the offspring. We examined for associations of maternal folate status and dietary intake during pregnancy with brain growth and childhood behavioural difficulties in the offspring. METHODS: In a prospective cohort study, maternal red blood cell folate (RCF) was measured at 14 weeks of pregnancy and total folate intake (TFI) from food and supplements was assessed in early and late pregnancy. The offspring's head circumference and body weight were measured at birth and in infancy, and 100 mothers reported on children's behavioural difficulties at a mean age of 8.75 years using the Strengths and Difficulties Questionnaire. RESULTS: Lower maternal RCF and TFI in early pregnancy were associated with higher childhood hyperactivity (RCF: beta = -.24; p = .013; TFI: beta = -.24; p = .022) and peer problems scores (RCF: beta = -.28; p = .004; TFI: beta = -.28; p = .009) in the offspring. Maternal gestational RCF was positively associated with head circumference at birth (adjusted for gestational age), and mediation analyses showed significant inverse indirect associations of RCF with hyperactivity/inattention and peer problems via fetal brain growth. Adjustment for mother's smoking and drinking alcohol during pregnancy did not change the results. CONCLUSIONS: Although the associations are small and residual confounding is possible, our data provide preliminary support for the hypothesis that lower folate status in early pregnancy might impair fetal brain development and affect hyperactivity/inattention and peer problems in childhood.		Schlotz (2010) J Child Psychol Psychiatry 51: 594-602
Infant birth size is not associated with maternal intake and status of folate during the second trimester in Norwegian pregnant women	Cohort study	Maternal folate status and smoking are potentially strong risk factors for infant birth size. We assessed the association of several folate indicators and smoking with birth outcomes in a subsample of participants in the Norwegian Mother and Child Cohort Study, consisting of 2934 singleton pregnancies in 2002-2003. Blood plasma folate and cotinine concentrations and self-reported intake of food folate and supplemental folic acid were measured during the second trimester (median 18 wk). Birth outcomes included gestational age, infant birth weight, head circumference, crown-heel length, and small for gestational age (SGA). Mean total dietary folate intake from foods (mean 268.0 microg/d) and supplements (mean 187.7 microg/d) was 455.7 microg/d. Smokers (plasma cotinine > or = 85 nmol/L) had substantially lower supplemental folic acid intake than nonsmokers, but they did not differ regarding folate intake from food only. Nevertheless, smoking was correlated with plasma folate both before and after adjusting for total dietary folate intake (both P < 0.001). We found no significant associations of food folate intake, supplemental folic acid use, total dietary folate intake, or plasma folate with the various birth outcomes after adjustment for potential confounders. Consistent with previous studies, infant birth size was strongly predicted by maternal smoking (adjusted odds ratio for SGA: 2.3; 95% CI: 1.6, 3.3). This study of well-nourished Norwegian pregnant women suggests that dietary folate and plasma folate during the second trimester are not risk factors for infant birth size.		Nilsen (2010) J Nutr 140: 572-9
Effects and safety of periconceptional folate	Cochrane review	BACKGROUND: It has been reported that neural tube defects can be prevented with periconceptional folic acid supplementation. The effects of different doses,	Authoritative.	De-Regil (2010) Cochrane

supplementation for preventing birth defects		forms and schemes of folate supplementation for the prevention of other birth defects and maternal and infant outcomes are unclear. OBJECTIVES: This review updates and expands a previous Cochrane Review assessing the effects of periconceptional supplementation with folic acid to reduce neural tube defects (NTDs). We examined whether folate supplementation before and during early pregnancy can reduce neural tube and other birth defects (including cleft palate) without causing adverse outcomes for mothers or babies. SEARCH STRATEGY: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (July 2010). Additionally, we searched the international clinical trials registry platform and contacted relevant organisations to identify ongoing and unpublished studies. SELECTION CRITERIA: We included all randomised or quasi-randomised trials evaluating the effect of periconceptional folate supplementation alone, or in combination with other vitamins and minerals, in women independent of age and parity. DATA COLLECTION AND ANALYSIS: We assessed trials for methodological quality using the standard Cochrane criteria. Two authors independently assessed the trials for inclusion, one author extracted data and a second checked for accuracy. MAIN RESULTS: Five trials involving 6105 women (1949 with a history of a pregnancy affected by a NTD and 4156 with no history of NTDs) were included. Overall, the results are consistent in showing a protective effect of daily folic acid supplementation (alone or in combination with other vitamins and minerals) in preventing NTDs compared with no interventions/placebo or vitamins and minerals without folic acid (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.15 to 0.52). Only one study assessed the incidence of NTDs and the effect was not statistically significant (RR 0.08, 95% CI 0.00 to 1.33) although no events were found in the group that received folic acid. Folic acid had a significant protective effect for reoccurrence (RR 0.32, 95% CI 0.17 to 0.60). There is no statistically significant evidence of any effects on prevention of cleft palate, cleft lip, congenital cardiovascular defects, miscarriages or any other birth defects. There were no included trials assessing the effects of this intervention on maternal blood folate or anaemia at term. We found no evidence of short-term side effects. AUTHORS' CONCLUSIONS: Folic acid, alone or in combination with vitamins and minerals, prevents NTDs but does not have a clear effect on other birth defects.		Database Syst Rev CD007950
Protective effect of periconceptional folic acid supplements on the risk of congenital heart defects: a registry-based case-control study in the northern Netherlands	Case-control study	AIMS: To investigate the potentially protective of periconceptional folic acid use on the risk of congenital heart defects (CHDs) relative to other non-folate related malformations. METHODS AND RESULTS: We analysed data from a large regional register of birth defects (EUROCAT-Northern Netherlands), over a 10 year period (1996-2005) for a case-control study. The cases were mothers who had delivered infants with isolated or complex heart defects, without any related syndrome or genetic abnormality (n = 611). We used two control groups; one from the EUROCAT database and another from the general population. The registry controls consisted of mothers of children with a known chromosomal or genetic defect, and with infants with other non-folate related congenital malformations (n = 2401). Additional folic acid was taken as a single supplement or as a multivitamin containing folic acid in a dose of >or=400 microg daily. Mothers who	A thorough study, recognising its limitations. Not possible to distinguish between those using folic acid alone and those using multivitamins	van Beynum (2010) Eur Heart J 31: 464-71

		had used folate antagonists or who had diabetes, and mothers of children with oral clefts, hypospadias, limb reduction- or neural tube defects, were excluded from both groups. Potentially confounding factors of periconceptional folic acid use in relation to CHD were explored, including baby's birth year, maternal body mass index, education, maternal age at delivery of index baby, smoking behaviour, and alcohol use during pregnancy. Periconceptional folic acid use revealed an odds ratio (OR) of 0.82 (95% CI 0.68-0.98) for all types of CHD relative to other malformations. The estimated relative risk for CHDs of additional folic acid use compared with the general population was comparable [OR 0.74 (95%CI 0.62-0.88)]. Subgroup analysis showed an OR of 0.62 (95% CI 0.47-0.82) for isolated septal defects. The proportions of the potential confounders between mothers of case and control infants did not differ significantly. CONCLUSION: Our results support the hypothesis that additional periconceptional folic acid use reduces CHD risk in infants. Use of periconceptional folic acid supplements was related to approximately 20% reduction in the prevalence of any CHD. Given the relatively high prevalence of CHD worldwide, our findings are important for public health.		
Periconceptional nutrient intakes and risks of neural tube defects in California	Observational	BACKGROUND: This study investigated the association of neural tube defects (NTDs) with maternal periconceptional intake of folic acid-containing supplements and dietary nutrients, including folate, among deliveries that occurred after folic acid fortification in selected California counties. METHODS: The population-based case-control study included fetuses and live born infants with spina bifida (189) or anencephaly (141) and 625 nonmalformed, live born controls delivered from 1999 to 2003. Mothers reported supplement use during telephone interviews, which included a 107-item food frequency questionnaire. For dietary nutrients, intakes <25th, 25th to <75th (reference), and > or =75th percentile were compared, based on control distributions. RESULTS: After adjustment for potential confounders, any versus no supplement intake resulted in ORs of 0.8 (95% CI, 0.5-1.3) for anencephaly and 0.8 (95% CI, 0.6-1.2) for spina bifida. After stratification by maternal intake of vitamin supplements, most factors in the glycemic pathway were not associated with either NTD, with the exception of low levels of fructose and glucose that were significantly associated with anencephaly. Some nutrients that contribute to one-carbon metabolism showed lowered risks (folate, riboflavin, vitamins B6 and B12); others did not (choline, methionine, zinc). Antioxidant nutrients tended to be associated with lowered risks (vitamins C, E, A, beta-carotene, lutein). CONCLUSIONS: Mothers' intake of vitamin supplements was modestly if at all associated with a lowered risk of NTDs. Dietary intake of several nutrients contributing to one-carbon metabolism and oxidative stress were associated with reduced NTD risk.		Carmichael (2010) Birth Defects Res A Clin Mol Teratol 88: 670-8
Effect of folic acid, with or without other B vitamins, on cognitive decline: meta-analysis	Meta-analysis	PURPOSE: We aimed to quantify the effect of folic acid supplementation on the prevention of cognitive decline. METHODS: We conducted a meta-analysis of 9 placebo-controlled randomized trials (2835 participants, median duration 6 months) of folic acid, with or without other B vitamins, on cognitive function. Standardized mean differences in cognitive function test scores were calculated	Median duration of trials reviewed was 6 months – too short to get an effect	Wald (2010) Am J Med 123: 522-527 e2

of randomized trials		between folic acid and placebo-treated groups. RESULTS: The standardized mean difference in cognitive function test scores was 0.01 (95% confidence interval [95% CI], -0.08 to 0.10), or an increase of 1% (95% CI, -8% to 10%) of 1 standard deviation. The results were similar within each of the 4 categories of cognitive function (memory, speed, language, and executive function); standardized mean differences were 0.01 (95% CI, -0.08 to 0.09), -0.01 (95% CI, -0.10 to 0.13), -0.05 (95% CI, -0.15 to 0.04), and 0.03 (95% CI, -0.13 to 0.19), respectively. CONCLUSION: Randomized trials show no effect of folic acid, with or without other B vitamins, on cognitive function within 3 years of the start of treatment. Trials of longer duration, recording the incidence of dementia, as well as cognitive decline, are needed.		
Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment. A randomized controlled trial	Clinical trial	Background. An increased rate of brain atrophy is often observed in older subjects, in particular those who suffer from cognitive decline. Homocysteine is a risk factor for brain atrophy, cognitive impairment and dementia. Plasma concentrations of homocysteine can be lowered by dietary administration of B vitamins. Objective: To determine whether supplementation with B vitamins that lower levels of plasma total homocysteine can slow the rate of brain atrophy in subjects with mild cognitive impairment in a randomised controlled trial (VITACOG, ISRCTN 94410159). Methods and Findings. Single-center, randomized, double-blind controlled trial of high-dose folic acid, vitamins B6 and B12 in 271 individuals (of 646 screened) over 70 y old with mild cognitive impairment. A subset (187) volunteered to have cranial MRI scans at the start and finish of the study. Participants were randomly assigned to two groups of equal size, one treated with folic acid (0.8 mg/d), vitamin B12 (0.5 mg/d) and vitamin B6 (20 mg/d), the other with placebo; treatment was for 24 months. The main outcome measure was the change in the rate of atrophy of the whole brain assessed by serial volumetric MRI scans. Results: A total of 168 participants (85 in active treatment group; 83 receiving placebo) completed the MRI section of the trial. The mean rate of brain atrophy per year was 0.76 % [95% CI, 0.63-0.90] in the active treatment group and 1.08 % [0.94-1.22] in the placebo group (P=0.001). The treatment response was related to baseline homocysteine levels: the rate of atrophy in participants with homocysteine >13 μmol/L was 53% lower in the active treatment group (P=0.001). A greater rate of atrophy was associated with a lower final cognitive test scores. There was no difference in serious adverse events according to treatment category. Conclusions and significance. The accelerated rate of brain atrophy in elderly with mild cognitive impairment can be slowed by treatment with homocysteine-lowering B vitamins. Sixteen percent of those over 70 y old have mild cognitive impairment and half of these develop Alzheimer's disease. Since accelerated brain atrophy is a characteristic of subjects with mild cognitive impairment who convert to Alzheimer's disease, trials are needed to see if the same treatment will delay the development of Alzheimer's disease.		Smith (2010) PLoS ONE 5: e12244
Folic acid supplements modify the adverse	Prospective population	Maternal smoking during pregnancy leads to increased risks of neonatal complications. The use of folic acid supplements might reduce the adverse effects		Bakker (2011) J Nutr 141: 2172-

effects of maternal smoking on fetal growth and neonatal complications	cohort	of smoking. We examined whether folic acid supplement use modifies the associations of maternal smoking with first trimester plasma homocysteine concentrations, fetal growth characteristics, and risks of neonatal complications. The associations were studied in 6294 mothers participating in a prospective population-based cohort study in The Netherlands. Main outcomes measurements were first trimester plasma homocysteine concentrations, fetal growth characteristics, and neonatal complications, including preterm birth, low birth weight, and small-size-for-gestational-age. Continued maternal smoking was associated with higher first trimester plasma homocysteine concentrations [difference 0.52 mumol/L (95% range = 0.20, 2.14)], lower third trimester fetal weight (difference -44 g (95% CI = -57, -31)], and birth weight [difference -148 g (95% CI = -179, -118)]. There were significant interactions between maternal smoking and folic acid supplements on all outcome measures (all P-interaction < 0.040). Among mothers who continued smoking during pregnancy, those who did not use folic acid supplements had the highest risk of delivering a child with low birth weight [OR = 3.45 (95% CI = 1.25, 9.54)] compared to those who did use periconceptional folic acid supplements. No significant effects were observed for the risks of preterm birth and small-size-for-gestational-age at birth. Our results suggest that some adverse effects of maternal smoking on fetal growth and neonatal outcomes might be reduced by the use of folic acid supplements. The observed interaction seems to be mainly driven by smoking in the first trimester only.		2179
Long term maintenance of neural tube defects prevention in a high prevalence state		OBJECTIVE: To assess the efficacy of folic acid (FA) supplementation and fortification in preventing neural tube defects (NTDs) in a high prevalence region of the United States. STUDY DESIGN: Active and passive surveillance methods were used to identify all fetuses/infants affected with an NTD in South Carolina. Prevalence rates were compared with FA intake to determine the effects of increased intake on NTD occurrence and recurrence. RESULTS: From 1992 to 2009, 916 NTD cases occurred in South Carolina, with isolated defects comprising 79% of cases. The NTD rate decreased 58% during this period. There was one NTD-affected pregnancy in 418 subsequent pregnancies (0.2%) in mothers with earlier NTD-affected pregnancies who consumed periconceptional FA supplements, and there were 4 NTDs in 66 pregnancies (6.1%) in which the mother did not take FA supplements. FA supplementation increased from 8% to 35% from 1992 to 2007, and knowledge of the protective benefits of FA increased from 8% to 65% in women of childbearing age. CONCLUSIONS: Increased periconceptional intake of FA appeared to reduce NTDs in a high-prevalence region. The rate of spina bifida and anencephaly in South Carolina is now essentially the same (0.69 cases per 1000 live births and fetal deaths) as the 1998 to 2005 US rate (0.69).		Collins (2011) J Pediatr 159: 143-149 e2
Folic acid supplementation and risk reduction in	Short review	Letter, no abstract. Extract: These new findings should stimulate the introduction of 2 different preventive strategies: periconceptional folic acid or folic acid–containing multivitamin supplementation for reduction in neural tube defects, and perhaps some other		Czeizel (2011) Am J Clin Nutr 94: 1651-2

preterm birth		serious birth defects, and a higher dose of folic acid supplementation in the second half of pregnancy to reduce the risk of certain types of pre-term birth. These 2 preventive efforts can significantly reduce the 2 major factors associated with infant mortality and disabilities: congenital abnormalities and pre-term birth.		
Prevention of neural-tube defects with periconceptional folic acid, methylfolate, or multivitamins?	Review	Background/Aims: To review the main results of intervention trials which showed the efficacy of periconceptional folic acid-containing multivitamin and folic acid supplementation in the prevention of neural-tube defects (NTD). Methods and Results: The main findings of 5 intervention trials are known: (i) the efficacy of a multivitamin containing 0.36 mg folic acid in a UK nonrandomized controlled trial resulted in an 83-91% reduction in NTD recurrence, while the results of the Hungarian (ii) randomized controlled trial and (iii) cohort-controlled trial using a multivitamin containing 0.8 mg folic acid showed 93 and 89% reductions in the first occurrence of NTD, respectively. On the other hand, (iv) another multicenter randomized controlled trial proved a 71% efficacy of 4 mg folic acid in the reduction of recurrent NTD, while (v) a public health-oriented Chinese-US trial showed a 41-79% reduction in the first occurrence of NTD depending on the incidence of NTD. Conclusions: Translational application of these findings could result in a breakthrough in the primary prevention of NTD, but so far this is not widely applied in practice. The benefits and drawbacks of 4 main possible uses of periconceptional folic acid/multivitamin supplementation, i.e. (i) dietary intake, (ii) periconceptional supplementation, (iii) flour fortification, and (iv) the recent attempt for the use of combination of oral contraceptives with 6S-5-methytetrahydrofolate (methylfolate), are discussed. Obviously, prevention of NTD is much better than the frequent elective termination of pregnancies after prenatal diagnosis of NTD fetuses.		Czeizel (2011) Ann Nutr Metab 58: 263-271
Folic acid supplement use in the prevention of neural tube defects	Review of Irish situation	In 2008, planned folic acid fortification for the prevention of Neural Tube Defects (NTD) was postponed. Concurrently, the economic recession may have affected dietary folic acid intake, placing increased emphasis on supplement use. This study examined folic acid supplement use in 2009. A cross-sectional survey of 300 ante-natal women was undertaken to assess folic acid knowledge and use. Associations between demographic, obstetric variables and folic acid knowledge and use were examined. A majority, 284/297 (96%), had heard of folic acid, and 178/297 (60%) knew that it could prevent NTD. Most, 270/297 (91%) had taken it during their pregnancy, but only 107/297 (36%) had used it periconceptionally. Being older, married, planned pregnancy and better socioeconomic status were associated with periconceptional use. Periconceptional folic acid use in 2009 was very low, little changed from earlier years. Continuous promotion efforts are necessary. Close monitoring of folic acid intake and NTD rates is essential, particularly in the absence of fortification.		Delany (2011) Ir Med J 104: 12-5
Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in	Clinical trial	Homocysteine is a risk factor for Alzheimer's disease. In the first report on the VITACOG trial, we showed that homocysteine-lowering treatment with B vitamins slows the rate of brain atrophy in mild cognitive impairment (MCI). Here we report the effect of B vitamins on cognitive and clinical decline (secondary outcomes) in the same study. METHODS: This was a double-blind, single-centre study, which		de Jager et al. (2011) Int J Geriatr Psychiatry (on-line ahead of

mild cognitive impairment: a randomized controlled trial		included participants with MCI, aged >/=70 y, randomly assigned to receive a daily dose of 0.8 mg folic acid, 0.5 mg vitamin B12 and 20 mg vitamin B6 (133 participants) or placebo (133 participants) for 2 y. Changes in cognitive or clinical function were analysed by generalized linear models or mixed-effects models. RESULTS: The mean plasma total homocysteine was 30% lower in those treated with B vitamins relative to placebo. B vitamins stabilized executive function (CLOX) relative to placebo (P = 0.015). There was significant benefit of B-vitamin treatment among participants with baseline homocysteine above the median (11.3 micromol/L) in global cognition (Mini Mental State Examination, P < 0.001), episodic memory (Hopkins Verbal Learning Test-delayed recall, P = 0.001) and semantic memory (category fluency, P = 0.037). Clinical benefit occurred in the B-vitamin group for those in the upper quartile of homocysteine at baseline in global clinical dementia rating score (P = 0.02) and IQCODE score (P = 0.01). CONCLUSION: In this small intervention trial, B vitamins appear to slow cognitive and clinical decline in people with MCI, in particular in those with elevated homocysteine. Further trials are needed to see if this treatment will slow or prevent conversion from MCI to dementia.		publication):
Folic Acid supplementation and pregnancy: more than just neural tube defect prevention	Review	Folate (vitamin B(9)) is an essential nutrient that is required for DNA replication and as a substrate for a range of enzymatic reactions involved in amino acid synthesis and vitamin metabolism. Demands for folate increase during pregnancy because it is also required for growth and development of the fetus. Folate deficiency has been associated with abnormalities in both mothers (anemia, peripheral neuropathy) and fetuses (congenital abnormalities). This article reviews the metabolism of folic acid, the appropriate use of folic acid supplementation in pregnancy, and the potential benefits of folic acid, as well as the possible supplementation of l-methylfolate for the prevention of pregnancy-related complications other than neural tube defects.		Greenberg (2011) Rev Obstet Gynecol 4: 52-9
Folic acid supplementation during pregnancy may protect against depression 21 months after pregnancy, an effect modified by MTHFR C677T genotype	Observational, cohort	Background/Objectives: As low folate status has been implicated in depression, high folate intake, in the form of supplements, during pregnancy might offer protection against depression during pregnancy and postpartum. Subjects/Methods: We examined the association between change in self-reported depressive symptoms (Edinburgh Postnatal Depression Scale) at different timepoints during and following pregnancy and self-reported folic acid supplementation during pregnancy in a prospective cohort of 6809 pregnant women. We also tested whether there was a main effect of methylenetetrahydrofolate reductase (MTHFR) C677T genotype (which influences folate metabolism and intracellular levels of folate metabolites and homocysteine) on change in depression scores, and carried out our analysis of folic acid supplementation and depression stratifying by genotype.Results:We found no strong evidence that folic acid supplementation reduced the risk of depression during pregnancy and up to 8 months after pregnancy. However, we did find evidence to suggest that folic acid supplements during pregnancy protected against depression 21 months postpartum, and that this effect was more pronounced in those with the MTHFR C677T TT genotype (change in depression		Lewis (2011) Eur J Clin Nutr in press:

		score from 8 months to 21 months postpartum among TT individuals was 0.66 (95% CI=0.31-1.01) among those not taking supplements, compared with -1.02 (95% CI=-2.22-0.18) among those taking supplements at 18 weeks pregnancy, P(difference)=0.01). Conclusions: Low folate is unlikely to be an important risk factor for depression during pregnancy and for postpartum depression, but may be a risk factor for depression outside of pregnancy, especially among women with the MTHFR C677T TT genotype.		
Folic acid in early pregnancy: a public health success story	Review	Folate is a water-soluble B vitamin that must be obtained in the diet or through supplementation. For >50 yr, it has been known that folate plays an integral role in embryonic development. In mice, inactivation of genes in the folate pathway results in malformations of the neural tube, heart, and craniofacial structures. It has been shown that diets and blood levels of women who had a fetus with a neural tube defect are low for several micronutrients, particularly folate. Periconceptional use of folic acid containing supplements decreased recurrent neural tube defects in the offspring of women with a previously affected child and the occurrence of a neural tube defect and possibly other birth defects in the offspring of women with no prior history. Based on these findings, the U.S. Public Health Service recommended that all women at risk take folic acid supplements, but many did not. Mandatory food fortification programs were introduced in numerous countries, including the United States, to improve folate nutritional status and have resulted in a major decrease in neural tube defect prevalence. The success story of folate represents the cooperation of embryologists, experimentalists, epidemiologists, public health scientists, and policymakers		Obican (2010) FASEB J 24: 4167-74
Folic acid supplements in pregnancy and severe language delay in children	Prospective population study	Prenatal folic acid supplements reduce the risk of neural tube defects and may have beneficial effects on other aspects of neurodevelopment. OBJECTIVE: To examine associations between mothers' use of prenatal folic acid supplements and risk of severe language delay in their children at age 3 years. DESIGN, SETTING, AND PATIENTS: The prospective observational Norwegian Mother and Child Cohort Study recruited pregnant women between 1999 and December 2008. Data on children born before 2008 whose mothers returned the 3-year follow-up questionnaire by June 16, 2010, were used. Maternal use of folic acid supplements within the interval from 4 weeks before to 8 weeks after conception was the exposure. Relative risks were approximated by estimating odds ratios (ORs) with 95% CIs in a logistic regression analysis. MAIN OUTCOME MEASURE: Children's language competency at age 3 years measured by maternal report on a 6-point ordinal language grammar scale. Children with minimal expressive language (only 1-word or unintelligible utterances) were rated as having severe language delay. RESULTS: Among 38,954 children, 204 (0.5%) had severe language delay. Children whose mothers took no dietary supplements in the specified exposure interval were the reference group (n = 9052 [24.0%], with severe language delay in 81 children [0.9%]). Adjusted ORs for 3 patterns of exposure to maternal dietary supplements were (1) other supplements, but no folic acid (n = 2480 [6.6%], with severe language delay in 22 children [0.9%]; OR, 1.04; 95% CI, 0.62-1.74); (2) folic acid only (n = 7127 [18.9%], with severe		Roth (2011) JAMA 306: 1566-73

		language delay in 28 children [0.4%]; OR, 0.55; 95% CI, 0.35-0.86); and (3) folic acid in combination with other supplements (n = 19,005 [50.5%], with severe language delay in 73 children [0.4%]; OR, 0.55; 95% CI, 0.39-0.78). CONCLUSION: Among this Norwegian cohort of mothers and children, maternal use of folic acid supplements in early pregnancy was associated with a reduced risk of severe language delay in children at age 3 years.		
Periconceptional intake of folic acid and food folate and risks of preterm delivery	Telephone interviews	We investigated multiple sources of folate and folic acid to determine whether their periconceptional intakes were associated with preterm delivery. Studied were controls from the National Birth Defects Prevention Study delivered September 1998 to December 2005. Telephone interviews were conducted with 5952 (68% of eligible) mothers. Women were queried about intake of vitamin supplements in the 12 weeks before conception through delivery. A version of the Nurse's Health Study food frequency questionnaire was used to assess food sources. Eight percent of infants (N = 487) were preterm (<37 weeks). Compared with women who began intake of supplements with folic acid before pregnancy, those who began any time during pregnancy had an ~20% lowered risk of preterm delivery. Lower dietary intakes showed a modest increased risk of preterm delivery: odds ratios were 1.44 (1.01 to 2.04) for lowest quartile intake of folate and 1.27 (0.95 to 1.69) for lowest quartile intake of folic acid compared with the highest. Findings suggest some evidence that folates influenced risks; however, an interpretation of results was also consistent with no association between intake of folates and preterm delivery.	Ambiguous outcome	Shaw (2011) Am J Perinatol
Reconciling the evidence on serum homocysteine and ischaemic heart disease: a meta-analysis	Meta-analysis	BACKGROUND: Results from genetic epidemiological studies suggest that raised serum homocysteine is a cause of ischaemic heart disease, but the results of randomised trials suggest otherwise. We aimed to update meta-analyses on each type of study using the latest published data and test a hypothesis based on antiplatelet therapy use in the trials to explain the discrepancy. METHODS AND FINDINGS: Meta-analyses of ischaemic heart disease using (i) 75 studies in which the prevalence of a mutation (CT) in the MTHFR gene (which increases homocysteine) was determined in cases (22,068) and controls (23,618), and (ii) 14 randomised trials (39,597 participants) of homocysteine lowering and ischaemic heart disease events. The summary estimates from the two analyses were compared. Meta-analysis of the MTHFR studies showed a statistically significantly increased risk of ischaemic heart disease in TT compared with CC homozygotes; odds ratio 1.16 (1.04 to 1.29) for a 1.9 micromol/L homocysteine difference (TT minus CC). Meta-analysis of randomised trials showed no significant reduction in IHD risk from folic acid; relative risk 1.00 (0.93 to 1.08), despite a reduction in homocysteine of 3.3 micromol/L. There was a statistically significant difference in risk reduction between the 5 trials with the lowest prevalence of antiplatelet therapy (60% on average, usually aspirin), RR 0.93 (0.84 to 1.05) and the 5 trials with the highest prevalence (91% on average), RR 1.09 (1.00 to 1.19), p = 0.037 for the difference. CONCLUSION: Discordant results from MTHFR studies and randomised trials could be explained by aspirin reducing or negating the anti-platelet effect of lowering homocysteine. On this	Folic acid for primary prevention – convincing case	Wald (2011) PLoS One 6: e16473

		basis, folic acid would have a role in the primary prevention of ischaemic heart disease, when aspirin is not taken routinely, but not in secondary prevention, when it is routine.		

Table 4S. Reports of potentially harmful effects of folic acid supplementation, or natural folate levels

Title	Type of study	Abstract	Comment	Reference
Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women	Cohort study	Folic acid (FA) supplements and food fortification are used to prevent neural tube defects and to lower plasma homocysteine. Through exposure to food fortification and vitamin supplement use, large populations in the United States and elsewhere have an unprecedented high FA intake. We evaluated dietary and supplemental intakes of folate and FA in relation to an index of immune function, natural killer cell (NK) cytotoxicity, among 105 healthy, postmenopausal women. Among women with a diet low in folate (<233 mug/d), those who used FA-containing supplements had significantly greater NK cytotoxicity (P = 0.01). However, those who consumed a folate-rich diet and in addition used FA supplements > 400 mug/d had reduced NK cytotoxicity compared with those consuming a low-folate diet and no supplements (P = 0.02). Prompted by this observation, we assessed the presence of unmetabolized FA in plasma as a biochemical marker of excess FA. Unmetabolized folic acid was detected in 78% of plasma samples from fasting participants. We found an inverse relation between the presence of unmetabolized FA in plasma and NK cytotoxicity. NK cytotoxicity was approximately 23% lower among women with detectable folic acid (P = 0.04). This inverse relation was stronger among women >/= 60 y old and more pronounced with increasing unmetabolized FA concentrations (P-trend = 0.002). Because of the increased intake of FA in many countries, our findings highlight the need for further studies on the effect of long-term high FA intake on immune function and health.	Important as first hint that unmetabolized folic acid may be harmful	Troen (2006) J Nutr 136: 189-94
Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Large prospective observational study	Background: Several epidemiologic studies suggest that higher folate intakes are associated with lower breast cancer risk, particularly in women with moderate alcohol consumption. Objective: We investigated the association between dietary folate, alcohol consumption, and postmenopausal breast cancer in women from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial cohort. Design: Dietary data were collected at study enrollment between 1993 and 2001. Folate content was assigned on the basis of prefortification (ie, pre-1998) databases. Of the 25 400 women participants with a baseline age of 55-74 y and with complete dietary and multivitamin information, 691 developed breast cancer between September 1993 and May 2003. We used Cox proportional hazard models with age as the underlying time metric to generate hazard ratios (HRs) and 95% CIs. Results: The adjusted HRs were 1.19 (95% CI: 1.01, 1.41; P for trend = 0.04) for women reporting supplemental folic acid intake ≥400 {micro}g/d compared with subjects	Shows that folic acid intake increases risk while natural folates do not	Stolzenberg-Solomon (2006) Am J Clin Nutr 83: 895-904

		reporting no supplemental intake. Comparison of the highest with the lowest quintile gave adjusted HRs of 1.04 (95% CI: 0.83, 1.31; P for trend = 0.56) and 1.32 (95% CI: 1.04, 1.68; P for trend = 0.03) for food and total folate intake, respectively. Alcohol consumption was positively associated with breast cancer risk (highest compared with lowest quintile: HR = 1.37; 95% CI: 1.08, 1.76; P for trend = 0.02); the risk was greatest in women with lower total folate intake. Conclusions: Our results do not support the hypothesis that high folate intake reduces breast cancer risk; instead, they suggest that a high intake, generally attributable to supplemental folic acid, may increase the risk in postmenopausal women. However, our results confirm previous studies showing positive associations between moderate alcohol consumption and breast cancer.		
Folate Intake, MTHFR Polymorphisms, and Risk of Esophageal, Gastric, and Pancreatic Cancer: A Meta-analysis	Meta-analysis	Background & Aims: Increasing evidence suggests that a low folate intake and impaired folate metabolism may be implicated in the development of gastrointestinal cancers. We conducted a systematic review with meta-analysis of epidemiologic studies evaluating the association of folate intake or genetic polymorphisms in 5,10-methylenetetrahydrofolate reductase (MTHFR), a central enzyme in folate metabolism, with risk of esophageal, gastric, or pancreatic cancer. Methods: A literature search was performed using MEDLINE for studies published through March 2006. Study-specific relative risks were weighted by the inverse of their variance to obtain random-effects summary estimates. Results: The summary relative risks for the highest versus the lowest category of dietary folate intake were 0.66 (95% confidence interval [CI], 0.53-0.83) for esophageal squamous cell carcinoma (4 case-control), 0.50 (95% CI, 0.39-0.65) for esophageal adenocarcinoma (3 case-control), and 0.49 (95% CI, 0.35-0.67) for pancreatic cancer (1 case-control, 4 cohort); there was no heterogeneity among studies. Results on dietary folate intake and risk of gastric cancer (9 case-control, 2 cohort) were inconsistent. In most studies, the MTHFR 677TT (variant) genotype, which is associated with reduced enzyme activity, was associated with an increased risk of esophageal squamous cell carcinoma, gastric cardia adenocarcinoma, noncardia gastric cancer, gastric cancer (all subsites), and pancreatic cancer; all but one of 22 odds ratios were >1, of which 13 estimates were statistically significant. Studies of the MTHFR A1298C polymorphism were limited and inconsistent. Conclusions: These findings support the hypothesis that folate may play a role in carcinogenesis of the esophagus, stomach, and pancreas.	Folate intake protective. Note MTHFR TT increased risk	Larsson (2006) Gastroenterology 131: 1271-83
Commentary: a case for minimizing folate supplementation in clinical regimens with pemetrexed based on the marked sensitivity of the drug to	Cell culture experiments	Pemetrexed is a novel antifolate recently approved for the treatment of pleural mesothelioma and non-small cell lung cancer. In clinical regimens, pemetrexed is administered in conjunction with folic acid to minimize toxicity. However, excessive folate supplementation may also diminish the activity of this agent. The current study demonstrates, in several human solid tumor cell lines, that when extracellular 5-formyltetrahydrofolate levels are increased in vitro, within the range of normal human blood levels, there		Chattopadhyay (2007) Oncologist 12: 808-15

folate availability		is a substantial decrease in pemetrexed activity upon continuous exposure to the drug. This was accompanied by a comparable lower level of trimetrexate activity consistent with an expansion of tumor cell folate pools. Likewise, when cells were exposed to pemetrexed with a schedule that simulates in vivo pharmacokinetics, there was markedly less cell killing with higher extracellular folate levels. Data are provided to indicate that 5-formyltetrahydrofolate is an acceptable surrogate for 5-methyltetrahydrofolate, the major blood folate, for this type of in vitro study. These observations and other reports suggest that, in view of the rise in serum folate and fall in serum homocysteine that has accompanied folic acid supplementation of food in the U.S., the addition of folic acid to regimens with pemetrexed should be limited to the lowest recommended level that provides optimal protection from pemetrexed toxicity.		
Folic acid for the prevention of colorectal adenomas: a randomized clinical trial	Clinical trial	Laboratory and epidemiological data suggest that folic acid may have an antineoplastic effect in the large intestine. OBJECTIVE: To assess the safety and efficacy of folic acid supplementation for preventing colorectal adenomas. DESIGN, SETTING, AND PARTICIPANTS: A double-blind, placebo-controlled, 2-factor, phase 3, randomized clinical trial conducted at 9 clinical centers between July 6, 1994, and October 1, 2004. Participants included 1021 men and women with a recent history of colorectal adenomas and no previous invasive large intestine carcinoma. INTERVENTION: Participants were randomly assigned in a 1:1 ratio to receive 1 mg/d of folic acid (n = 516) or placebo (n = 505), and were separately randomized to receive aspirin (81 or 325 mg/d) or placebo. Follow-up consisted of 2 colonoscopic surveillance cycles (the first interval was at 3 years and the second at 3 or 5 years later). MAIN OUTCOME MEASURES: The primary outcome measure was occurrence of at least 1 colorectal adenoma. Secondary outcomes were the occurrence of advanced lesions (> or =25% villous features, high-grade dysplasia, size > or =1 cm, or invasive cancer) and adenoma multiplicity (0, 1-2, or > or =3 adenomas). RESULTS: During the first 3 years, 987 participants (96.7%) underwent colonoscopic follow-up, and the incidence of at least 1 colorectal adenoma was 44.1% for folic acid (n = 221) and 42.4% for placebo (n = 206) (unadjusted risk ratio [RR], 1.04; 95% confidence interval [CI], 0.90-1.20; P = .58). Incidence of at least 1 advanced lesion was 11.4% for folic acid (n = 57) and 8.6% for placebo (n = 42) (unadjusted RR, 1.32; 95% CI, 0.90-1.92; P = .15). A total of 607 participants (59.5%) underwent a second follow-up, and the incidence of at least 1 colorectal adenoma was 41.9% for folic acid (n = 127) and 37.2% for placebo (n = 113) (unadjusted RR, 1.13; 95% CI, 0.93-1.37; P = .23); and incidence of at least 1 advanced lesion was 11.6% for folic acid (n = 35) and 6.9% for placebo (n = 21) (unadjusted RR, 1.67; 95% CI, 1.00-2.80; P = .05). Folic acid was associated with higher risks of having 3 or more adenomas and of noncolorectal cancers. There was no significant effect modification by sex, age, smoking, alcohol use, body mass index, baseline plasma folate,	Folic acid was associated with higher risks of having 3 or more adenomas and of noncolorectal cancers (prostate)	Cole (2007) Jama 297: 2351-9

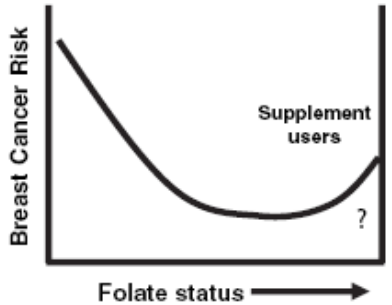
		or aspirin allocation. CONCLUSIONS: Folic acid at 1 mg/d does not reduce colorectal adenoma risk. Further research is needed to investigate the possibility that folic acid supplementation might increase the risk of colorectal neoplasia		
High folate intake is associated with lower breast cancer incidence in postmenopausal women in the Malmo Diet and Cancer cohort	Observational cohort study	Background: Epidemiologic studies of associations between folate intake and breast cancer are inconclusive, but folate and other plant food nutrients appear protective in women at elevated risk. Objective: The objective was to examine the association between folate intake and the incidence of postmenopausal breast cancer. Design: This prospective study included all women aged [≥]50 y (n = 11699) from the Malmo Diet and Cancer cohort. The mean follow-up time was 9.5 y. We used a modified diet-history method to collect nutrient intake data. At the end of follow-up, 392 incident invasive breast cancer cases were verified. We used proportional hazard regression to calculate hazard ratios (HRs). Results: Compared with the lowest quintile, the incidence of invasive breast cancer was reduced in the highest quintile of dietary folate intake (HR: 0.56; 95% CI: 0.35, 0.90; P for trend = 0.02); total folate intake, including supplements (HR: 0.56; 95% CI: 0.34, 0.91; P for trend = 0.006); and dietary folate equivalents (HR: 0.59; 95% CI: 0.36, 0.97; P for trend = 0.01). Conclusion: A high folate intake was associated with a lower incidence of postmenopausal breast cancer in this cohort.	N.B. Association only significant after multiple adjustments. See also Ericson Ericson (2009) Am J Clin Nutr 90: 1380-1389 {Ericson, 2010 #406}	Ericson (2007) Am J Clin Nutr 86: 434-443
MTHFR C677T and colorectal cancer risk: A meta-analysis of 25 populations	Meta-analysis	The common functional methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism may influence the risk of colorectal cancer (CRC), but data from published studies with individually low statistical power are conflicting. To clarify the role of MTHFR C677T genotype in CRC, we considered all available studies in a meta-analysis. Studies reporting on MTHFR C677T genotype and CRC were searched in PubMed up to April 2006. The principle prior hypothesis was that homozygosity for MTHFR 677TT would be associated with reduced risk of CRC. Data were available for 29,931 subjects, including 12,243 with CRC, from 25 independent populations. Compared to the homozygous CC genotype, the MTHFR 677TT genotype was associated with a reduced risk of CRC (odds ratio (OR): 0.83; 95% confidence interval (CI): 0.75-0.93; p = 0.001). There was some heterogeneity among the results of individual studies, but this was not statistically significant (heterogeneity p = 0.12; I2 = 25.8%). Heterozygosity for MTHFR 677 did not influence CRC risk (OR: 0.99; 95% CI: 0.94-1.04). These findings indicate that individuals homozygous for the MTHFR 677TT genotype are at moderately reduced risk of CRC, and support the proposal that common genetic variation in the MTHFR gene contributes to CRC susceptibility, probably accounting for at least 9% of the total incidence.	MTHFR 677TT at reduced risk. Subgroups	Hubner (2007) Int J Cancer 120: 1027-35
Thymidylate synthase polymorphisms, folate and B-vitamin intake, and risk	Case-control study	The effects of polymorphisms in genes coding for key folate metabolism enzymes such as thymidylate synthetase (TS) on colorectal neoplasia risk are likely to be influenced by gene-gene and gene-nutrient interactions. We	Subgroups	Hubner (2007) Br J Cancer 97: 1449-56

of colorectal adenoma		investigated the combined effects of three polymorphisms in the TS gene region, TSER, TS 3R G>C, and TS 1494del6, dietary intakes of folate and other B vitamins, and genotype for other folate metabolism variants, in a colorectal adenoma (CRA) case-control study. Individuals homozygous for TS 1494del6 del/del were at significantly reduced CRA risk compared to those with either ins/del or ins/ins genotypes (odds ratio 0.52; 95% confidence interval: 0.31-0.85, P=0.009). We also observed evidence of interactions between TS 1494del6 genotype and intake of folate, and vitamins B6 and B12, and MTHFR C677T genotype, with the reduction in risk in del/del homozygotes being largely confined to individuals with high nutrient intakes and MTHFR 677CC genotype (P interaction=0.01, 0.006, 0.03, and 0.07, respectively). TSER genotype, when considered either alone or in combination with TS 3R G>C genotype, did not significantly influence CRA risk. These findings support a role for TS in colorectal carcinogenesis, and provide further evidence that functional polymorphisms in folate metabolism genes act as low-risk alleles for colorectal neoplasia and participate in complex gene-gene and gene-nutrient interactions.		
MTHFR C677T has differential influence on risk of MSI and MSS colorectal cancer	Case-control study	The majority of colorectal cancer (CRC) exhibiting the micosatellite instability (MSI) phenotype is due to hypermethylation of the hMLH1 gene promoter. We aimed to test the hypothesis that polymorphisms in genes coding for enzymes involved in folate metabolism play a role in altered promoter-specific hypermethylation and thus predispose to MSI CRC. Analysis of MSI was performed in 1,685 CRCs, and polymorphism genotypes were determined in germline DNA for all cases and 2,692 cancer-free controls. MSI was observed in 171 cancers (10.1%). Compared to homozygous wild-type individuals, those with MTHFR 677TT genotype were more likely to have MSI than microsatellite stable (MSS) CRC (odds ratio (OR) 1.90; 95% confidence interval (CI): 1.09-3.31). When MTHFR C677T genotype frequencies in MSS CRC cases were compared to controls, individuals with homozygous variant genotype were at 19% reduced risk of cancer compared to wild-type (OR = 0.81; 95%CI: 0.65-1.02). Conversely, when MSI CRC cases were compared to controls, individuals with one or two MTHFR 677T alleles were at 42% increased cancer risk (OR = 1.42; 95%CI: 1.02-1.96). Our observations indicate that MTHFR 677TT homozygous individuals are more likely to develop MSI CRC than those with wild-type genotype, and this common polymorphism has differential influences on MSI and MSS CRC risk. Stratification by MSI status should aid future studies investigating the complex relationships between genotype, environmental factors, and CRC risk.	N.B. difference between the sub-types of colorectal cancer with regard to MTHFR genotype	{Hubner, 2007 #432}
Folate related genes and the risk of tobacco-related cancers in Central Europe	Case-control study	Folate has been hypothesized to protect against aero-digestive cancers although the evidence is not yet conclusive due to possible confounding by other dietary factors. Sequence variants in folate pathway were suggested to be associated with plasma folate levels and are unlikely to be	Note that folate intake seemed to protect against TT effect on cancer risk	Hung (2007) Carcinogenesis 28: 1334-40

		confounded by other lifestyle factors. We therefore investigated the effects of key folate genetic variants on the risk of aero-digestive cancers and their potential effect modification by folate intake in a multicenter study in Central Europe. A total of 2250 lung cases, 811 upper-aerodigestive tract (UADT) cases, and 2899 controls were recruited with blood samples. The MTHFR C677T variant was associated with an increased risk of lung cancer with an OR for homozygote variant of 1.37 (95%CI= 1.10-1.71). The two MTHFR variants were in strong linkage disequilibrium, and 677T-1298A appeared to be the primary haplotype associated with cancer risk. The risk estimates for MTHFR 677T/677T genotype was more prominent among lung cancer patients with young onset (OR=1.92, 95%CI=1.12-3.29). When stratified by dietary intake of folate, the effect of the MTHFR 677T variant was more prominent among subjects with low intake of folate: the ORs for 677T/677T genotype among subjects with the lowest decile were 2.60 (95%CI=1.39-4.88) and 4.14 (95%CI= 1.47-11.7) for lung and UADT cancer, respectively. In conclusion, we identified a moderate effect of MTHFR C677T on lung cancer risk and a possible effect modification by folate intake which is consistent with the functional data. These results support an important role of folate in protecting against tobacco-related cancers.	cf. Ebbing result in trial	
Folate and colorectal cancer: An evidence-based critical review	Review	Currently available evidence from epidemiologic, animal, and intervention studies does not unequivocally support the role of folate, a water-soluble B vitamin and important cofactor in one-carbon transfer, in the development and progression of colorectal cancer (CRC). However, when the portfolio of evidence from these studies is analyzed critically, the overall conclusion supports the inverse association between folate status and CRC risk. It is becoming increasingly evident that folate possesses dual modulatory effects on colorectal carcinogenesis depending on the timing and dose of folate intervention. Folate deficiency has an inhibitory effect whereas folate supplementation has a promoting effect on the progression of established colorectal neoplasms. In contrast, folate deficiency in normal colorectal mucosa appears to predispose it to neoplastic transformation, and modest levels of folic acid supplementation suppress, whereas supraphysiologic supplemental doses enhance, the development of cancer in normal colorectal mucosa. Several potential mechanisms relating to the disruption of one-carbon transfer reactions exist to support the dual modulatory role of folate in colorectal carcinogenesis. Based on the lack of compelling supportive evidence and on the potential tumor-promoting effect, routine folic acid supplementation should not be recommended as a chemopreventive measure against CRC at present.	Authoritative reviwe	Kim (2007) Mol Nutr Food Res 51: 267-292
Folate and risk of breast cancer: a meta-analysis	Meta-analysis of case-control and prospective	Epidemiologic findings are inconsistent concerning risk for breast cancer associated with low folate intake or blood folate levels. We performed a meta-analysis of prospective and case-control studies to examine folate intake and levels in relation to risk of breast cancer. Methods We searched	Possible interaction with alcohol consumption	Larsson (2007) J Natl Cancer Inst 99: 64-76

	studies	MEDLINE for studies of this association that were published in any language from January 1, 1966, through November 1, 2006. Study-specific risk estimates were pooled by use of a random-effects model. All statistical tests were two-sided. Results Folate intake in increments of 200 mug/day was not associated with the risk of breast cancer in prospective studies (estimated summary relative risk [RR] = 0.97, 95% confidence interval [CI] = 0.88 to 1.07, for dietary folate [eight studies; 302 959 participants and 8367 patients with breast cancer], and RR = 1.01, 95% CI = 0.97 to 1.05, for total folate [six studies; 306 209 participants and 8165 patients with breast cancer]) but was statistically significantly inversely associated with risk in case-control studies (estimated summary odds ratio [OR] = 0.80, 95% CI = 0.72 to 0.89, for dietary folate [13 studies; 8558 case patients and 10 812 control subjects], and OR = 0.93, 95% CI = 0.81 to 1.07, for total folate [three studies; 2184 case patients and 3233 control subjects]). High blood folate levels versus low levels were not statistically significantly associated with the risk of breast cancer in prospective studies (OR = 0.81, 95% CI = 0.59 to 1.10 [three studies]) or in case-control studies (OR = 0.41, 95% CI = 0.15 to 1.10 [two studies]). Among the two prospective studies and two case-control studies that stratified by alcohol consumption, high folate intake (comparing the highest with the lowest category) was associated with a statistically significant decreased risk of breast cancer among women with moderate or high alcohol consumption (summary estimate = 0.51, 95% CI = 0.41 to 0.63) but not among women with low or no alcohol consumption (summary estimate = 0.95, 95% CI = 0.78 to 1.15). Few studies examined whether the relation between folate intake and breast cancer was modified by intakes of methionine or vitamins B6 and B12, and the findings were inconsistent. Conclusion No clear support for an overall relationship between folate intake or blood folate levels and breast cancer risk was found. Adequate folate intake may reduce the increased risk of breast cancer that has been associated with moderate or high alcohol consumption.		
Folic acid and risk of twinning: a systematic review of the recent literature, July 1994 to July 2006	Review	OBJECTIVE: To assess the evidence of an association between periconceptional folic acid (FA) supplementation or fortification of foods with FA and the risk of twinning, using the Food Standards Australia New Zealand (FSANZ) framework for assessing evidence when substantiating nutrition, health and related claims on foods. DATA SOURCES: The Cochrane Library Database, MEDLINE, MEDLINE in Process, EMBASE, PubMed National Library of Medicine, and CINAHL were searched to identify systematic reviews and primary intervention and observational studies published from 1 July 1994 to 7 July 2006. STUDY SELECTION: One prospective and five retrospective cohort studies that assessed the rate of twinning in populations exposed to FA through supplementation, and six retrospective registry-based cohort studies examining twinning rates after fortification of foods with FA. DATA EXTRACTION: Two reviewers appraised eligible studies and evaluated data independently.		Muggli (2007) Med J Aust 186: 243-8

		DATA SYNTHESIS: The best maximal risk estimates of twinning after FA supplementation were an adjusted odds ratio (adjOR) of 1.26 (95% CI, 0.91-1.73) for preconceptional supplementation and dizygotic twinning and an adjOR of 1.02 (95% CI, 0.85-1.24) for overall twinning. Data from four FA fortification studies in the United States that allowed for calculation of an annual percentage increase showed a maximal annual increase in twinning rates of 4.6%. CONCLUSIONS: Overall, under the FSANZ framework, there is possible evidence for a relationship between periconceptional FA intake and increased twinning. To support this tentative relationship, more well designed, long-term follow-up studies are needed in places where fortification with FA has been introduced, focusing on dose-response and obtaining accurate data on infertility treatments.		
Dietary intake of folate and co-factors in folate metabolism, MTHFR polymorphisms, and reduced rectal cancer	Case-control study	Little is known about the contribution of polymorphisms in the methylenetetrahydrofolate reductase gene (MTHFR) and the folate metabolism pathway in rectal cancer alone. Data were from participants in a case-control study conducted in Northern California and Utah (751 cases and 979 controls). We examined independent associations and interactions of folate, B vitamins, methionine, alcohol, and MTHFR polymorphisms (MTHFR C677T and A1298C) with rectal cancer. Dietary folate intake was associated with a reduction in rectal cancer OR 0.66, 95% CI 0.48-0.92 (>475 mcg day compared to < = 322 mcg) as was a combination of nutrient intakes contributing to higher methyl donor status (OR 0.79, 95% CI 0.66-0.95). Risk was reduced among women with the 677 TT genotype (OR 0.54, 95% CI 0.30-0.9), but not men (OR 1.11, 95% CI 0.70-1.76) and with the 1298 CC genotype in combined gender analysis (OR 0.67, 95% CI 0.46-0.98). These data are consistent with a protective effect of increasing dietary folate against rectal cancer and suggest a protective role of the MTHFR 677 TT genotype in women and 1298 CC in men and women. Folate intake, low methyl donor status, and MTHFR polymorphisms may play independent roles in the etiology of rectal cancer.	Subgroups	Murtaugh (2007) Cancer Causes Control 18: 153-63
Medication use during pregnancy and the risk of childhood cancer in the offspring	Observational	The young age at onset of many cancers in childhood has led to investigations on maternal exposures during pregnancy. Data from a population-based case-control study in Germany (1992-1997) that included 1,867 cases and 2,057 controls was used to investigate this question. Maternal use of vitamin, folate or iron supplementation was associated with a reduced risk of non-Hodgkin lymphoma and tumors and, less clearly, with leukemia, but not with CNS tumors. An increased risk of neuroblastoma was associated most markedly with diuretics and other antihypertensives, but also with vitamin, folate or iron supplementation. No associations were seen with pain relievers, antinauseants or cold medications, nor with delivery by Caesarian section. The strengths of this study are its population base, the large number of cases and the inclusion of different case groups to identify disease specificity of associations. The limitation of this study is an exposure assessment relying on maternal self-	Unreliable, since mothers questioned up to 3 years after birth, after diagnosis!	Schuz (2007) Eur J Pediatr 166: 433-41

		reports. In conclusion, these data indicate a potential influence of some maternal medication during pregnancy on the risk of childhood cancer in the offspring; however, no clear picture is seen.		
Folate and cancer prevention: a closer look at a complex picture	Review	Editorial on the Ericson paper, shows hypothetical inverted U figure relating folate intake to risk 		Ulrich (2007) Am J Clin Nutr 86: 271-273
Folate and cancer--timing is everything	Editorial	No abstract. Extracts "…the prevalence of colorectal polyps among individuals older than 60 years approximates 30%.11 The question of the effect of folic acid on unresected polyps is particularly concerning," " a better understanding is needed about the dosage, duration, and timing effects of folic acid on the growth of early neoplastic lesions and slow-growing tumors, including, for example, a subset of prostate cancers.	Concern about folate intake in those with slow-growing preneoplastic tissues.	Ulrich (2007) JAMA 297: 2408-9
Dietary folate intake in combination with MTHFR C677T genotype and promoter methylation of tumor suppressor and DNA repair genes in sporadic colorectal adenomas	Case-control study	Methylation of the promoter region of tumor suppressor genes is increasingly recognized to play a role in cancer development through silencing of gene transcription. We examined the associations between dietary folate intake, MTHFR C677T genotype, and promoter methylation of six tumor suppressor and DNA repair genes. Patients with colorectal adenoma (n = 149) and controls (n = 286) with folate intake in the upper or lower tertile with the CC or TT genotype were selected from a case-control study. Methylation-specific PCRs were conducted on colorectal adenoma specimens. The percentages of promoter methylation ranged from 15.7% to 64.2%. In case-case comparisons, folate was inversely associated with promoter methylation, especially among TT homozygotes. Case-control comparisons suggested that folate was not associated with the occurrence of adenomas with promoter methylation, and increased the risk of unmethylated adenomas, especially in TT homozygotes. The interactions between folate and MTHFR genotype were most pronounced for O(6)-MGMT: compared with CC homozygotes with low folate intake, the adjusted odds ratios (95% confidence interval) of having a methylated O(6)-MGMT promoter were 3.39 (0.82-13.93) for TT homozygotes with low folate intake and 0.37 (0.11-1.29) for TT homozygotes with high folate intake (P interaction = 0.02); the odds ratios for the occurrence of	NB sub-groups again	van den Donk (2007) Cancer Epidemiol Biomarkers Prev 16: 327-33

		adenomas without methylation were 0.57 (0.16-2.11) for TT homozygotes with low folate intake and 3.37 (1.17-9.68) for TT homozygotes with high folate intake (P interaction = 0.03). In conclusion, folate intake seems to be inversely associated with promoter methylation in colorectal adenomas in case-case comparisons, and was positively associated with the occurrence of adenomas without promoter methylation in case-control comparisons, especially for TT homozygotes		
Folic acid fortification and public health: report on threshold doses above which unmetabolised folic acid appear in serum	Experimental clinical study	BACKGROUND: All flour in the USA is fortified with folic acid at a level of 140 microg/100 g which is estimated to supply an extra 100 microg daily to the average diet. Some researchers have advocated that this be increased to double and even four times this amount. Based on previous research these higher levels are likely to lead to the appearance of unmetabolised vitamin in the circulation, which may have safety implications for sub-groups of the population. The UK and the Republic of Ireland will likely introduce mandatory fortification also in the next year or so.The aim of this study was to capture the short-term effect of folic acid fortification on unmetabolised folic acid in serum after chronic consumption of folic acid. METHODS: After pre-saturation with 400 microg folic acid supplements daily for 14-weeks, healthy folate replete adults (n = 20) consumed folic acid fortified bread, at three different levels (400 microg, 200 microg, 100 microg) over a period of one week each. The dose was administered in two-equal sized slices consumed at 09.00 hrs and 13.00 hrs. Serum samples for total folate and folic acid were collected at baseline, after 14-weeks of supplementation, and pre and post (at 1, 2, 3 and 4 hours) each dose tested. RESULTS: Unmetabolised folic acid was detected after the 14-week supplementation period. Folic acid was not detected in either the 200 microg or 100 microg (current US regime) doses tested but was present at the highest level (400 microg) tested. CONCLUSION: Our findings suggest that persons exposed to the current US fortification programme supplying an average of 100 microg per day or less are unlikely to have unmetabolised folic acid in serum. It also seems that daily consumption of the higher level of 200 microg or less is unlikely to be problematic. Increasing the level however to 400 microg on the other hand is likely to lead to unmetabolised folic acid appearance.		Sweeney (2007) BMC Public Health 7: 41
Molecular basis of antifolate resistance	Review	Folates play a key role in one-carbon metabolism essential for the biosynthesis of purines, thymidylate and hence DNA replication. The antifolate methotrexate has been rationally-designed nearly 60 years ago to potently block the folate-dependent enzyme dihydrofolate reductase (DHFR) thereby achieving temporary remissions in childhood acute leukemia. Recently, the novel antifolates raltitrexed and pemetrexed that target thymidylate synthase (TS) and glycineamide ribonucleotide transformylase (GARTF) were introduced for the treatment of colorectal cancer and malignant pleural mesothelioma. (Anti)folates are divalent anions which predominantly use the reduced folate carrier (RFC) for their	Detailed review of mechanisms. Note: “The expansion of the intracellular folate pool resulted in a marked increase in antifolate resistance, particularly to hydrophilic	Assaraf (2007) Cancer Metastasis Rev 26: 153-81

		cellular uptake. (Anti)folates are retained intracellularly via polyglutamylation catalyzed by folylpoly-gamma-glutamate synthetase (FPGS). As the intracellular concentration of antifolates is critical for their pharmacologic activity, polyglutamylation is a key determinant of antifolate cytotoxicity. However, anticancer drug resistance phenomena pose major obstacles towards curative cancer chemotherapy. Pre-clinical and clinical studies have identified a plethora of mechanisms of antifolate-resistance; these are frequently associated with qualitative and/or quantitative alterations in influx and/or efflux transporters of (anti)folates as well as in folate-dependent enzymes. These include inactivating mutations and/or down-regulation of the RFC and various alterations in the target enzymes DHFR, TS and FPGS. Furthermore, it has been recently shown that members of the ATP-binding cassette (ABC) superfamily including multidrug resistance proteins (MRP/ABCC) and breast cancer resistance protein (BCRP/ABCG2) are low affinity, high capacity ATP-driven (anti)folate efflux transporters. This transport activity is in addition to their established facility to extrude multiple cytotoxic agents. Hence, by actively extruding antifolates, overexpressed MRPs and/or BCRP confer antifolate resistance. Moreover, down-regulation of MRPs and/or BCRP results in decreased folate efflux thereby leading to expansion of the intracellular folate pool and antifolate resistance. This chapter reviews and discusses the panoply of molecular modalities of antifolate-resistance in pre-clinical tumor cell systems in vitro and in vivo as well as in cancer patients. Currently emerging novel strategies for the overcoming of antifolate-resistance are presented. Finally, experimental evidence is provided that the identification and characterization of the molecular mechanisms of antifolate-resistance may prove instrumental in the future development of rationally-based novel antifolates and strategies that could conceivably overcome drug-resistance phenomena.	antifolates that depend on polyglutamylation for their pharmacological activity”	
Folate and colo-rectal cancer risk	Expert consensus	The UK Food Standards Agency convened a group of expert scientists to review current research investigating folate and colo-rectal cancer risk. The workshop aimed to examine current research and establish research priorities. The timing of folate exposure with respect to carcinogenesis, as well as the dose and form of folate, were considered key issues for future research. Also, the need to study further the influence of genetically defined subgroups was highlighted for future research.	Subgroups important	Sanderson (2007) Br J Nutr 98: 1299-304
Circulating concentrations of folate and vitamin B12 in relation to prostate cancer risk: results from the European Prospective Investigation into Cancer	Case-control study	BACKGROUND: Determinants of one-carbon metabolism, such as folate and vitamin B(12), have been implicated in cancer development. Previous studies have not provided conclusive evidence for the importance of circulating concentrations of folate and vitamin B(12) in prostate cancer etiology. The aim of the present study was to investigate the relationship between prostate cancer risk and circulating concentrations of folate and vitamin B(12) in a large prospective cohort. METHODS: We analyzed circulating concentrations of folate and vitamin B(12) in 869 cases and		Johansson (2008) Cancer Epidemiol Biomarkers Prev 17: 279-85

and Nutrition study		1,174 controls, individually matched on center, age, and date of recruitment, nested within the European Prospective Investigation into Cancer and Nutrition cohort. Relative risks (RR) for prostate cancer were estimated using conditional logistic regression models. RESULTS: Overall, no significant associations were observed for circulating concentrations of folate (P(trend) = 0.62) or vitamin B(12) (P(trend) = 0.21) with prostate cancer risk. RRs for a doubling in folate and vitamin B(12) concentrations were 1.03 [95% confidence interval (95% CI), 0.92-1.16] and 1.12 (95% CI, 0.94-1.35), respectively. In the subgroup of cases diagnosed with advanced stage prostate cancer, elevated concentrations of vitamin B(12) were associated with increased risk (RR for a doubling in concentration, 1.69; 95% CI, 1.05-2.72, P(trend) = 0.03). No other subgroup analyses resulted in a statistically significant association. CONCLUSION: This study does not provide strong support for an association between prostate cancer risk and circulating concentrations of folate or vitamin B12. Elevated concentrations of vitamin B12 may be associated with an increased risk for advanced stage prostate cancer, but this association requires examination in other large prospective studies.		
Folate intake and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort	Large population study	BACKGROUND: Folate is a B vitamin involved in one-carbon metabolism and has been postulated to influence the risk of breast cancer. However, epidemiologic studies of folate intake in relation to breast cancer risk are inconclusive. We examined the association between dietary folate intake and the risk of breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status of the breast tumor in the Swedish Mammography Cohort. METHODS: Our study population consisted of 61,433 women who completed a food frequency questionnaire at baseline (1987-1990) and again in 1997. Cox proportional hazards models were used to estimate rate ratios (RR) with 95% confidence intervals (95% CI). RESULTS: During an average of 17.4 years of follow-up, 2,952 incident cases of invasive breast cancer were ascertained. We observed no association between dietary folate intake and risk of total breast cancer or ER+/PR+ or ER-/PR- tumors. The multivariate RR of total breast cancer comparing extreme quintiles of folate intake was 1.01 (95% CI, 0.90-1.13; P(trend) = 0.84). However, folate intake was inversely associated with risk of ER+/PR- breast cancer (n = 417 cases; RR for highest versus lowest quintile, 0.79; 95% CI, 0.59-1.07; P(trend) = 0.01). Results did not vary by alcohol intake or menopausal status. CONCLUSIONS: These findings do not support an overall association between folate intake and risk of breast cancer but suggest that folate intake may be inversely associated with ER+/PR- tumors.	Subgroup appear to be protected by folate, but see Lin below	Larsson (2008) Cancer Epidemiol Biomarkers Prev 17: 3444-9
Plasma folate, vitamin B-6, vitamin B-12, and risk of breast cancer in women	Case-control study	BACKGROUND: B vitamins such as folate, vitamin B-6, and vitamin B-12 are coenzymes that are important for DNA integrity and stability. Deficiency in these B vitamins may promote tumor carcinogenesis. OBJECTIVE: We prospectively evaluated plasma concentrations of folate, pyridoxal 5-	Differs from Larsson above in that high folate levels were associated	Lin (2008) Am J Clin Nutr 87: 734-43

		phosphate (PLP; the principal active form of vitamin B-6), and vitamin B12 in relation to breast cancer risk. DESIGN: We included 848 incident cases of invasive breast cancer identified as of 31 March 2004, and 848 individually matched control subjects from 28 345 women in the Women's Health Study aged >/=45 y who provided blood samples and had no history of cancer and cardiovascular disease at baseline in 1993. Logistic regression controlling for matching factors and other risk factors for breast cancer was used to estimate relative risks (RRs) and 95% CIs. All statistical tests were 2 sided. RESULTS: Plasma concentrations of folate, PLP, and vitamin B-12 were not associated with overall risk of breast cancer. Women in the highest quintile group relative to those in the lowest quintile had multivariate RRs of 1.42 (95% CI: 1.00, 2.02) for plasma folate (P for trend = 0.21), 0.91 (95% CI: 0.63, 1.30) for plasma PLP (P for trend = 0.48), and 1.29 (95% CI: 0.92, 1.82) for plasma vitamin B12 (P for trend = 0.18). However, higher plasma folate concentrations were moderately associated with an increased risk of developing premenopausal breast cancer (P for trend = 0.04) and for developing estrogen receptor (ER)-positive or progesterone receptor (PR)-positive breast tumors (P for trend </= 0.06). Conversely, an inverse association was seen between plasma PLP and postmenopausal breast cancer (P for trend = 0.04). CONCLUSIONS: Data from this study suggest that B vitamins, including folate, vitamin B-6, and vitamin B12, may confer little or no reduction in overall risk of developing breast cancer. The observed positive associations of folate status with risk of developing premenopausal breast cancer and ER-positive or PR-positive tumors are unexpected. Additional research is needed to elucidate the role of folate in breast cancer development.	with an increased risk of ER+ or PR+ tumours. Note that Lin measured folate levels, while Larsson estimated intake	
Effect of combined folic acid, vitamin B6, and vitamin B12 on cancer risk in women: a randomized trial	Clinical trial	CONTEXT: Folate, vitamin B(6), and vitamin B(12) are thought to play an important role in cancer prevention. OBJECTIVE: To evaluate the effect of combined folic acid, vitamin B(6), and vitamin B(12) treatment on cancer risk in women at high risk for cardiovascular disease. DESIGN, SETTING, AND PARTICIPANTS: In the Women's Antioxidant and Folic Acid Cardiovascular Study, 5442 US female health professionals aged 42 years or older, with preexisting cardiovascular disease or 3 or more coronary risk factors, were randomly assigned to receive either a daily combination of folic acid, vitamin B(6), and vitamin B(12) or a matching placebo. They were treated for 7.3 years from April 1998 through July 31, 2005. INTERVENTION: Daily supplementation of a combination of 2.5 mg of folic acid, 50 mg of vitamin B(6), and 1 mg of vitamin B(12) (n = 2721) or placebo (n = 2721). MAIN OUTCOME MEASURES: Confirmed newly diagnosed total invasive cancer or breast cancer. RESULTS: A total of 379 women developed invasive cancer (187 in the active treatment group and 192 in the placebo group). Compared with placebo, women receiving the active treatment had similar risk of developing total invasive cancer (101.1/10,000 person-years for the active treatment group vs 104.3/10,000	Note trial started before fortification and continued afterwards. So placebo group serum folate went up from 8.8 to 15.4 ng/mL. N.B. age interacted with treatment and they found a protective effect in women > 65y: “A significantly reduced risk was observed for total invasive cancer (HR, 0.75; 95% CI, 0.57-0.99)	Zhang (2008) JAMA 300: 2012-21

		person-years for placebo group; hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.79-1.18; P = .75), breast cancer (37.8/10,000 person-years vs 45.6/10,000 person-years, respectively; HR, 0.83; 95% CI, 0.60-1.14; P = .24), or any cancer death (24.6/10,000 person-years vs 30.1/10,000 person-years, respectively; HR, 0.82; 95% CI, 0.56-1.21; P = .32). CONCLUSION: Combined folic acid, vitamin B(6), and vitamin B(12) treatment had no significant effect on overall risk of total invasive cancer or breast cancer among women during the folic acid fortification era.	and breast cancer (HR,0.62; 95% CI, 0.40-0.98) among women aged 65 years or older at study entry, but no reductions in risk were observed among younger women (40-54 years or 55-64 years)."	
Folic acid supplementation and cancer risk: point	Review	No Abstract, Extract: What can we conclude about the effect of folic acid fortification and supplementation on cancer risk? From the discussion above, it seems that folic acid fortification and periconceptional supplementation may reduce the risk of certain childhood cancers in the offspring (40-42). Furthermore, folic acid supplementation may prevent the development of cancers in normal tissues (9, 21, 22, 24-29). However, folic acid supplementation and fortification may promote the progression of already existing preneoplastic and neoplastic lesions (9, 19, 21-23, 39, 66, 68). However, the threshold level above which folic acid supplementation may exert the tumor promoting effect on preneopalstic and neoplastic lesions as well as dose-response of such a effect associated with folic acid supplementation have not been clearly established in humans nor can they be extrapolated from animal studies because inherent differences in folate absorption and metabolism between humans and rodents. Furthermore, it is unclear whether the potential tumor-promoting effect is limited to folic acid, the synthetic form of folate, and is generalizable to naturally occurring folate present in foods		Kim (2008) Cancer Epidemiol Biomarkers Prev 17: 2220-5
Folate and cancer prevention--where to next? Counterpoint	Review	No abstract. Extract: In summary, the recently completed Aspirin/Folate Polyp Prevention Trial has added an important chapter to the story of folate and cancer: the results raise concerns about the use of folic acid in older individuals who may harbor cancer precursors, as well as cancer patients. The exposure of the public to synthetic folic acid is high, particularly among consumers of supplements and fortified health foods. Thus, it is critical that we continue research on the effects of folate on carcinogenesis in the context of our knowledge of cancer biology. A dual role of folate in carcinogenesis is the most likely explanation for the somewhat contradictory research findings from epidemiology and the cancer prevention trial. Yet, we still need better quantitative experimental data on the growth-promoting effects of folate in carcinogenesis of the colon and other tissues to clarify the potential of adverse effects of folate at varied doses. A research agenda on folate and		Ulrich (2008) Cancer Epidemiol Biomarkers Prev 17: 2226-30

		cancer should aim to fill gaps in understanding the biological mechanisms (especially effects of folate status on epigenetics) and cancer etiology (dose response, genetic variability, and non-colon cancers). Yet, particularly important from a public health perspective are studies on the effects of high or excessive folate intakes in patients with cancer precursors or cancer, and the effects of these high intakes on their prognosis. In the absence of these important data to inform our decision making, what should be the current public health recommendations? First, as a safeguard, clinicians should inquire about the use of supplements among cancer patients and caution them against high intakes of folic acid from supplements, particularly when their nutritional intake in general is adequate or good. Second, countries that are currently considering mandatory fortification with folic acid (such as Australia and several European countries) may be best advised to defer decisions until more is known about the potential cancer-promoting effects of added folic acid.		
Does folic acid supplementation prevent or promote colorectal cancer? Results from model-based predictions	Mathematical model	Folate is essential for nucleotide synthesis, DNA replication, and methyl group supply. Low-folate status has been associated with increased risks of several cancer types, suggesting a chemopreventive role of folate. However, recent findings on giving folic acid to patients with a history of colorectal polyps raise concerns about the efficacy and safety of folate supplementation and the long-term health effects of folate fortification. Results suggest that undetected precursor lesions may progress under folic acid supplementation, consistent with the role of folate role in nucleotide synthesis and cell proliferation. To better understand the possible trade-offs between the protective effects due to decreased mutation rates and possibly concomitant detrimental effects due to increased cell proliferation of folic acid, we used a biologically based mathematical model of colorectal carcinogenesis. We predict changes in cancer risk based on timing of treatment start and the potential effect of folic acid on cell proliferation and mutation rates. Changes in colorectal cancer risk in response to folic acid supplementation are likely a complex function of treatment start, duration, and effect on cell proliferation and mutations rates. Predicted colorectal cancer incidence rates under supplementation are mostly higher than rates without folic acid supplementation unless supplementation is initiated early in life (before age 20 years). To the extent to which this model predicts reality, it indicates that the effect on cancer risk when starting folic acid supplementation late in life is small, yet mostly detrimental. Experimental studies are needed to provide direct evidence for this dual role of folate in colorectal cancer and to validate and improve the model predictions.	Model suggests that adults will suffer increased cancer, while children will be protected from later development of cancer	Luebeck (2008) Cancer Epidemiol Biomarkers Prev 17: 1360-7
Folic acid use in pregnancy and embryo selection	Observational, population	OBJECTIVE: Folic acid supplement use is recommended in pregnancy to reduce the risk of neural tube defect but concerns have been raised that increasing folic acid intake may select for embryos with genotypes that		Haggarty (2008) Bjog 115: 851-6

		increase disease risk in the offspring. Our aim was to test for this effect. DESIGN: Observational prospective cohort study. SETTING: Aberdeen Maternity Hospital. POPULATION OR SAMPLE: Women born before the introduction of folic acid advice (1970-80) and carrying singleton pregnancies (n = 1234) and their offspring (n = 1083) born after (2001-03). METHODS: We measured the genotype (MTHFR C677T and A1298C, MTR A2756G, MTRR A66G and TCN G776C) of mothers and their offspring, maternal supplement intake, intake of folate and vitamin B12 from natural foods and maternal blood folate and B12 status at 19 weeks of gestation. MAIN OUTCOME MEASURES: B vitamin related genotype of the offspring. RESULTS: There were no significant differences in any of the five genotype frequencies between mothers and their babies. There was no deviation from Hardy-Weinberg equilibrium in either generation and no change in the frequency of doubly homozygous MTHFR variants (677 TT/1298 CC). The genotype of the offspring was not related to maternal periconceptual supplement use, folate intake from foods or plasma and red cell folate measured at 19 weeks of gestation. CONCLUSIONS: We found no evidence to support the concern that folic acid fortification or supplement use in pregnancy results in selection of deleterious genotypes.		
Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study	Cohort study	AIMS/HYPOTHESIS: Raised maternal plasma total homocysteine (tHcy) concentrations predict small size at birth, which is a risk factor for type 2 diabetes mellitus. We studied the association between maternal vitamin B12, folate and tHcy status during pregnancy, and offspring adiposity and insulin resistance at 6 years. METHODS: In the Pune Maternal Nutrition Study we studied 700 consecutive eligible pregnant women in six villages. We measured maternal nutritional intake and circulating concentrations of folate, vitamin B12, tHcy and methylmalonic acid (MMA) at 18 and 28 weeks of gestation. These were correlated with offspring anthropometry, body composition (dual-energy X-ray absorptiometry scan) and insulin resistance (homeostatic model assessment of insulin resistance [HOMA-R]) at 6 years. RESULTS: Two-thirds of mothers had low vitamin B(12) (<150 pmol/l), 90% had high MMA (>0.26 mumol/l) and 30% had raised tHcy concentrations (>10 mumol/l); only one had a low erythrocyte folate concentration. Although short and thin (BMI), the 6-year-old children were relatively adipose compared with the UK standards (skinfold thicknesses). Higher maternal erythrocyte folate concentrations at 28 weeks predicted higher offspring adiposity and higher HOMA-R (both $p < 0.01$). Low maternal vitamin B(12) (18 weeks; $p = 0.03$) predicted higher HOMA-R in the children. The offspring of mothers with a combination of high folate and low vitamin B(12) concentrations were the most insulin resistant. CONCLUSIONS/INTERPRETATION: Low maternal vitamin B(12) and high folate status may contribute to the epidemic of adiposity and type 2 diabetes in India.	Possible epigenetic effect	Yajnik (2008) Diabetologia 51: 29-38
Folic acid supplements	Letter arising out	No Abstract		Baggott (2008)

are good (not bad) for rheumatoid arthritis patients treated with low-dose methotrexate	of article by Smith et al.	Smith reply refer to paper by Arabelovic cited in Table 2 Arabelovic (2007) J Am Coll Nutr 26: 453-5		Am J Clin Nutr 88: 479-80; author reply 480
Risk of colorectal cancer associated with the C677T polymorphism in 5,10-methylenetetrahydrofolate reductase in Portuguese patients depends on the intake of methyl-donor nutrients	Case-control study	BACKGROUND: Polymorphisms located in genes involved in the metabolism of folate and some methyl-related nutrients are implicated in colorectal cancer (CRC). OBJECTIVE: We evaluated the association of 3 genetic polymorphisms [C677T MTHFR (methylene tetrahydrofolate reductase), A2756G MTR (methionine synthase), and C1420T SHMT (serine hydroxymethyltransferase)] with the intake of methyl-donor nutrients in CRC risk. DESIGN: Patients with CRC (n = 196) and healthy controls (n = 200) matched for age and sex were evaluated for intake of methyl-donor nutrients and the 3 polymorphisms. RESULTS: Except for folate intake, which was significantly lower in patients (P = 0.02), no differences were observed in the dietary intake of other methyl-donor nutrients between groups. High intake of folate (>406.7 microg/d) was associated with a significantly lower risk of CRC (odds ratio: 0.67; 95% CI: 0.45, 0.99). The A2756G MTR polymorphism was not associated with the risk of developing CRC. In contrast, homozygosity for the C677T MTHFR variant (TT) presented a 3.0-fold increased risk of CRC (95% CI: 1.3, 6.7). Similarly, homozygosity for the C1420T SHMT polymorphism also had a 2.6-fold increased risk (95% CI: 1.1, 5.9) of developing CRC. When interactions between variables were studied, low intake of all methyl-donor nutrients was associated with an increased risk of CRC in homozygous participants for the C677T MTHFR polymorphism, but a statistically significant interaction was only observed for folate (odds ratio: 14.0; 95% CI: 1.8, 108.5). No significant associations were seen for MTR or SHMT polymorphisms. CONCLUSION: These results show an association between the C677T MTHFR variant and different folate intakes on risk of CRC.	Strong interaction between gene for MTHFR and folate in cancer risk: low folate and TT: odds ratio of 14. Subgroups again	Guerreiro (2008) Am J Clin Nutr 88: 1413-8
The effect of folic acid supplementation on the pharmacokinetics and pharmacodynamics of oral methotrexate during the remission-induction period of treatment for moderate-to-severe plaque psoriasis	Clinical Trial	OBJECTIVE: We assessed the effect of folic acid (FA) on the pharmacokinetics and pharmacodynamics of low-dose oral methotrexate (MTX) during the remission-induction phase of psoriasis treatment. METHODS: In a 32-week, open-label, two-way cross-over study, patients (n=20, seven men, aged 35-70 years) with moderate-to-severe plaque psoriasis were randomly assigned to receive MTX plus FA (20 mg/week) for 16 weeks followed by MTX monotherapy (three doses of MTX separated by 12-h intervals once a week) for an additional 16 weeks (treatment arm A, n=10) or to receive the opposite sequence of treatments (arm B, n=10). Dosing of MTX was individualised with the help of pre-study evaluation of plasma MTX pharmacokinetics. The Psoriasis Area and Severity Index (PASI), biochemistry and haematology tests and erythrocyte concentration of MTX polyglutamates (MTXPG) were evaluated throughout	Excellent study. Reduction if efficacy of MTX by folic acid treatment occurred at plasma folate levels between 20 and 40 nmol/L, i.e. levels attained by a large part of the population in USA after fortification	Chladek (2008) Eur J Clin Pharmacol 64: 347-55

		the study. RESULTS: In arms A and B, the mean (range) concentrations of MTXPG (nmol/L) were comparable [week 16: 96.2 (32.0-157) vs. 111 (73.7-175), P=0.32; week 32: 103 (55.8-173) vs. 83.6 (27.4-129), P=0.24]. After 16 weeks, the mean+/-SEM PASI decreased from 20.1+/-2.1 to 8.8+/-1.3 in arm A, while a greater reduction from 27.2+/-2.1 to 5.1+/-1.0 occurred in arm B (P<0.001). Positive correlations were found between the percent improvement in PASI at week 16 and the ratios of the concentration of MTXPG to plasma folate (rho=0.59, P=0.008) or RBC folate concentration (rho=0.56, P=0.013). Due to an accelerated decline in PASI in arm A and a trend to its worsening in arm B after crossing over of treatments, the mean absolute PASI scores in both arms were comparable at week 32. CONCLUSION: The antipsoriatic effect of MTX during the remission-induction phase of treatment is influenced by folate status and may be significantly less if combined treatment with FA is used, irrespective of pre-treatment folate levels. The individual tailoring of MTX dosing needs further attention because the mean percent PASI improvement from baseline was 83% and the inter-patient variability in response was low after 16 weeks of monotherapy with MTX.		
In utero supplementation with methyl donors enhances allergic airway disease in mice	Animal experiment	Asthma is a complex heritable disease that is increasing in prevalence and severity, particularly in developed countries such as the United States, where 11% of the population is affected. The contribution of environmental and genetic factors to this growing epidemic is currently not well understood. We developed the hypothesis, based on previous literature, that changes in DNA methylation resulting in aberrant gene transcription may enhance the risk of developing allergic airway disease. Our findings indicate that in mice, a maternal diet supplemented with methyl donors enhanced the severity of allergic airway disease that was inherited transgenerationally. Using a genomic approach, we discovered 82 gene-associated loci that were differentially methylated after in utero supplementation with a methyl-rich diet. These methylation changes were associated with decreased transcriptional activity and increased disease severity. Runt-related transcription factor 3 (Runx3), a gene known to negatively regulate allergic airway disease, was found to be excessively methylated, and Runx3 mRNA and protein levels were suppressed in progeny exposed in utero to a high-methylation diet. Moreover, treatment with a demethylating agent increased Runx3 gene transcription, further supporting our claim that a methyl-rich diet can affect methylation status and consequent transcriptional regulation. Our findings indicate that dietary factors can modify the heritable risk of allergic airway disease through epigenetic mechanisms during a vulnerable period of fetal development in mice.		Hollingsworth (2008) J Clin Invest 118: 3462-9
Prenatal maternal diet affects asthma risk in offspring	Editorial	No abstract. “One cannot ignore the observation that the increase in asthma prevalence over recent decades approximately coincides with worldwide campaigns that recommend periconceptional dietary folate	Useful and balanced	Miller (2008) J Clin Invest 118: 3265-8

		supplementation."		
Effect of supplemental folic acid in pregnancy on childhood asthma: A prospective birth cohort study	Observational cohort study	This study aimed to investigate the effect of the timing, dose, and source of folate during pregnancy on childhood asthma by using data from an Australian prospective birth cohort study (n = 557) from 1998 to 2005. At 3.5 years and 5.5 years, 490 and 423 mothers and children participated in the study, respectively. Maternal folate intake from diet and supplements was assessed by food frequency questionnaire in early (<16 weeks) and late (30-34 weeks) pregnancy. The primary outcome was physician-diagnosed asthma, obtained by maternal-completed questionnaire. Asthma was reported in 11.6% of children at 3.5 years (n = 57) and in 11.8% of children at 5.5 years (n = 50). Folic acid taken in supplement form in late pregnancy was associated with an increased risk of childhood asthma at 3.5 years (relative risk (RR) = 1.26, 95% confidence interval (CI): 1.08, 1.43) and with persistent asthma (RR = 1.32, 95% CI: 1.03, 1.69). The effect sizes did not change with adjustment for potential confounders. The association was similar at 5.5 years but did not reach statistical significance (RR = 1.17, 95% CI: 0.96, 1.42) in univariable models. These findings on childhood asthma support previous observations that supplementation with folate in pregnancy leads to an allergic asthma phenotype in mice via epigenetic mechanisms and is associated with poorer respiratory outcomes in young children.	Careful study	Whitrow (2009) Am J Epidemiol 170: 1486-93
Folic acid supplements in pregnancy and early childhood respiratory health	Observational population study	BACKGROUND: Folate supplementation is recommended for pregnant women to reduce the risk of congenital malformations. Maternal intake of folate supplements during pregnancy might also influence childhood immune phenotypes via epigenetic mechanisms. OBJECTIVE: To investigate the relationship between folate supplements in pregnancy and risk of lower respiratory tract infections and wheeze in children up to 18 months of age. METHODS: In the Norwegian Mother and Child Cohort Study, questionnaire data collected at several time points during pregnancy and after birth on 32,077 children born between 2000 and 2005 were used to assess the effects of folate supplements during pregnancy on respiratory outcomes up to 18 months of age, while accounting for other supplements in pregnancy and supplementation in infancy. RESULTS: Folate supplements in the first trimester were associated with increased risk of wheeze and respiratory tract infections up to 18 months of age. Adjusting for exposure later in pregnancy and in infancy, the relative risk for wheeze for children exposed to folic acid supplements in the first trimester was 1.06 (95% CI 1.03 to 1.10), the relative risk for lower respiratory tract infections was 1.09 (95% CI 1.02 to 1.15) and the relative risk for hospitalisations for lower respiratory tract infections was 1.24 (95% CI 1.09 to 1.41). CONCLUSIONS: Folic acid supplements in pregnancy were associated with a slightly increased risk of wheeze and lower respiratory tract infections up to 18 months of age. The results suggest that methyl donors in the maternal diet during pregnancy may influence		Haberg (2009) Arch Dis Child 94: 180-4

		respiratory health in children consistent with epigenetic mechanisms.		
Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review	Review	BACKGROUND: Methotrexate is a folic acid antagonist widely used for the treatment of inflammatory disorders for more than 50 years. Methotrexate is a standard systemic therapy for severe psoriasis and rheumatoid arthritis. Folic acid supplementation has been advocated to limit the toxicity of methotrexate on blood cells, gastrointestinal tract and liver. However, there is still controversy regarding the usefulness of folic acid supplementation. OBJECTIVES: We sought to assess the evidence for the efficacy of folic acid supplementation in patients treated with methotrexate for inflammatory diseases. We also investigated whether folic acid supplementation may decrease the efficacy of methotrexate. METHODS: Cochrane and MEDLINE databases were systematically searched. Randomized controlled trials in patients treated with methotrexate for rheumatoid arthritis or psoriasis with or without arthritis were included. Study selection, assessment of methodological quality, data extraction and analysis were carried out by two independent researchers. We selected double-blind randomized placebo-controlled trials. Analysis was performed for each subgroup of side-effects: gastrointestinal, mucocutaneous, haematological and hepatic. RESULTS: Six randomized controlled trials met the inclusion criteria, with a total sample of 648 patients. There were 257 patients in the placebo group, 198 patients treated with folic acid, and 193 patients treated with folinic acid. The statistical analysis showed a significant reduction of 35.8% of hepatic side-effects induced by methotrexate for patients with supplementation with folic or folinic acid (95% confidence interval -0.467 to -0.248). There was no statistical difference for mucocutaneous and gastrointestinal side-effects although there was a trend in favour of supplementation. The effect of supplementation on haematological side-effects could not be assessed accurately due to a low incidence of these events in the population studied. We were unable to analyse the effect of supplementation on the effectiveness of methotrexate, as markers of activity used in each study were not comparable. CONCLUSIONS: Supplementation with folic acid is an effective measure to reduce hepatic adverse effects associated with methotrexate treatment. There is no difference between folinic acid and folic acid, but the lower cost of the latter promotes its use	Cite 3 studies on RA in which a higher dose of MTX was required in patients treated with folate, one was statistically significant. In psoriasis, one trial showed lower efficacy in folate group, the other trial no difference. But the review was done before publication of the paper by Chladek Chladek et al. (2008) Eur J Clin Pharmacol 64: 347-55	Prey (2009) Br J Dermatol 160: 622-8
A randomized trial on folic acid supplementation and risk of recurrent colorectal adenoma	Clinical trial	BACKGROUND: Evidence from observational studies suggests that inadequate folate status enhances colorectal carcinogenesis, but results from some randomized trials do not support this hypothesis. OBJECTIVE: To assess the effect of folic acid supplementation on recurrent colorectal adenoma, we conducted a cost-efficient, double-blind, randomized trial among participants of 2 large prospective cohorts, the Health Professionals Follow-Up Study and the Nurses' Health Study. DESIGN: Participants were randomly assigned to receive folic acid (1 mg/d) (n = 338) or placebo (n = 334) for 3-6.5 y. The primary endpoint was any new diagnosis of adenoma	Note non-linear relationship. See discussion by Lee Lee (2011) Gastroenterology 141: 16-20	Wu (2009) Am J Clin Nutr 90: 1623-1631

		during the study period (May 1996-March 2004). Secondary outcomes were adenoma by site, stage, and number of recurrent adenomas. Associations were also examined by plasma folate concentrations at baseline. RESULTS: Incidence of at least one recurrent adenoma was not significantly associated with folic acid supplementation [relative risk (RR): 0.82; 95% CI: 0.59,1.13; P = 0.22]. Among participants with low plasma folate concentrations at baseline (</=7.5 ng/mL), those randomly assigned to receive folic acid experienced a significant decrease in adenoma recurrence (RR: 0.61; 95% CI: 0.42, 0.90; P = 0.01), whereas for subjects with high folate concentrations at baseline (>7.5 ng/mL), supplemental folic acid had no significant effect (RR: 1.28; 95% CI: 0.82, 1.99; P = 0.27, P(interaction) = 0.01). Contrary to findings from another clinical trial, there was no evidence for an increased risk of advanced or multiple adenomas. CONCLUSIONS: Our results do not support an overall protective effect of folic acid supplementation on adenoma recurrence. Folic acid supplementation may be beneficial among those with lower folate concentrations at baseline.		
Folate, cancer risk, and the Greek god, Proteus: a tale of two chameleons	Review	Evidence indicates that an abundant intake of foodstuffs rich in folate conveys protection against the development of colorectal cancer, and perhaps some other common cancers as well. The issue is complex, however, since some observations in animal and human studies demonstrate that an overly abundant intake of folate among those who harbor existing foci of neoplasia might instead produce a paradoxical promotion of tumorigenesis. The pharmaceutical form of the vitamin, folic acid, might affect the process in a manner that is distinct from natural forms of the vitamin, although this remains a speculative concept. Our limited understanding of this complex relationship is impeding efforts to move ahead with widespread folic acid fortification, but this delay may be necessary to ensure that such programs are instituted in a safe manner.	Thoughtful and balanced	Mason (2009) Nutr Rev 67: 206-12
Folate and colorectal cancer prevention	Review	Anti-folate chemotherapy agents such as methotrexate and fluorouracil reduce proliferation of neoplastic cells by inhibiting DNA synthesis. Paradoxically epidemiological data suggests an inverse relationship between dietary folate intake and incidence of colorectal cancer (CRC). On the basis of this and other putative health benefits around 35% of the North American population take folic acid supplements, in addition to natural food folates and fortified flour and cereal grains. Recently, randomised controlled trials investigating folic acid as a secondary preventative agent in colorectal neoplasia have shed further light on the relationship between folate and colorectal carcinogenesis, corroborating data from animal models indicating opposing effects dependent on the timing of exposure in relation to the development of neoplastic foci. A 'dual-modulator' role for folate in colorectal carcinogenesis has been proposed in which moderate dietary increases initiated before the establishment of neoplastic foci have a protective influence, whereas excessive intake or increased intake once	Balanced review. Makes a point about subgroups: “It is highly probable…..that studies seeking to define the relationship between folate intake and CRC risk that do not stratify subjects by genotype at two or three polymorphic loci at	Hubner (2009) Br J Cancer 100: 233-239

		early lesions are established increases tumorigenesis. Functional polymorphic variants in genes encoding key enzymes in the folate metabolic pathway add a further layer of complexity to the relationship between folate and CRC risk. Here, we review the evidence concerning the efficacy and safety of folate as a potential CRC chemopreventive agent.	the very least will miss important disease–nutrient associations in subgroups of the population defined by these genetic variants."	
Folate intake, methylenetetrahydrofolate reductase polymorphisms, and breast cancer risk in women from the Malmö Diet and Cancer Cohort	Observational cohort study	BACKGROUND: Single nucleotide polymorphisms (SNP) of the folate-metabolizing enzyme methylenetetrahydrofolate reductase (MTHFR) may modify associations between folate intake and breast cancer. We examined if the association between tertiles of dietary folate equivalents (DFE) and breast cancer was different in subgroups according to genotypes of the MTHFR 677 C>T (rs1801133) and 1298A>C (rs1801131) SNPs and if the polymorphisms per se were associated with breast cancer.METHODS: This nested case-control study included 544 incident cases with invasive breast cancer and 1,088 controls matched on age and blood sampling date from the population-based Malmo Diet and Cancer cohort. Genotyping of the MTHFR SNPs was done with PCR-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Odds ratios (OR) were obtained by unconditional logistic regression.RESULTS: DFE was positively associated with breast cancer in MTHFR 677CT/TT-1298AA women (P for trend = 0.01) but inversely associated in compound heterozygous women (P for trend = 0.01). Interaction was observed between DFE and the 1298C allele (P = 0.03). The 677T allele was associated with increased breast cancer risk in women above 55 years [multivariate adjusted OR, 1.34; 95% confidence interval (95% CI), 1.01-1.76] and an interaction was observed between the T allele and age (P = 0.03). Homozygosis for the 1298C allele was associated with increased risk in women between 45 and 55 years (multivariate adjusted OR, 1.89; 95% CI, 1.09-3.29).CONCLUSION: In conclusion, a positive association between DFE and breast cancer was observed in MTHFR 677CT/TT-1298AA women but an inverse association was observed in 677CT-1298AC women. The 677T allele was associated with higher breast cancer risk in women above 55 years of age.	Important example of subgroups determining the outcome of folate effects	Ericson (2009) Cancer Epidemiol Biomarkers Prev 18: 1101-10
Increased breast cancer risk at high plasma folate concentrations among women with the MTHFR 677T allele	Cohort study	BACKGROUND: Folate is involved in DNA synthesis and methylation and may thereby influence carcinogenesis. OBJECTIVES: We examined plasma folate (P-folate) concentration in relation to genotypes of the folate-metabolizing enzyme methylenetetrahydrofolate reductase [MTHFR 677C<--T (rs1801133) and 1298A<--C (rs1801131)]. We also explored whether P-folate was associated with risk of postmenopausal breast cancer overall and in subgroups with genetic variants of the MTHFR single nucleotide polymorphisms (SNPs). DESIGN: This nested case-control study included 313 cases (age 55-73 y at baseline) with invasive breast cancer and 626 control subjects, matched on age and blood-sample date,	Sub-groups again. Compare Ericson Ericson et al. (2007) Am J Clin Nutr 86: 434-443{Ericson, 2010 #406}	Ericson et al. (2009) Am J Clin Nutr 90: 1380-1389

		from the population-based Malmo Diet and Cancer cohort. P-folate and MTHFR genotypes were determined for 310 cases and 611 controls. P-folate according to genotype was calculated by using analysis of variance. Odds ratios were obtained by using logistic regression. All tests were 2-sided. RESULTS: The variant 677T allele was associated with lower P-folate. In women with the 677T allele, a high P-folate concentration was associated with increased breast cancer risk (P for trend across P-folate tertiles = 0.03). Interaction was seen between the 677C<--T SNP and P-folate (P = 0.002). A positive association, which was seen between P-folate and breast cancer risk in 1298AA women (P = 0.01), was probably due to linkage between the 2 SNPs. Overall, and in women with other genotypes, no significant associations were observed. CONCLUSIONS: Our results suggest an association of high P-folate concentration with increased risk of postmenopausal breast cancer in carriers of the 677T allele. The findings underline the importance of genetic variation of MTHFR in the complex relation between folate and cancer.		
Effect of folic acid supplementation on the progression of colorectal aberrant crypt foci	Animal experiment	Whether or not folic acid supplementation promotes the progression of colorectal preneoplastic lesions to cancer is an important public health issue, given mandatory fortification and widespread supplemental use of folic acid in North America. We investigated the effect of folic acid supplementation on the progression of aberrant crypt foci (ACF), the earliest precursor of colorectal cancer. Male Sprague-Dawley rats (n = 152) were placed on a control diet (2 mg folic acid/kg diet) at weaning and ACF were induced by azoxymethane. Six weeks post-ACF induction, rats were randomized to receive 0, 2, 5 or 8 mg folic acid/kg diet. At 34 weeks of age, rats were killed, and colorectal tumor parameters, plasma folate and homocysteine (a sensitive inverse indicator of tissue folate status) concentrations and rectal epithelial proliferation were determined. Although the number of ACF increased as dietary folic acid levels increased (P = 0.015), the incidence of colorectal tumors did not differ significantly among the four dietary groups. However, tumor multiplicity was positively correlated with dietary folic acid levels (r = 0.32; P = 0.002) and inversely with plasma homocysteine concentrations (r = -0.32; P = 0.005). Tumor burden was positively correlated with dietary folic acid levels (r = 0.35; P = 0.001) and plasma folate concentrations (r = 0.33; P = 0.008) and inversely with plasma homocysteine concentrations (r = -0.42; P < 0.001). Rectal epithelial proliferation was positively correlated with dietary folic acid levels (r = 0.39; P < 0.001) and plasma folate concentrations (r = 0.34; P < 0.001) and inversely with plasma homocysteine concentrations (r = -0.37; P < 0.001). Our data suggest that folic acid supplementation may promote the progression of ACF to colorectal tumors.	Note striking correlations between plasma folate and progression	Lindzon (2009) Carcinogenesis 30: 1536-43
Cancer incidence and mortality after treatment with folic acid and vitamin	Clinical trial	CONTEXT: Recently, concern has been raised about the safety of folic acid, particularly in relation to cancer risk. OBJECTIVE: To evaluate effects of treatment with B vitamins on cancer outcomes and all-cause mortality in	NB subgroups. Smokers, those with MTHFR TT and those with high folate	Ebbing (2009) Jama 302: 2119-26

B12		2 randomized controlled trials. DESIGN, SETTING, AND PARTICIPANTS: Combined analysis and extended follow-up of participants from 2 randomized, double-blind, placebo-controlled clinical trials (Norwegian Vitamin Trial and Western Norway B Vitamin Intervention Trial). A total of 6837 patients with ischemic heart disease were treated with B vitamins or placebo between 1998 and 2005, and were followed up through December 31, 2007. INTERVENTIONS: Oral treatment with folic acid (0.8 mg/d) plus vitamin B(12) (0.4 mg/d) and vitamin B(6) (40 mg/d) (n = 1708); folic acid (0.8 mg/d) plus vitamin B(12) (0.4 mg/d) (n = 1703); vitamin B(6) alone (40 mg/d) (n = 1705); or placebo (n = 1721). MAIN OUTCOME MEASURES: Cancer incidence, cancer mortality, and all-cause mortality. RESULTS: During study treatment, median serum folate concentration increased more than 6-fold among participants given folic acid. After a median 39 months of treatment and an additional 38 months of posttrial observational follow-up, 341 participants (10.0%) who received folic acid plus vitamin B(12) vs 288 participants (8.4%) who did not receive such treatment were diagnosed with cancer (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.03-1.41; P = .02). A total of 136 (4.0%) who received folic acid plus vitamin B(12) vs 100 (2.9%) who did not receive such treatment died from cancer (HR, 1.38; 95% CI, 1.07-1.79; P = .01). A total of 548 patients (16.1%) who received folic acid plus vitamin B(12) vs 473 (13.8%) who did not receive such treatment died from any cause (HR, 1.18; 95% CI, 1.04-1.33; P = .01). Results were mainly driven by increased lung cancer incidence in participants who received folic acid plus vitamin B(12). Vitamin B(6) treatment was not associated with any significant effects. CONCLUSION: Treatment with folic acid plus vitamin B12 was associated with increased cancer outcomes and all-cause mortality in patients with ischemic heart disease in Norway, where there is no folic acid fortification of foods.	after treatment. Those in highest quartile of serum folate (>22.66 ng/mL, i.e. 60 nmol/L) showed greatest risk of cancer incidence, cancer mortality and all-cause mortality. (Table e2)	
Folic acid and risk of prostate cancer: results from a randomized clinical trial	Clinical trial	Data regarding the association between folate status and risk of prostate cancer are sparse and conflicting. We studied prostate cancer occurrence in the Aspirin/Folate Polyp Prevention Study, a placebo-controlled randomized trial of aspirin and folic acid supplementation for the chemoprevention of colorectal adenomas conducted between July 6, 1994, and December 31, 2006. Participants were followed for up to 10.8 (median = 7.0, interquartile range = 6.0-7.8) years and asked periodically to report all illnesses and hospitalizations. Aspirin alone had no statistically significant effect on prostate cancer incidence, but there were marked differences according to folic acid treatment. Among the 643 men who were randomly assigned to placebo or supplementation with folic acid, the estimated probability of being diagnosed with prostate cancer over a 10-year period was 9.7% (95% confidence interval [CI] = 6.5% to 14.5%) in the folic acid group and 3.3% (95% CI = 1.7% to 6.4%) in the placebo group (age-adjusted hazard ratio = 2.63, 95% CI = 1.23 to 5.65, Wald test P = .01). In contrast, baseline dietary folate intake and plasma folate in	Important difference between folic acid supplements and folate status	Figueiredo (2009) J Natl Cancer Inst 101: 432-435

		nonmultivitamin users were inversely associated with risk of prostate cancer, although these associations did not attain statistical significance in adjusted analyses. These findings highlight the potential complex role of folate in prostate cancer and the possibly different effects of folic acid-containing supplements vs natural sources of folate.		
Periconceptional maternal folic acid use of 400 microg per day is related to increased methylation of the IGF2 gene in the very young child	Observational, Case-control	BACKGROUND: Countries worldwide recommend women planning pregnancy to use daily 400 microg of synthetic folic acid in the periconceptional period to prevent birth defects in children. The underlying mechanisms of this preventive effect are not clear, however, epigenetic modulation of growth processes by folic acid is hypothesized. Here, we investigated whether periconceptional maternal folic acid use and markers of global DNA methylation potential (S-adenosylmethionine and S-adenosylhomocysteine blood levels) in mothers and children affect methylation of the insulin-like growth factor 2 gene differentially methylation region (IGF2 DMR) in the child. Moreover, we tested whether the methylation of the IGF2 DMR was independently associated with birth weight. METHODOLOGY/PRINCIPAL FINDINGS: IGF2 DMR methylation in 120 children aged 17 months (SD 0.3) of whom 86 mothers had used and 34 had not used folic acid periconceptionally were studied. Methylation was measured of 5 CpG dinucleotides covering the DMR using a mass spectrometry-based method. Children of mother who used folic acid had a 4.5% higher methylation of the IGF2 DMR than children who were not exposed to folic acid (49.5% vs. 47.4%; p = 0.014). IGF2 DMR methylation of the children also was associated with the S-adenosylmethionine blood level of the mother but not of the child (+1.7% methylation per SD S-adenosylmethionine; p = 0.037). Finally, we observed an inverse independent association between IGF2 DMR methylation and birth weight (-1.7% methylation per SD birthweight; p = 0.034). CONCLUSIONS: Periconceptional folic acid use is associated with epigenetic changes in IGF2 in the child that may affect intrauterine programming of growth and development with consequences for health and disease throughout life. These results indicate plasticity of IGF2 methylation by periconceptional folic acid use.		Steegers-Theunissen (2009) PLoS One 4: e7845
Higher serum folate levels are associated with a lower risk of atopy and wheeze	Population observational study	BACKGROUND: Folic acid is known to be associated with inflammatory diseases, but the relationship between folic acid and allergic diseases is unclear. OBJECTIVES: The purpose of the study was to examine the relationship between serum folate levels and markers of atopy, wheeze, and asthma. METHODS: Data were obtained from the 2005-2006 National Health and Nutrition Examination Survey in which serum folate and total IgE levels were measured in 8083 subjects 2 years of age and older. A high total IgE level was defined as greater than 100 kU/L. Allergen-specific IgE levels were measured for a panel of 5 common aeroallergens. Atopy was defined as at least 1 positive allergen-specific IgE level. Doctor-diagnosed asthma and wheeze in the previous 12 months were assessed		Matsui (2009) J Allergy Clin Immunol 123: 1253-9 e2

		by means of questionnaire. RESULTS: Serum folate levels were inversely associated with total IgE levels (P < .001). The odds of a high total IgE level, atopy, and wheeze decreased across quintiles of serum folate levels, indicating a dose-response relationship between serum folate levels and these outcomes. Each of these associations remained statistically significant after adjusting for age, sex, race/ethnicity, and poverty index ratio. Adjusted odds ratios associated with the fifth quintile of folate relative to the first quintile were as follows: high IgE level, 0.70 (95% CI, 0.53-0.92); atopy, 0.69 (95% CI, 0.57-0.85); and wheeze, 0.60 (95% CI, 0.44-0.82). Higher folate levels were also associated with a lower risk of doctor-diagnosed asthma, but this finding was not statistically significant (odds ratio for fifth quintile vs first quintile, 0.84 [95% CI, 0.70-1.02]). CONCLUSIONS: Serum folate levels are inversely associated with high total IgE levels, atopy, and wheeze.		
Role of diet in the development of immune tolerance in the context of allergic disease	Review	PURPOSE OF REVIEW: Diet is arguably one of the most significant environmental exposures during early development. Here, we explore the effects of key perinatal dietary exposures on immune development and susceptibility to allergic disease. RECENT FINDINGS: Dietary changes are at the centre of the emerging epigenetic paradigms that underpin the rise in many modern diseases. There is growing evidence that exposures in pregnancy and the early postnatal period can modify gene expression and disease susceptibility. Specific nutrients, including antioxidants, oligosaccharides, polyunsaturated fatty acids, folate and other vitamins, have documented effects on immune function. Some have also been implicated in modified risk of allergic disease in observational studies. Intervention studies are largely limited to trials with polyunsaturated fatty acids and oligosaccharides, showing preliminary but yet unconfirmed benefits in allergy prevention. Avoidance of food allergens in pregnancy, lactation or infancy has provided no clear evidence in allergy prevention and is no longer recommended. Rather there is focus on their role in tolerance induction. SUMMARY: Modern dietary changes are clearly implicated in the rising propensity for inflammatory immune responses. These dietary changes, which appear to be providing less tolerogenic conditions during early immune programming, may provide important avenues for preventing disease.	Balanced review	West (2010) Curr Opin Pediatr 22: 635-41
Folic acid and prevention of colorectal adenomas: A combined analysis of randomized clinical trials	Combined analysis of 3 trials	Observational data suggest that lower folate status is associated with an increased risk of colorectal neoplasia, implying that folate may be useful as a chemopreventive agent. We conducted a combined analysis of three large randomized trials of folic acid supplementation for the prevention of metachronous adenomas in patients with an adenoma history. Participants included 2,632 men and women with a history of adenomas randomized to either 0.5 or 1.0 mg/day of folic acid or placebo, and who had a follow-up endoscopy 6 to 42 months after randomization (mean=30.6 (standard deviation=8.1) months). We used random-effects meta-analysis to estimate	Short time-scale. But note tendency to protective effect in those with low folate baseline	Figueiredo (2010) Int J Cancer

		risk ratios (RR's) and 95% confidence intervals (CI). The RR comparing folic acid vs. placebo was 0.98 (95% CI=0.82-1.17) for all adenomas and 1.06 (95% CI=0.81-1.39) for advanced lesions. Folic acid was associated with a non-significant decreased risk of any adenoma among subjects in the lowest quartile of baseline plasma folate (</=11 nmol/L) and no effect among individuals in the highest quartile (>29 nmol/L, p for trend = 0.17). There was a non-significant trend of decreasing risk of any adenoma associated with folic acid supplements with increasing alcohol intake. During the early follow-up reported here, more deaths occurred in the placebo group than in the folic acid group (1.7% vs. 0.5%, p=.002). In conclusion, after up to 3.5 years of folic acid use, there is no clear decrease or increase in the occurrence of new adenomas in patients with a history of adenoma.		
Plasma folate concentrations are positively associated with risk of estrogen receptor {beta} negative breast cancer in a Swedish nested case control study	Observational, case-control	Folate's role in breast cancer development is controversial. Not only estrogen receptor (ER) {alpha} status, but also ER{beta} status of tumors may have confounded results from previous epidemiological studies. We aimed to examine associations between plasma folate concentration and postmenopausal breast cancer defined by ER status. This nested case-control study, within the Malmo diet and cancer cohort, included 204 incident breast cancer cases with information on ER{alpha} and ER{beta} status determined by immunochemistry on tissue micro-array sections. Plasma folate concentration was analyzed for the cases and 408 controls (matched on age and blood sample date). Odds ratios (OR) for ER-defined breast cancers in tertiles of plasma folate concentration were calculated with unconditional logistic regression. All tests were 2-sided. Women in the third tertile of plasma folate concentration (>12 nmol/L) had higher incidence of ER{beta}- breast cancer than women in the first tertile (OR: 2.67; 95% CI: 1.44-4.92; P-trend = 0.001). We did not observe significant associations between plasma folate concentration and other breast cancer subgroups defined by ER status. We observed a difference between risks for ER{beta} + and ER{beta}- cancer (P-heterogeneity = 0.003). Our findings, which indicate a positive association between plasma folate and ER{beta}- breast cancer, highlight the importance of taking ER{beta} status into consideration in studies of folate and breast cancer. The study contributes knowledge concerning folate's multifaceted role in cancer development. If replicated in other populations, the observations may have implications for public health, particularly regarding folic acid fortification.	Importance of sub-groups	{Ericson, 2010 #406}
Folate and other one-carbon metabolism-related nutrients and risk of postmenopausal breast cancer in the Cancer Prevention Study II	Prospective cohort study	BACKGROUND: Epidemiologic studies of the association of folate intake with breast cancer risk have been inconclusive, and few have investigated how related nutrients modify this association. OBJECTIVE: We investigated the association of dietary (food folate plus folic acid from fortification) and total folate (food folate, folic acid from fortification, and folic acid from supplements), vitamin B6, vitamin B12, methionine, and alcohol intakes with postmenopausal breast cancer among women in the		Stevens (2010) Am J Clin Nutr 91: 1708-15

Nutrition Cohort		Cancer Prevention Study II Nutrition Cohort. The modification of the folate associations by the other nutrients was also investigated. DESIGN: This prospective cohort study included 70,656 postmenopausal women for whom dietary information was collected in 1992. Of these, 3898 developed breast cancer between enrollment in 1992 and June 2005. Cox proportional hazards modeling was used to calculate multivariate-adjusted hazard rate ratios and 95% CIs. RESULTS: Compared with the lowest quintile, the highest quintile of dietary folate intake was associated with a higher risk of breast cancer (rate ratio: 1.12; 95% CI: 1.01, 1.24). However, the test for trend was not significant (P for trend = 0.15). No association was found for total folate, vitamin B-6, or vitamin B-12, but methionine was inversely associated with breast cancer risk (P for trend = 0.04). The association of dietary folate with breast cancer was not modified by other nutrients or alcohol. CONCLUSIONS: This study suggests that dietary folate intake may be positively associated with postmenopausal breast cancer. However, no dose-response relation was observed. The extent to which increased supplement use and folate fortification contributes to breast cancer risk warrants further research.		
Total folate and folic acid intake from foods and dietary supplements in the United States: 2003-2006	Population study	BACKGROUND: The term total folate intake is used to represent folate that occurs naturally in food as well as folic acid from fortified foods and dietary supplements. Folic acid has been referred to as a double-edged sword because of its beneficial role in the prevention of neural tube defects and yet possible deleterious effects on certain cancers and cognitive function. Previous monitoring efforts did not include folic acid from dietary supplements and are therefore not complete. OBJECTIVE: Our objective was to combine data on dietary folate (as measured by two 24-h recalls) and folic acid from dietary supplements (collected with a 30-d frequency questionnaire) with the use of the bias-corrected best power method to adjust for within-person variability. DESIGN: The National Health and Nutrition Examination Survey (NHANES) is a nationally representative, cross-sectional survey. Linear contrasts were constructed to determine differences in dietary and total folate intake for age and racial-ethnic groups by sex; prevalence of inadequate and excessive intakes is presented. RESULTS: In 2003-2006, 53% of the US population used dietary supplements; 34.5% used dietary supplements that contained folic acid. Total folate intake (in dietary folate equivalents) was higher for men (813 +/- 14) than for women (724 +/- 16) and higher for non-Hispanic whites (827 +/- 19) than for Mexican Americans (615 +/- 11) and non-Hispanic blacks (597 +/- 12); 29% of non-Hispanic black women had inadequate intakes. Total folate and folic acid intakes are highest for those aged >/=50 y, and 5% exceed the Tolerable Upper Intake Level. CONCLUSIONS: Improved total folate intake is warranted in targeted subgroups, which include women of childbearing age and non-Hispanic black women, whereas other population groups are at risk of excessive intake		Bailey (2010) Am J Clin Nutr 91: 231-237

Unmetabolized serum folic acid and its relation to folic acid intake from diet and supplements in a nationally representative sample of adults aged >=60 y in the United States	Population study	Background: Unmetabolized serum folic acid (UMFA) has been detected in adults. Previous research indicates that high folic acid intakes may be associated with risk of cancer. Objective: The objective was to examine UMFA concentrations in relation to dietary and supplemental folate and status biomarkers in the US population aged [≥]60 y. Design: Surplus sera were analyzed with the use of data from the National Health and Nutrition Examination Survey (NHANES) 2001-2002, a cross-sectional, nationally representative survey (n = 1121). Results: UMFA was detected in 38% of the population, with a mean concentration of 4.4 {+/-} 0.6 nmol/L (median: 1.2{+/-} 0.2 nmol/L). The group with UMFA (UMFA+) had a significantly higher proportion of folic acid supplement users than did the group without UMFA (60% compared with 41%). UMFA+ men and women also had higher supplemental and total (food + supplements) folic acid intakes than did their counterparts without UMFA. Forty percent of the UMFA+ group was in the highest quartile of total folic acid intake, but total folic acid intake was only moderately related to UMFA concentrations (r2 = 0.07). Serum folate concentrations were significantly higher in the UMFA+ group and were predictive of UMFA concentrations (r2 = 0.15). Serum 5-methyltetrahydrofolate and vitamin B-12 concentrations were higher in the UMFA+ group, whereas there was no difference between the 2 UMFA groups in red blood cell folate, serum homocysteine, or methylmalonic acid concentrations. Conclusions: Approximately 40% of older adults in the United States have UMFA that persists after a fast, and the presence of UMFA is not easily explained in NHANES by folic acid intakes alone. Given the possibility that excessive folic acid exposure may relate to cancer risk, monitoring of UMFA may be warranted.		{Bailey, 2010 #450}
Concentrations of unmetabolized folic acid and primary folate forms in pregnant women at delivery and in umbilical cord blood	Observational	Background: The importance of unmetabolized folic acid in maternal and fetal blood is not known.Objective: We investigated total folate, tetrahydrofolate (THF), 5-methyltetrahydrofolate (5-MTHF), formyl-THF, 5,10-methenylTHF, and folic acid concentrations in women and in umbilical cord blood at delivery.Design: The study included 87 pregnant women and 29 cord blood samples, including 24 mother-infant pairs. We measured serum concentrations of folate forms by using ultraperformance liquid chromatography–tandem mass spectrometry.Results: Pregnant women who received 400 μg folic acid daily (n = 25) had higher total folate (P = 0.041), 5-MTHF (P = 0.049), and formyl-THF (P < 0.001) concentrations and slightly higher THF (P = 0.093) concentrations than did nonsupplemented pregnant women (n = 61). We measured folic acid concentrations >0.20 nmol/L in 38 (44%) pregnant women and in 55% of the cord serum samples, but these measurements were not explained by maternal supplement use. Concentrations of folic acid were nonsignificantly higher in cord blood from supplemented women than in cord blood from nonsupplemented women (P = 0.154). Proportions of folic		Obeid (2010) Am J Clin Nutr 92: 1416-1422

		acid to total folate in cord serum did not differ according to maternal supplement usage (0.54% compared with 0.43% in supplemented and nonsupplemented women, respectively). Concentrations of folic acid did not differ between maternal and cord serum. However, folic acid constituted a significantly lower proportion of total folate in cord serum than in maternal serum.Conclusions: We detected unmetabolized folic acid in more than one-half of cord blood samples. Folic acid (400 µg/d) supplied during pregnancy is not likely to accumulate in the fetus, in contrast to 5-MTHF and THF, which accumulate in the fetus.		
Some, but not complete, reassurance on the safety of folic acid fortification	Editorial	No abstract. Comment on Obeid article.	Plenty of speculation	Beaudet (2010) Am J Clin Nutr 92: 1287-1288
Plasma folate, related genetic variants, and colorectal cancer risk in EPIC	Case-control study	BACKGROUND: A potential dual role of folate in colorectal cancer (CRC) is currently subject to debate. We investigate the associations between plasma folate, several relevant folate-related polymorphisms, and CRC risk within the large European Prospective Investigation into Cancer and Nutrition cohort. METHODS: In this nested case-control study, 1,367 incident CRC cases were matched to 2,325 controls for study center, age, and sex. Risk ratios (RR) were estimated with conditional logistic regression and adjusted for smoking, education, physical activity, and intake of alcohol and fiber. RESULTS: Overall analyses did not reveal associations of plasma folate with CRC. The RR (95% confidence interval; Ptrend) for the fifth versus the first quintile of folate status was 0.94 (0.74-1.20; 0.44). The polymorphisms MTHFR677C-->T, MTHFR1298A-->C, MTR2756A-->G, MTRR66A-->G, and MTHFD11958G-->A were not associated with CRC risk. However, in individuals with the lowest plasma folate concentrations, the MTHFR 677TT genotype showed a statistically nonsignificant increased CRC risk [RR (95% CI; Ptrend) TT versus CC=1.39 (0.87-2.21); 0.12], whereas those with the highest folate concentrations showed a nonsignificant decreased CRC risk [RR TT versus CC=0.74 (0.39-1.37); 0.34]. The SLC19A180G-->A showed a positive association with CRC risk [RR AA versus GG 1.30 (1.06-1.59); <0.01]. CONCLUSIONS: This large European prospective multicenter study did not show an association of CRC risk with plasma folate status nor with MTHFR polymorphisms. IMPACT: Findings of the present study tend to weaken the evidence that folate plays an important role in CRC carcinogenesis. However, larger sample sizes are needed to adequately address potential gene-environment interactions.		Eussen (2010) Cancer Epidemiol Biomarkers Prev 19: 1328-40
Serum B vitamin levels and risk of lung cancer	Case-control study	CONTEXT: B vitamins and factors related to 1-carbon metabolism help to maintain DNA integrity and regulate gene expression and may affect cancer risk. OBJECTIVE: To investigate if 1-carbon metabolism factors are associated with onset of lung cancer. DESIGN, SETTING, AND PARTICIPANTS: The European Prospective Investigation into Cancer and Nutrition (EPIC) recruited 519,978 participants from 10 countries between		Johansson (2010) JAMA 303: 2377-85

		1992 and 2000, of whom 385,747 donated blood. By 2006, 899 lung cancer cases were identified and 1770 control participants were individually matched by country, sex, date of birth, and date of blood collection. Serum levels were measured for 6 factors of 1-carbon metabolism and cotinine. MAIN OUTCOME MEASURE: Odds ratios (ORs) of lung cancer by serum levels of 4 B vitamins (B2, B6, folate, and B12), methionine, and homocysteine. RESULTS: Within the entire EPIC cohort, the age-standardized incidence rates of lung cancer (standardized to the world population, aged 35-79 years) were 6.6, 44.9, and 156.1 per 100,000 person-years among never, former, and current smokers for men, respectively. The corresponding incidence rates for women were 7.1, 23.9, and 100.9 per 100,000 person-years, respectively. After accounting for smoking, a lower risk for lung cancer was seen for elevated serum levels of B(6) (fourth vs first quartile OR, 0.44; 95% confidence interval [CI], 0.33-0.60; P for trend <.000001), as well as for serum methionine (fourth vs first quartile OR, 0.52; 95% CI, 0.39-0.69; P for trend <.000001). Similar and consistent decreases in risk were observed in never, former, and current smokers, indicating that results were not due to confounding by smoking. The magnitude of risk was also constant with increasing length of follow-up, indicating that the associations were not explained by preclinical disease. A lower risk was also seen for serum folate (fourth vs first quartile OR, 0.68; 95% CI, 0.51-0.90; P for trend = .001), although this was apparent only for former and current smokers. When participants were classified by median levels of serum methionine and B(6), having above-median levels of both was associated with a lower lung cancer risk overall (OR, 0.41; 95% CI, 0.31-0.54), as well as separately among never (OR, 0.36; 95% CI, 0.18-0.72), former (OR, 0.51; 95% CI, 0.34-0.76), and current smokers (OR, 0.42; 95% CI, 0.27-0.65). CONCLUSION: Serum levels of vitamin B6 and methionine were inversely associated with risk of lung cancer.		
Pooled analyses of 13 prospective cohort studies on folate intake and colon cancer	Review	OBJECTIVE: Studies of folate intake and colorectal cancer risk have been inconsistent. We examined the relation with colon cancer risk in a series of 13 prospective studies. METHODS: Study- and sex-specific relative risks (RRs) were estimated from the primary data using Cox proportional hazards models and then pooled using a random-effects model. RESULTS: Among 725,134 participants, 5,720 incident colon cancers were diagnosed during follow-up. The pooled multivariate RRs (95% confidence interval [CI]) comparing the highest vs. lowest quintile of intake were 0.92 (95% CI 0.84-1.00, p-value, test for between-studies heterogeneity = 0.85) for dietary folate and 0.85 (95% CI 0.77-0.95, p-value, test for between-studies heterogeneity = 0.42) for total folate. Results for total folate intake were similar in analyses using absolute intake cutpoints (pooled multivariate RR = 0.87, 95% CI 0.78-0.98, comparing		Kim (2010) Cancer Causes Control 21: 1919-30

		>/=560 mcg/days vs. <240 mcg/days, p-value, test for trend = 0.009). When analyzed as a continuous variable, a 2% risk reduction (95% CI 0-3%) was estimated for every 100 mug/day increase in total folate intake. CONCLUSION: These data support the hypothesis that higher folate intake is modestly associated with reduced risk of colon cancer.		
Folate intake, post-folic acid grain fortification, and pancreatic cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Large population study	BACKGROUND: Folate plays a critical role in DNA methylation, synthesis, and repair. Several epidemiologic studies suggest that higher folate intake is associated with decreased pancreatic cancer risk. OBJECTIVE: We investigated the association between dietary folate intake and pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) cohort. DESIGN: Dietary data were collected with the use of a self-administered food-frequency questionnaire (1998-2005). Among the 51,988 male and 57,187 female participants, aged 55-74 y at enrollment, with complete dietary and multivitamin information, 162 men and 104 women developed pancreatic cancer during follow-up (January 1998 to December 2006; median: 6.5 y). We used Cox proportional hazards regression with age as the time metric to calculate hazard ratios (HRs) and 95% CIs. RESULTS: The highest compared with the lowest quartile of food folate was associated with a significantly decreased pancreatic cancer risk among women (> or = 253.3 compared with < or = 179.1 microg/d; HR = 0.47; 95% CI: 0.23, 0.94; P for trend: 0.09) but not among men (> or = 229.6 compared with < or = 158.0 microg/d; HR = 1.20; 95% CI: 0.70, 2.04; P for trend: 0.67; P for interaction by sex: 0.03). There was also a significant inverse trend in risk of pancreatic cancer across increasing quartiles of total folate in women (P for trend: 0.04) but not in men (P for trend: 0.65). Folic acid supplements were not associated with pancreatic cancer. CONCLUSION: These findings support an association between higher food and total folate intakes and decreased risk of pancreatic cancer in women but not in men.	NB gender difference	Oaks (2010) Am J Clin Nutr 91: 449-55
Folate and other one-carbon metabolism-related nutrients and risk of postmenopausal breast cancer in the Cancer Prevention Study II Nutrition Cohort	Population cohort study	BACKGROUND: Epidemiologic studies of the association of folate intake with breast cancer risk have been inconclusive, and few have investigated how related nutrients modify this association. OBJECTIVE: We investigated the association of dietary (food folate plus folic acid from fortification) and total folate (food folate, folic acid from fortification, and folic acid from supplements), vitamin B6, vitamin B12, methionine, and alcohol intakes with postmenopausal breast cancer among women in the Cancer Prevention Study II Nutrition Cohort. The modification of the folate associations by the other nutrients was also investigated. DESIGN: This prospective cohort study included 70,656 postmenopausal women for whom dietary information was collected in 1992. Of these, 3898 developed breast cancer between enrollment in 1992 and June 2005. Cox proportional hazards modeling was used to calculate multivariate-adjusted hazard rate ratios and 95% CIs. RESULTS: Compared with the lowest quintile, the highest quintile of dietary folate intake was associated with a	Lack of dose response may be because the effect is non-linear, See Lee Lee et al. (2011) Gastroenterology 141: 16-20	Stevens et al. (2010) Am J Clin Nutr 91: 1708-15

		higher risk of breast cancer (rate ratio: 1.12; 95% CI: 1.01, 1.24). However, the test for trend was not significant (P for trend = 0.15). No association was found for total folate, vitamin B-6, or vitamin B-12, but methionine was inversely associated with breast cancer risk (P for trend = 0.04). The association of dietary folate with breast cancer was not modified by other nutrients or alcohol. CONCLUSIONS: This study suggests that dietary folate intake may be positively associated with postmenopausal breast cancer. However, no dose-response relation was observed. The extent to which increased supplement use and folate fortification contributes to breast cancer risk warrants further research.		
Circulating folate, vitamin B12, homocysteine, vitamin B12 transport proteins, and risk of prostate cancer: a case-control study, systematic review, and meta-analysis	Observational	BACKGROUND: Disturbed folate metabolism is associated with an increased risk of some cancers. Our objective was to determine whether blood levels of folate, vitamin B(12), and related metabolites were associated with prostate cancer risk. METHODS: Matched case-control study nested within the U.K. population-based Prostate testing for cancer and Treatment (ProtecT) study of prostate-specific antigen-detected prostate cancer in men ages 50 to 69 years. Plasma concentrations of folate, B(12) (cobalamin), holo-haptocorrin, holo-transcobalamin total transcobalamin, and total homocysteine (tHcy) were measured in 1,461 cases and 1,507 controls. ProtecT study estimates for associations of folate, B(12), and tHcy with prostate cancer risk were included in a meta-analysis, based on a systematic review. RESULTS: In the ProtecT study, increased B(12) and holo-haptocorrin concentrations showed positive associations with prostate cancer risk [highest versus lowest quartile of B(12) odds ratio (OR) = 1.17 (95% confidence interval, 0.95-1.43); P(trend) = 0.06; highest versus lowest quartile of holo-haptocorrin OR = 1.27 (1.04-1.56); P(trend) = 0.01]; folate, holo-transcobalamin, and tHcy were not associated with prostate cancer risk. In the meta-analysis, circulating B12 levels were associated with an increased prostate cancer risk [pooled OR = 1.10 (1.01-1.19) per 100 pmol/L increase in B12; P = 0.002]; the pooled OR for the association of folate with prostate cancer was positive [OR = 1.11 (0.96-1.28) per 10 nmol/L; P = 0.2) and conventionally statistically significant if ProtecT (the only case-control study) was excluded [OR = 1.18 (1.00-1.40) per 10 nmol/L; P = 0.02]. CONCLUSION: Vitamin B(12) and (in cohort studies) folate were associated with increased prostate cancer risk. IMPACT: Given current controversies over mandatory fortification, further research is needed to determine whether these are causal associations.	In cohort studies, but not in a large case-control study, serum folate was associated with an increased risk of prostate cancer	Collin (2010) Cancer Epidemiol Biomarkers Prev 19: 1632-42
Associations of folate, vitamin B12, homocysteine, and folate-pathway polymorphisms with prostate-specific	Observational	BACKGROUND: Vitamin B(12), holo-haptocorrin, and the folate-pathway single-nucleotide polymorphisms MTR 2756A>G and SHMT1 1420C>T have been associated with an increased risk of prostate cancer. We investigated whether these and other elements of folate metabolism were associated with prostate-specific antigen (PSA) velocity (PSAV) as a proxy measure of prostate cancer progression in men with localized prostate	See also: Petersen (2011) BJU Int and Tomaszewski (2011) Prostate	Collin (2010) Cancer Epidemiol Biomarkers Prev 19: 2833-8

antigen velocity in men with localized prostate cancer		cancer. METHODS: We measured plasma folate, B12, holo-haptocorrin, holo-transcobalamin, total transcobalamin, and total homocysteine at diagnosis in 424 men (ages 45-70 years) with localized prostate cancer in a U.K.-wide population-based cohort. Thirteen folate-pathway single-nucleotide polymorphisms were genotyped for 311 of these men. Postdiagnosis PSAV (continuous measure and with a threshold set a priori at 2 ng/mL/y) was estimated from repeat PSA measurements. RESULTS: Median follow-up time was 2.5 (range, 0.8-5.6) years. Vitamin B12, holo-haptocorrin, holo-transcobalamin, total transcobalamin, and total homocysteine were not associated with postdiagnosis PSAV. Folate was associated with an increased risk of PSAV >2 ng/mL/y [odds ratio (OR) per unit increase in log(e) concentration, 1.57; 95% confidence interval (95% CI), 0.98-2.51; P = 0.06]. MTRR 66A>G (rs1801394) was associated with a reduced risk (recessive model OR, 0.33; 95% CI, 0.11-0.97; P = 0.04), and SHMT1 1420C>T (rs1979277) with an increased risk (per-allele OR, 1.49; 95% CI, 0.93-2.37; P = 0.09) of PSAV >2 ng/mL/y. CONCLUSIONS: We found weak evidence that higher folate levels may be associated with faster progression of localized prostate cancer. IMPACT: Long-term follow-up is needed to test associations with metastases and mortality, and the observed genetic effects require replication.		
Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: Meta-analysis of 8 randomized trials involving 37 485 individuals	Meta-analysis	Elevated plasma homocysteine levels have been associated with higher risks of cardiovascular disease, but the effects on disease rates of supplementation with folic acid to lower plasma homocysteine levels are uncertain. Individual participant data were obtained for a meta-analysis of 8 large, randomized, placebo-controlled trials of folic acid supplementation involving 37 485 individuals at increased risk of cardiovascular disease. The analyses involved intention-to-treat comparisons of first events during the scheduled treatment period. There were 9326 major vascular events (3990 major coronary events, 1528 strokes, and 5068 revascularizations), 3010 cancers, and 5125 deaths. Folic acid allocation yielded an average 25% reduction in homocysteine levels. During a median follow-up of 5 years, folic acid allocation had no significant effects on vascular outcomes, with rate ratios (95% confidence intervals) of 1.01 (0.97-1.05) for major vascular events, 1.03 (0.97-1.10) for major coronary events, and 0.96 (0.87-1.06) for stroke. Likewise, there were no significant effects on vascular outcomes in any of the subgroups studied or on overall vascular mortality. There was no significant effect on the rate ratios (95% confidence intervals) for overall cancer incidence (1.05 [0.98-1.13]), cancer mortality (1.00 [0.85-1.18]) or all-cause mortality (1.02 [0.97-1.08]) during the whole scheduled treatment period or during the later years of it. Dietary supplementation with folic acid to lower homocysteine levels had no significant effects within 5 years on cardiovascular events or on overall cancer or mortality in the populations studied.	Restricted to CVD trials, so no purely cancer trials included. Some subgroups (including smokers) are described in Table e4 but not MTHFR. Note overall RR for cancer incidence was 1.05 and almost significant (95% CI 0.98-1.13) so there could have been a 4-5% increase in cancer incidence. No power estimates were given. Unlikely that the study was actually powered to show 5% significant increase in cancer. Power estimates suggest that one could	Clarke (2010) Arch Intern Med 170: 1622-31

			only detect a significant increase of 5% if ~70,000 subjects in each group, if a new trial was done	
Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates	Population data	BACKGROUND: The American Cancer Society, the Centers for Disease Control and Prevention (CDC), the National Cancer Institute (NCI), and the North American Association of Central Cancer Registries (NAACCR) collaborate annually to provide updated information regarding cancer occurrence and trends in the United States. This year's report includes trends in colorectal cancer (CRC) incidence and death rates and highlights the use of microsimulation modeling as a tool for interpreting past trends and projecting future trends to assist in cancer control planning and policy decisions. METHODS: Information regarding invasive cancers was obtained from the NCI, CDC, and NAACCR; and information on deaths was obtained from the CDC's National Center for Health Statistics. Annual percentage changes in the age-standardized incidence and death rates (based on the year 2000 US population standard) for all cancers combined and for the top 15 cancers were estimated by joinpoint analysis of long-term trends (1975-2006) and for short-term fixed-interval trends (1997-2006). All statistical tests were 2-sided. RESULTS: Both incidence and death rates from all cancers combined significantly declined ($P < .05$) in the most recent time period for men and women overall and for most racial and ethnic populations. These decreases were driven largely by declines in both incidence and death rates for the 3 most common cancers in men (ie, lung and prostate cancers and CRC) and for 2 of the 3 leading cancers in women (ie, breast cancer and CRC). The long-term trends for lung cancer mortality in women had smaller and smaller increases until 2003, when there was a change to a nonsignificant decline. Microsimulation modeling demonstrates that declines in CRC death rates are consistent with a relatively large contribution from screening and with a smaller but demonstrable impact of risk factor reductions and improved treatments. These declines are projected to continue if risk factor modification, screening, and treatment remain at current rates, but they could be accelerated further with favorable trends in risk factors and higher utilization of screening and optimal treatment. CONCLUSIONS: Although the decrease in overall cancer incidence and death rates is encouraging, rising incidence and mortality for some cancers are of concern.	Very useful data on colorectal cancer with figures. Do not confirm a significant increase after fortification, although the incidence plots still show a blip.	Edwards (2010) Cancer 116: 544-73
Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system	Population data	BACKGROUND: The American Cancer Society, the Centers for Disease Control and Prevention (CDC), the National Cancer Institute, and the North American Association of Central Cancer Registries (NAACCR) collaborate annually to provide updated information on cancer occurrence and trends in the United States. This year's report highlights brain and other nervous system (ONS) tumors, including nonmalignant brain tumors, which became	NB prostate cancer increase	{Kohler, 2011 #517}

		reportable on a national level in 2004. METHODS: Cancer incidence data were obtained from the National Cancer Institute, CDC, and NAACCR, and information on deaths was obtained from the CDC's National Center for Health Statistics. The annual percentage changes in age-standardized incidence and death rates (2000 US population standard) for all cancers combined and for the top 15 cancers for men and for women were estimated by joinpoint analysis of long-term (1992-2007 for incidence; 1975-2007 for mortality) trends and short-term fixed interval (1998-2007) trends. Analyses of malignant neuroepithelial brain and ONS tumors were based on data from 1980-2007; data on nonmalignant tumors were available for 2004-2007. All statistical tests were two-sided. RESULTS: Overall cancer incidence rates decreased by approximately 1% per year; the decrease was statistically significant (P < .05) in women, but not in men, because of a recent increase in prostate cancer incidence. The death rates continued to decrease for both sexes. Childhood cancer incidence rates continued to increase, whereas death rates continued to decrease. Lung cancer death rates decreased in women for the first time during 2003-2007, more than a decade after decreasing in men. During 2004-2007, more than 213 500 primary brain and ONS tumors were diagnosed, and 35.8% were malignant. From 1987-2007, the incidence of neuroepithelial malignant brain and ONS tumors decreased by 0.4% per year in men and women combined. CONCLUSIONS: The decrease in cancer incidence and mortality reflects progress in cancer prevention, early detection, and treatment. However, major challenges remain, including increasing incidence rates and continued low survival for some cancers. Malignant and nonmalignant brain tumors demonstrate differing patterns of occurrence by sex, age, and race, and exhibit considerable biologic diversity. Inclusion of nonmalignant brain tumors in cancer registries provides a fuller assessment of disease burden and medical resource needs associated with these unique tumors.		
Folate intake and risk of pancreatic cancer: pooled analysis of prospective cohort studies	Pooled analysis	Background Epidemiological studies evaluating the association between folate intake and risk of pancreatic cancer have produced inconsistent results. The statistical power to examine this association has been limited in previous studies partly because of small sample size and limited range of folate intake in some studies. Methods We analyzed primary data from 14 prospective cohort studies that included 319 716 men and 542 948 women to assess the association between folate intake and risk of pancreatic cancer. Folate intake was assessed through a validated food-frequency questionnaire at baseline in each study. Study-specific relative risks (RRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models and then pooled using a random effects model. All statistical tests were two-sided. Results During 7-20 years of follow-up across studies, 2195 pancreatic cancers were identified. No association was observed between folate intake and risk of pancreatic cancer in men and women (highest vs lowest quintile: dietary folate intake,		Bao (2011) J Natl Cancer Inst

		pooled multivariable RR = 1.06, 95% CI = 0.90 to 1.25, P(trend) = .47; total folate intake [dietary folate and supplemental folic acid], pooled multivariable RR = 0.96, 95% CI = 0.80 to 1.16, P(trend) = .90). No between-study heterogeneity was observed (for dietary folate, P(heterogeneity) = .15; for total folate, P(heterogeneity) = .22). Conclusion Folate intake was not associated with overall risk of pancreatic cancer in this large pooled analysis.		
Maternal use of folic acid supplements during pregnancy and childhood respiratory health and atopy: the PIAMA birth cohort study	Population cohort study	Previous studies have suggested possible adverse side effects of maternal use of folic acid containing supplements (FACSs) during pregnancy on wheeze and asthma in early childhood.We investigated the association between maternal use of (FACSs) and childhood respiratory health and atopy in the first 8 years of life.Data on maternal use of FACSs, collected during pregnancy, were available for 3,786 children participating in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study. Questionnaire data on children's respiratory and allergic symptoms were collected annually and allergic sensitization and bronchial hyperresponsiveness (BHR) were measured at 8 years.No overall (from 1 to 8 years) associations were observed between maternal use of FACSs and (frequent) asthma symptoms, wheeze, lower respiratory tract infection (RTI), frequent RTI and eczema. Maternal folic acid use was associated with wheeze at 1 year (prevalence ratio: 1.20 (95% Confidence Interval: 1.04-1.39), but not with wheeze at later ages. Prenatal exposure to FACSs was not associated with sensitization and BHR. Apart from a small increased risk of early wheeze, we observed no adverse respiratory or allergic outcomes associated with prenatal FACSs exposure in our study population.		Bekkers (2011) Eur Respir J
Dietary folate deficiency blocks prostate cancer progression in the TRAMP model	Animal experiments; Dietary manipulation	Dietary folate is essential in all tissues to maintain several metabolite pools and cellular proliferation. Prostate cells, due to specific metabolic characteristics, have increased folate demand to support proliferation and prevent genetic and epigenetic damage. Although several studies found that dietary folate interventions can affect colon cancer biology in rodent models, impact on prostate is unknown. The purpose of this study was to determine if dietary folate manipulation, possibly being of primary importance for prostate epithelial cell metabolism, could significantly affect prostate cancer (CaP) progression. Strikingly, mild dietary folate depletion arrested CaP progression in 25/26 transgenic TRAMP mice, where tumorigenesis is prostate specific and characteristically aggressive. The significant effect on CaP growth was characterized by size, grade, proliferation and apoptosis analyses. Folate supplementation had a mild, non significant beneficial effect on grade. In addition, characterization of folate pools (correlated with serum), metabolite pools (polyamines, nucleotides), genetic and epigenetic damage, and expression of key biosynthetic enzymes in prostate tissue revealed interesting correlations with tumor progression. These findings indicate that CaP is highly sensitive		Bistulfi (2011) Cancer Prev Res (Phila) 4: 1825-34

		to folate manipulation and suggest that antifolates, paired to current therapeutic strategies, might significantly improve treatment of CaP, the most commonly diagnosed cancer in American men.		
Maternal B vitamin supplementation from preconception through weaning suppresses intestinal tumorigenesis in Apc1638N mouse offspring	Animal experiments	Objective Variations in the intake of folate are capable of modulating colorectal tumorigenesis; however, the outcome appears to be dependent on timing. This study sought to determine the effect of altering folate (and related B vitamin) availability during in-utero development and the suckling period on intestinal tumorigenesis. Design Female wildtype mice were fed diets either mildly deficient, replete or supplemented with vitamins B(2), B(6), B(12) and folate for 4 weeks before mating to Apc(1638N) males. Females remained on their diet throughout pregnancy and until weaning. After weaning, all Apc(1638N) offspring were maintained on replete diets for 29 weeks. Results At 8 months of age tumour incidence was markedly lower among offspring of supplemented mothers (21%) compared with those of replete (59%) and deficient (55%) mothers (p=0.03). Furthermore, tumours in pups born to deficient dams were most likely to be invasive (p=0.03). The expression of Apc, Sfrp1, Wif1 and Wnt5a-all of which are negative regulatory elements of the Wnt signalling cascade-in the normal small intestinal mucosa of pups decreased with decreasing maternal B vitamin intake, and for Sfrp1 this was inversely related to promoter methylation. beta-Catenin protein was elevated in offspring of deficient dams. Conclusions These changes indicate a de-repression of the Wnt pathway in pups of deficient dams and form a plausible mechanism by which maternal B vitamin intake modulates tumorigenesis in offspring. These data indicate that maternal B vitamin supplementation suppresses, while deficiency promotes, intestinal tumorigenesis in Apc(1638N) offspring.		Ciappio (2011) Gut
The relationship between maternal folate status in pregnancy, cord blood folate levels, and allergic outcomes in early childhood	Observational study	Background: Dietary changes may epigenetically modify fetal gene expression during critical periods of development to potentially influence disease susceptibility. This study examined whether maternal and/or fetal folate status in pregnancy is associated with infant allergic outcomes. Methods: Pregnant women (n = 628) were recruited in the last trimester of pregnancy. Folate status determined by both food frequency questionnaires and folate levels in maternal and cord blood serum was examined in relation to infant allergic outcomes at 1 year of age (n = 484). Results: Infants who developed allergic disease (namely eczema) did not show any differences in cord blood or maternal folate levels compared with children without disease. Although maternal folate intake from foods was also not different, folate derived from supplements was higher (P = 0.017) in children with subsequent eczema. Furthermore, infants exposed to >500 mug folic acid/day as a supplement in utero were more likely to develop eczema than those taking <200 mug/day (OR [odds ratio] = 1.85; 95% CI 1.14-3.02; P = 0.013), remaining significant after adjustment for maternal allergy and other confounders. There was a nonlinear relationship between		Dunstan (2011) Allergy on-line ahead of publication:

		cord blood folate and sensitization, with folate levels <50 nmol/l (OR = 3.02; 95% CI 1.16-7.87; P = 0.024) and >75 nmol/l (OR = 3.59; 95% CI 1.40-9.20; P = 0.008) associated with greater sensitization risk than levels between 50 and 75 nmol/l. Conclusion: Fetal levels between 50 and 75 nmol/l appeared optimal for minimizing sensitization. While folate taken as a supplement in higher doses during the third trimester was associated with eczema, there was no effect on other allergic outcomes including sensitization. Further studies are needed to determine the significance of this.		
Pre- and postfortification intake of folate and risk of colorectal cancer in a large prospective cohort study in the United States	Very large prospective population study	BACKGROUND: A higher folate intake is associated with a decreased colorectal cancer risk in observational studies, but recent evidence suggests that excessive folate supplementation may increase colorectal cancer risk in some individuals. Therefore, mandatory folic acid fortification of grain products in the United States may have unintended negative consequences. OBJECTIVE: We examined the association between folate intake and colorectal cancer risk, including 8.5 y of postfortification follow-up. DESIGN: We examined the association between folate intake and colorectal cancer in the NIH-AARP Diet and Health Study-a US cohort study of 525,488 individuals aged 50-71 y initiated in 1995-1996. Dietary, supplemental, and total folate intakes were calculated for the pre- and postfortification periods (before and after 1 July 1997) based on a baseline food-frequency questionnaire. HRs and 95% CIs were calculated by using multivariable Cox proportional hazards regression models. RESULTS: During follow-up through 31 December 2006 (mean follow-up: 9.1 y), 7212 incident colorectal cancer cases were identified. In the postfortification analysis (6484 cases), a higher total folate intake was associated with a decreased colorectal cancer risk (HR for >/=900 compared with <200 mug/d: 0.70; 95% CI: 0.58, 0.84). The highest intakes specifically from supplements (HR: 0.82; 95% CI: 0.72, 0.92) or from diet (HR: 0.81; 95% CI: 0.67, 0.97) were also protective. The pattern of associations was similar for the prefortification period, and no significant differences between time periods were observed. CONCLUSIONS: In this large prospective cohort study that included 8.5 y of postfortification follow-up, folate intake was associated with a decreased colorectal cancer risk. Given that the adenoma-carcinoma sequence may take >/=10 y, additional follow-up time is needed to fully examine the effect of folic acid fortification.		Gibson (2011) Am J Clin Nutr
Maternal folate levels in pregnancy and asthma in children at age 3 years	Case-control study	Letter. No abstract. Extract: "There was an increased risk of asthma at age 3 years for children with maternal plasma folate levels in pregnancy in the highest compared with the lowest quintile (adjusted odds ratio, 1.66; 95% CI, 1.16-2.37). There was a trend of increasing risk across quintiles of plasma folate (P trend 5 .006)."		Haberg (2011) J Allergy Clin Immunol 127: 262-4, 264 e1
Folic acid	Cell culture of	For over a decade, folic acid (FA) supplementation has been widely prescribed to pregnant women to prevent neural tube closure defects in		Junaid (2011)

supplementation dysregulates gene expression in lymphoblastoid cells - Implications in nutrition	human cells	newborns. Although neural tube closure occurs within the first trimester, high doses of FA are given throughout pregnancy, the physiological consequences of which are unknown. FA can cause epigenetic modification of the cytosine residues in the CpG dinucleotide, thereby affecting gene expression. Dysregulation of crucial gene expression during gestational development may have lifelong adverse effects or lead to neurodevelopmental defects, such as autism. We have investigated the effect of FA supplementation on gene expression in lymphoblastoid cells by whole-genome expression microarrays. The results showed that high FA caused dysregulation by four-fold up or down to more than 1000 genes, including many imprinted genes. The aberrant expression of three genes (FMR1, GPR37L1, TSSK3) was confirmed by Western blot analyses. The level of altered gene expression changed in an FA concentration-dependent manner. We found significant dysregulation in gene expression at concentrations as low as 15ng/ml, a level that is lower than what has been achieved in the blood through FA fortification guidelines. We found evidence of aberrant promoter methylation in the CpG island of the TSSK3 gene. Excessive FA supplementation may require careful monitoring in women who are planning for, or are in the early stages of pregnancy. Aberrant expression of genes during early brain development may have an impact on behavioural characteristics.		Biochem Biophys Res Commun 412: 688-92
Folate intake and the risk of colorectal cancer: a systematic review and meta-analysis	Meta-analysis of intake studies	Folic acid fortification and supplementation to prevent neural tube defects has led to concerns regarding increased risk of colorectal cancer. The results of existing studies have been inconclusive. The purpose was to examine the relationship between level of folate intake and the incidence of colorectal cancer. METHODS: A systematic review and meta analysis were conducted. MEDLINE, Embase, and SCOPUS were searched from inception to October 2009 with the following search terms "folic acid," "folate", "colorectal cancer," "colon neoplasms," rectal neoplasms." Observational studies in adult populations were included that defined levels of folate intake and incidence of colorectal cancer. RESULT: Out of 6427 references, 27 studies met our inclusion criteria. The summary risk estimate for case control studies comparing high versus low total folate intake was 0.85 (CI 95% 0.74-0.99) with no significant heterogeneity among studies. Similarly, for cohort studies, the resulting summary risk estimate for high versus low dietary folate intake was 0.92 (CI 95% 0.81-1.05) with no significant heterogeneity. However, defining what represents a higher intake of folic acid is difficult as there is variability in the upper limit of folic acid intake used in the studies. DISCUSSION: These results suggest that higher folate intake levels offer a reduction in one of the perceived risks associated with developing colorectal cancer. These data can serve to help reassure women planning a pregnancy to increase folic intake during the preconception period to levels sufficient to prevent neural tube defects.		Kennedy (2011) Cancer Epidemiol 35: 2-10

Folic acid and colorectal cancer: unwarranted fears	Opinion	Question Some of my female patients are afraid of taking folic acid because they "fear cancer." What is the evidence for this? Answer Theoretical evidence in experimental models is sharply contrasted by 3 recent meta-analyses of randomized and observational studies. Women planning to become pregnant should supplement with the folate dose they need to prevent neural tube defects.	Emotional. She consults for 2 companies that sell folic acid	Koren (2011) Can Fam Physician 57: 889-90
Folate intake and breast cancer mortality in a cohort of Swedish women	Population study	Folate may influence breast cancer development and progression through its role in one-carbon metabolism. However, epidemiologic data on the relation between folate and breast cancer survival are limited. We investigated whether dietary folate intake was associated with survival in 3,116 women diagnosed with breast cancer in the population-based Swedish Mammography Cohort. Participants completed a 67-item food frequency questionnaire in 1987. Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for death from breast cancer and death from any cause. During 25,716 person-years of follow-up from 1987 to 2008, there were 852 deaths with 381 breast cancer deaths. Dietary folate intake was inversely associated with breast cancer and overall mortality. Women in the highest quartile of folate intake had a multivariable HR (95% CI) of death from breast cancer of 0.78 (0.58-1.03) compared to those in the lowest quartile (P (trend) = 0.03). The corresponding HR (95% CI) for death from any cause was 0.79 (0.66-0.96; P (trend) = 0.004). The protective association between dietary folate intake and breast cancer death was strongest among those with ER-negative tumors (HR = 0.42; 95% = CI 0.22-0.79; P (trend) = 0.01) comparing the highest to lowest quartile. Our findings suggest that folate intake before breast cancer diagnosis may improve breast cancer and overall survival. While these findings need to be confirmed in future studies, they do offer assurance that dietary folate intake at the levels observed in our population does not unfavorably affect survival after breast cancer.	Subgroups ER	Harris (2011) Breast Cancer Res Treat
High levels of folate from supplements and fortification are not associated with increased risk of colorectal cancer	Large population study	Folate intake has been inversely associated with colorectal cancer risk in several prospective epidemiologic studies. However, no study fully assessed the influence of the high levels of folate that are frequently consumed in the United States as a result of mandatory folate fortification, which was fully implemented in 1998, and the recent increase in use of folate-containing supplements. There is evidence that consumption of high levels of folic acid, the form of folate used for fortification and in supplements, has different effects on biochemical pathways than natural folates and might promote carcinogenesis. METHODS: We investigated the association between folate intake and colorectal cancer among 43,512 men and 56,011 women in the Cancer Prevention Study II (CPS-II) Nutrition Cohort; 1023 were diagnosed with colorectal cancer between 1999 and 2007, a period entirely after folate fortification began. Cox proportional hazards regression was used to calculate multivariate hazards	Excellent study. NB all subjects recruited after fortification, i.e. when folate levels were already high.	Stevens (2011) Gastroenterology 141: 98-105, 105 e1

		ratios (RR) and 95% confidence interval (CI). RESULTS: Intake of high levels of natural folate (RRQ5vsQ1=0.86; 95% CI: 0.70-1.06; P trend=.12) or folic acid (RRQ5vsQ1=0.84; 95% CI: 0.68-1.03; P trend=.06) were not significantly associated with risk of colorectal cancer. Total folate intake was significantly associated with lower risk (RRQ5vsQ1=0.81; 95% CI: 0.66-0.99; P trend=.047). CONCLUSIONS: Intake of high levels of total folate reduces risk of colorectal cancer; there is no evidence that dietary fortification or supplementation with this vitamin increases colorectal cancer risk.		
Fruit, vegetables, and folate: cultivating the evidence for cancer prevention	Editorial	No abstract. Comment on Stevens paper and on Aune (fruit and veg.)	Stresses non-linear analysis. Those with low folate at baseline seem to be protected see Wu et al. (2009) Am J Clin Nutr 90: 1623-1631 Figueiredo et al. (2010) Int J Cancer	Lee et al. (2011) Gastroenterology 141: 16-20
Effect of maternal and postweaning folic acid supplementation on mammary tumor risk in the offspring	Mice, diet supplementation	Intrauterine and early life exposure to folic acid has significantly increased in North America owing to folic acid fortification, widespread supplemental use, and periconceptional supplementation. We investigated the effects of maternal and postweaning folic acid supplementation on mammary tumor risk in the offspring. Female rats were placed on a control or folic acid-supplemented diet prior to mating and during pregnancy and lactation. At weaning, female pups from each maternal diet group were randomized to the control or supplemented diet and mammary tumors were induced with 7,12 dimethylbenz[a]anthracene at puberty. At necropsy, mammary tumor parameters, genomic DNA methylation, and DNA methyltransferase activity were determined in the offspring. Both maternal and postweaning folic acid supplementation significantly increased the risk of mammary adenocarcinomas in the offspring (OR = 2.1, 95% CI 1.2-3.8, P = 0.008 and OR = 1.9, 95% CI 1.1-3.3, P = 0.03, respectively). Maternal folic acid supplementation also significantly accelerated the rate of mammary adenocarcinoma appearance (P = 0.002) and increased the multiplicity of mammary adenocarcinomas (P = 0.008) in the offspring. Maternal, but not postweaning, folic acid supplementation significantly reduced global DNA methylation (P = 0.03), whereas postweaning, but not maternal, folic acid supplementation significantly decreased DNA methyltransferase activity (P = 0.05) in nonneoplastic mammary glands of the offspring. Our findings suggest that a high intrauterine and postweaning dietary exposure to folic acid may increase the risk of mammary tumors in the offspring. Further, they suggest that this tumor-promoting effect may be mediated in part by altered DNA methylation and DNMT activity.		Ly (2011) Cancer Res 71: 988-97
Folic Acid use in	Cohort study	Recently, folic acid supplementation during pregnancy was implicated as a potential risk factor for atopic diseases in childhood. OBJECTIVE: To		Magdelijns

pregnancy and the development of atopy, asthma, and lung function in childhood		investigate whether folic acid supplementation and higher intracellular folic acid (ICF) levels during pregnancy increase the risk of childhood atopic diseases. METHODS: In the KOALA Birth Cohort Study (N=2834), data on eczema and wheeze were collected by using repeated questionnaires at 3, 7, 12, and 24 months, 4 to 5 years, and 6 to 7 years after delivery. Atopic dermatitis and total and specific immunoglobulin E levels were determined at age 2 years and asthma and lung function at age 6 to 7 years. We defined folic acid use as stand-alone and/or multivitamin supplements according to the period of use before and/or during pregnancy. ICF levels were determined in blood samples taken at approximately 35 weeks of pregnancy (n=837). Multivariable logistic and linear regression analyses were conducted, with generalized estimating equation models for repeated outcomes. RESULTS: Maternal folic acid supplement use during pregnancy was not associated with increased risk of wheeze, lung function, asthma, or related atopic outcomes in the offspring. Maternal ICF level in late pregnancy was inversely associated with asthma risk at age 6 to 7 years in a dose-dependent manner (P for trend=.05). CONCLUSIONS: Our results do not confirm any meaningful association between folic acid supplement use during pregnancy and atopic diseases in the offspring. Higher ICF levels in pregnancy tended, at most, toward a small decreased risk for developing asthma.		(2011) Pediatrics 128: e135-44
Folic acid supplementation can adversely affect murine neural tube closure and embryonic survival	Dietary supplementation in mice	Neural tube defects (NTDs), a common birth defect in humans, result from the failure of the embryonic neural tube (NT) to close properly. NT closure is a complex, poorly understood morphogenetic process influenced by genes and environment. The most effective environmental influence in decreasing the risk for NTDs is folic acid (FA) fortification and supplementation, and these findings led to the recommendation of periconceptual FA intake and mandatory fortification of the US grain supply in 1998. To explore the relationship between genetics and responsiveness to FA supplementation, we used five mouse NTDs models-Zic2, Shroom3, Frem2, Grhl2 (Grainyhead-like 2) and L3P (Line3P)-and a long-term generational FA supplementation scheme. Contrary to expectations, we find that three genetic mutants respond adversely to FA supplementation with increased incidence of NTDs in homozygous mutants, occurrence of NTDs in heterozygous embryos and embryonic lethality prior to NT closure. Because of these unexpected responses, we examined NTD risk after short-term FA supplementation. Our results indicate that, for the same genetic allele, NTD risk can depend on the length of FA exposure. Our data indicate that, depending on the gene mutation, FA supplementation may adversely influence embryonic development and NT closure.		Marean (2011) Hum Mol Genet 20: 3678-83
Folic acid supplementation in early pregnancy and asthma in	Prospective cohort	The objective of the study was to assess whether folic acid intake during the first trimester of pregnancy is related to asthma in the offspring by the age of 6 years. STUDY DESIGN: This was a prospective cohort study of 1499 women who were followed up from the first trimester of pregnancy.		Martinussen (2011) Am J Obstet Gynecol

children aged 6 years		Their children were followed up until they were 6 years old. RESULTS: Fifty-one percent of the women used folic acid in the month before conception and 88% in the third month of pregnancy. The adjusted odds ratio for asthma per 100 mum increase in the average daily intake of folic acid was 0.98 (95% confidence interval, 0.93-1.04). For categories of daily folate intake, there was no evidence of associations with childhood asthma or evidence of any dose response relation for any time period (all P(trend) > .05). CONCLUSION: Our results do not support any association of folic acid supplementation in pregnancy and asthma risk in offspring by age 6 years.		
Mathematical modeling predicts the effect of folate deficiency and excess on cancer related biomarkers	Mathematical models	Folate is an essential B-vitamin that mediates one-carbon metabolism reactions, including nucleotide synthesis and others related to carcinogenesis. Both low and high folate status influences carcinogenesis.METHODS: We used a mathematical model of folate-mediated one-carbon metabolism to predict the effect of a range of intracellular epithelial folate concentrations (0.25 micromol/L-15.0 micromol/L) on methylation rate and purine and thymidylate synthesis. We also examined the interaction of these folate concentrations with polymorphisms in two enzymes [Methylene tetrahydrofolate reductase (MTHFR) and thymidylate synthase (TS)] in relation to the biochemical products.RESULTS: TS enzyme reaction rate increased markedly in response to the modeled higher intracellular folate concentrations. Changes in methylation rate were modest, while purine synthesis was only minimally related to increases in folate concentrations with an apparent threshold effect at 5.0-6.0 micromol/L. The relationship between folate concentrations and thymidylate synthesis was modified by genetic variation in TS, but less so by variation in MTHFR. These gene-folate interactions modestly influenced purine synthesis in a non-linear manner, but only affected methylation rate under conditions of very high MTHFR activity.CONCLUSION: Thymidylate synthesis is very sensitive to changes in epithelial intracellular folate and increased nearly five-fold under conditions of high intracellular folate. Individuals with genetic variations causing reduced TS activity may present even greater susceptibility to excessive folate.Impact: Our observation that thymidylate synthesis increases dramatically under conditions of very elevated intracellular folate provides biological support to observations that excessive folic acid intake increases risk of both precursor lesions (i.e., colorectal adenomas) and cancer.		Neuhouser (2011) Cancer Epidemiol Biomarkers Prev
A U-shaped relationship between plasma folate and pancreatic cancer risk in the European Prospective Investigation	Case-control study	Folate intake has shown an inverse association with pancreatic cancer; nevertheless, results from plasma measurements were inconsistent. The aim of this study is to examine the association between plasma total homocysteine, methionine, folate, cobalamin, pyridoxal 5'-phosphate, riboflavin, flavin mononucleotide and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). We		Chuang (2011) Eur J Cancer

into Cancer and Nutrition		conducted a nested case-control study in the EPIC cohort, which has an average of 9.6years of follow-up (1992-2006), using 463 incident pancreatic cancer cases. Controls were matched to each case by center, sex, age (+/-1year), date (+/-1year) and time (+/-3h) at blood collection and fasting status. Conditional logistic regression was used to calculate the odds ratios (OR) and 95% confidence intervals (CI), adjusting for education, smoking status, plasma cotinine concentration, alcohol drinking, body mass index and diabetes status. We observed a U-shaped association between plasma folate and pancreatic cancer risk. The ORs for plasma folate 5, 5-10, 10-15 (reference), 15-20, and >20nmol/L were 1.58 (95% CI=0.72-3.46), 1.39 (0.93-2.08), 1.0 (reference), 0.79 (0.52-1.21), and 1.34 (0.89-2.02), respectively. Methionine was associated with an increased risk in men (per quintile increment: OR=1.17, 95% CI=1.00-1.38) but not in women (OR=0.91, 95% CI=0.78-1.07; p for heterogeneity <0.01). Our results suggest a U-shaped association between plasma folate and pancreatic cancer risk in both men and women. The positive association that we observed between methionine and pancreatic cancer may be sex dependent and may differ by time of follow-up. However, the mechanisms behind the observed associations warrant further investigation.		
Elevated physiological levels of folic acid can increase in vitro growth and invasiveness of prostate cancer cells	Cultured cell lines	Evidence has emerged identifying folic acid supplementation as a potential risk factor for cancer development or progression. Long-term folic acid supplementation has been shown to increase the risk of prostate cancer development by three-fold. Sarcosine is a byproduct of folate metabolism and has been proposed as a biomarker for aggressive prostate cancer phenotypes. We looked at the effects of physiologically relevant levels of folic acid on in vitro prostate cancer cell growth and invasion, and demonstrated that higher levels can have the effect of increasing both of these biological processes. We also show that these changes toward a more aggressive phenotype are not linked to increased sarcosine levels, however other metabolic pathways may be involved. OBJECTIVES: * To investigate the effects of different folic acid concentrations on the growth and invasiveness of prostate cancer cell lines. * To determine if observed changes are correlated with changes in levels of the potential prostate cancer biomarker, sarcosine, a byproduct of folate metabolism. MATERIALS AND METHODS: * The prostate cancer cell lines PC-3, LNCaP and DU145 were cultured in media containing 4, 20 or 100 nm of folic acid and assayed for growth over 9 days by counting viable cells at 3-day intervals, or for invasion by passage through a Matrigel-coated transwell membrane. * Cells grown in the different folic acid media were collected and subjected to metabolomic analysis by gas chromatography and mass spectrometry to measure levels of intracellular sarcosine. RESULTS: * The results show that higher levels of folic acid can increase cell growth in PC-3 and LNCaP prostate cancer cell lines, and may also increase the invasive capacity of PC-3, LNCaP and DU145 cells. * We did not observe a correlation between increased invasion from higher folic acid		Petersen et al. (2011) BJU Int

		concentrations and levels of sarcosine, but there were significant changes in other metabolites in cells grown in higher levels of folic acid. CONCLUSION: * These findings suggest that folic acid has an important and potentially negative role in prostate cancer progression.		
Increased cancer cell proliferation in prostate cancer patients with high levels of serum folate	Cohort study	A recent clinical trial revealed that folic acid supplementation is associated with an increased incidence of prostate cancer (Figueiredo et al., J Natl Cancer Inst 2009; 101(6): 432-435). As tumor cells in culture proliferate directly in response to available folic acid, the goal of our study was to determine if there is a similar relationship between patient folate status, and the proliferative capacity of tumors in men with prostate cancer. METHODS: Serum folate and/or prostate tissue folate was determined in 87 randomly selected patients undergoing surgery for prostate cancer, and compared to tumor proliferation in a subset. RESULTS: Fasting serum folate levels were positively correlated with prostate tumor tissue folate content (n = 15; r□ = 0.577, P□<□0.03). Mean serum folate was 62.6□nM (7.5-145.2□nM), 39.5% of patients used supplements containing folic acid (n□= 86). The top quartile of patients had serum folates above 82□nM, six times the level considered adequate. Of these, 48% reported no supplement use. Among 50 patients with Gleason 7 disease, the mean proliferation index as determined by Ki67 staining was 6.17□±□3.2% and 0.86□±□0.92% in the tumors from patients in the highest (117□±□15□nM) and lowest (18□±□9□nM) quintiles for serum folate, respectively (P□<□0.0001). CONCLUSIONS: Increased cancer cell proliferation in men with higher serum folate concentrations is consistent with an increase in prostate cancer incidence observed with folate supplementation. Unexpectedly, more than 25% of patients had serum folate levels greater than sixfold adequate. Nearly half of these men reported no supplement use, suggesting either altered folate metabolism and/or sustained consumption of folic acid from fortified foods.	Striking correlation between high folate and Ki-67 staining – a risk factor for death in prostate cancer patients Aaltomaa (2006) Anticancer Res 26: 4873-8 Note that even those who did not take supplements had very high serum folate levels. They suggest “It is likely that their folate levels are due to sustained consumption of fortified food.”	Tomaszewski et al. (2011) Prostate
High intake of folic acid disrupts embryonic development in mice	Dietary supplements to mice	Folic acid fortification and supplementation has increased folate intake and blood folate concentrations and successfully reduced the incidence of neural tube defects. However, the developmental consequences of high folate intake are unknown. This study investigated the impact of high folate intake, alone or with methylenetetrahydrofolate reductase (MTHFR) deficiency, on embryonic and placental development in mice. METHODS: Mthfr +/+ or +/- pregnant mice on a control diet (CD; recommended intake of folic acid for rodents) or folic acid-supplemented diet (FASD; 20-fold higher than the recommended intake) were examined for embryonic loss, delay, and defects at 10.5 and 14.5 days post coitum (dpc); 10.5-dpc placenta, and 14.5-dpc embryo hearts were studied histologically. RESULTS: Total plasma folate was 10-fold higher in FASD compared to CD mice; plasma homocysteine levels were not affected by diet. At 10.5 dpc, the FASD was associated with embryonic delay and growth	NB effect of MTHFR	Pickell (2011) Birth Defects Res A Clin Mol Teratol 91: 8-19

		retardation, and may confer susceptibility to embryonic defects. The FASD did not adversely affect 10.5-dpc placental development. At 14.5 dpc, embryos from the FASD Mthfr +/+ group were delayed and the FASD was associated with thinner ventricular walls in embryonic hearts. There was a significant interaction between maternal MTHFR deficiency and a high folate diet for several developmental outcomes. CONCLUSIONS: Our study suggests that high folate intake may have adverse effects on fetal mouse development and that maternal MTHFR deficiency may improve or rescue some of the adverse outcomes. These findings underscore the need for additional studies on the potential negative impact of high folate intake during pregnancy.		
The impact of folate status on the efficacy of colorectal cancer treatment	Review	Over the past three decades, numerous reports have addressed several aspects of drug resistance phenomena. However, little is known regarding the impact that dietary components and nutritional supplements have on the mechanisms of resistance that malignant cells develop to chemotherapeutic agents. The increased fortification of cereals, grains and bread with folic acid (FA) has resulted in a marked rise in folate levels in blood and tissues. Vitamin fortification that includes FA is rather commonly used by cancer patients, but FA is also used to protect against pemetrexed induced side effects in the treatment of non-small cell lung cancer and mesothelioma or that of the antifolate methotrexate in rheumatoid arthritis. Moreover, the reduced folate leucovorin (LV, 5-formyltetrahydrofolate) is also used along with 5-fluorouracil in the treatment of colorectal cancer. Likewise, LV is used to reduce toxicity of methotrexate in the treatment of leukemia. FA can also increase efficacy of unrelated regimens, containing cisplatin. Hence there is growing evidence that dietary supplements as folic acid, can mimic, intensify, or attenuate the effects of unrelated chemotherapeutic agents. The aim of this review is to highlight some new insights in the cellular and molecular mechanisms affected by folate status, leading to chemotherapy resistance, especially towards antifolates in colorectal cancer treatment. This encompasses the effect of folate status on drug export, as well as on the increased expression of mutated target enzymes involved in folate metabolism and on the augmentation of cellular folate pools that impair polyglutamylation of antifolates, ultimately affecting treatment efficacy.	Comprehensive review, but a little imprecise in places	Porcelli (2011) Curr Drug Metab
Folic acid in pregnancy - is there a link with childhood asthma or wheeze?	Review	Folic acid supplementation has an established role in early pregnancy for preventing neural tube defects. However, there is controversy over a possible link between late pregnancy folic acid supplementation and childhood asthma. OBJECTIVE: To review the evidence exploring the association between maternal folate exposure in pregnancy and childhood asthma or wheeze. RESULTS: Four relevant observational studies were identified. Two found statistically significant associations between childhood asthma and late (but not early) pregnancy maternal folic acid exposure. Another found a statistically significant association between		Sharland (2011) Aust Fam Physician 40: 421-4

		childhood wheeze and early (but not late) pregnancy maternal folic acid exposure. A fourth study found little association between maternal dietary folate in pregnancy and infantile wheeze. DISCUSSION: The currently available evidence regarding an association between folate in pregnancy and childhood asthma or wheeze is conflicting. We offer suggestions for discussing the potential risk with patients and recommend further research on this subject be conducted.		
Elevated maternal serum folate in the third trimester and reduced fetal growth: a longitudinal study	Cohort study	This study aimed to examine the association of fetal growth and elevated third trimester maternal serum folate due to folic acid (FA) supplement intake. Dietary intake, use of FA supplements, weight, and blood biomarkers of B-vitamins (serum folate, pyridoxal, vitamin B12, and plasma total homocysteine) were observed in 33 healthy pregnant women at the third trimester (average gestational age 35 wk). Birth outcomes were assessed through hospital birth records. Infant anthropometry and maternal blood biomarkers were followed up at 1 mo postpartum. Fourteen women were taking FA supplements at the third trimester. Dietary intake was similar among FA users and non-users, but serum folate and pyridoxal were significantly higher in users (11.6+/-6.7 vs. 6.1+/-3.2 ng/mL, and 13.8+/-21.7 vs. 3.2+/-1.4 ng/mL, respectively). Plasma total homocystein (tHcy) was higher in non-users compared to users, but not significantly. Nine FA users and eight non-users had low serum vitamin B12 values (<203 pg/mL). Nine FA users and all non-users had low serum pyridoxal values (<7.0 ng/mL). Infant birthweight was significantly lower in users compared to non-users (2,894+/-318 vs. 3,154+/-230 g). At 1 mo postpartum, infant weight and length were similar between FA users and non-users, but infant weight gain was larger in users. Higher serum folate values due to FA use in the third trimester was related to reduced fetal size. Excess FA under low vitamin B6 and B12 status may affect fetal growth.	Small number of subjects	Takimoto (2011) J Nutr Sci Vitaminol (Tokyo) 57: 130-7
Control of prostate cancer associated with withdrawal of a supplement containing folic acid, L-methyltetrahydrofolate and vitamin B12: a case report	Case report	This is the first report of possible direct stimulation of hormone-resistant prostate cancer or interference of docetaxel cytotoxicity of prostate cancer in a patient with biochemical relapse of prostatic-specific antigen. This observation is of clinical and metabolic importance, especially at a time when more than 80 countries have fortified food supplies with folic acid and some contemplate further fortification with vitamin B12. CASE PRESENTATION: Our patient was a 71-year-old Caucasian man who had been diagnosed in 1997 with prostate cancer, stage T1c, and Gleason score 3+4=7. His primary treatment included intermittent androgen deprivation therapy including leuprolide + bicalutamide + deutasteride, ketoconazole + hydrocortisone, nilandrone and flutamide to resistance defined as biochemical relapse of PSA. While undergoing docetaxel therapy to treat a continually increasing prostate-specific antigen level, withdrawal of 10 daily doses of a supplement containing 500mug of vitamin B12 as cyanocobalamin, as well as 400mug of folic acid as pteroylglutamic		Tisman (2011) J Med Case Reports 5: 413

		acid and 400mug of L-5-methyltetrahydrofolate for a combined total of 800mug of mixed folates, was associated with a return to a normal serum prostatic-specific antigen level. CONCLUSION: This case report illustrates the importance of the effects of supplements containing large amounts of folic acid, L-5-methyltetrahydrofolate, and cyanocobalamin on the metabolism of prostate cancer cells directly and/or B vitamin interference with docetaxel efficacy. Physicians caring for patients with prostate cancer undergoing watchful waiting, hormone therapy, and/or chemotherapy should consider the possible acceleration of tumor growth and/or metastasis and the development of drug resistance associated with supplement ingestion. We describe several pathways of metabolic and epigenetic interactions that could affect the observed changes in serum levels of prostate-specific antigen.		
Folate and related micronutrients, folate-metabolising genes and risk of ovarian cancer	Case-control study	Folates are essential for DNA synthesis and methylation, and thus may have a role in carcinogenesis. Limited evidence suggests folate-containing foods might protect against some cancers and may partially mitigate the increased risk of breast cancer associated with alcohol intake, but there is little information regarding ovarian cancer. Our aim was to evaluate the role of folate and related micronutrients, polymorphisms in key folate-metabolising genes and environmental factors in ovarian carcinogenesis. Subjects/Methods: Participants in the Australian Ovarian Cancer Study (1363 cases, 1414 controls) self-completed risk factor and food-frequency questionnaires. DNA samples (1638 cases, 1278 controls) were genotyped for 49 tag single-nucleotide polymorphisms (SNPs) in the methylene tetrahydrofolate reductase (MTHFR), methionine synthase (MTR) and MTR reductase (MTRR) genes. Logistic regression models were used to generate adjusted odds ratios and 95% confidence intervals. Results: We saw no overall association between the intake of folate, B vitamins or other methyl donors and ovarian cancer risk, although increasing folate from foods was associated with reduced risk among current smokers (P (trend)=0.03) and folic acid intake was associated with borderline significant increased risks among women who consumed >/=1 standard alcoholic drinks/day (odds ratio (OR)=1.64; 95% confidence interval (CI) 1.05-2.54, P (trend)=0.05). Two SNPs (rs7365052, rs7526063) showed borderline significant inverse associations with ovarian cancer risk; both had very low minor allele frequencies. There was little evidence for interaction between genotype and micronutrient intake or for variation between different histological subtypes of ovarian cancer. Conclusions: Our data provide little evidence to support a protective role for folate in ovarian carcinogenesis but suggest further evaluation of the joint effects of folic acid and alcohol is warranted.	NB Subgroups may be different	Webb (2011) Eur J Clin Nutr 65: 1133-40
The influence of one-carbon metabolism on gene promoter	Observational cohort study	Abnormal methylation in gene promoters is a hallmark phenomenon of the cancer genome including breast cancer; however, factors that may influence promoter methylation have not been well elucidated. One-carbon	Higher folate intake was associated with reduced methylation of CCND2	{Xu, 2011 #781}

methylation in a population-based breast cancer study		metabolism provides the universal methyl donor for methylation reactions; perturbation of one-carbon metabolism might influence DNA methylation and ultimately, affect gene functions. Utilizing ~800 breast cancer tumor tissues from a large population-based study, we investigated the relationships of dietary and genetic factors involved in the one-carbon metabolism pathway with promoter methylation of a panel of 13 breast cancer related genes. We found CCND2, HIN1 and CHD1 are the more "dietary sensitive" as their promoter methylation was associated with intakes of at least two out of eight dietary methyl factors examined. On the other hand, some micronutrients (i.e. B 2 and B 6) are more "epigenetically active" as their intake levels were correlated with promoter methylation status of 3 out of 13 breast cancer genes. Both positive (hypermethylation) and inverse (hypomethylation) associations with high micronutrient intakes were observed. Unlike the dietary factors, we did not observe any clear patterns between one-carbon genetic polymorphism and promoter methylation status of the genes examined. Our results provide preliminary evidence that one-carbon metabolism may have the capacity to influence the breast cancer epigenome. Given that epigenetic alterations are thought to occur early in cancer development and potentially reversible, dietary intervention may offer promising venues for cancer intervention and prevention.	gene	
Nutrients in folate-mediated, one-carbon metabolism and the risk of rectal tumors in men and women	Case-control	In an investigation of rectal tumors characterized by CpG island methylator phenotype (CIMP), KRAS2 mutation, and TP53 mutation, we examined associations with dietary and supplemental folate, riboflavin, vitamins B(6) and B(12), and methionine, nutrients involved in folate-mediated 1-carbon metabolism. We also examined folate intake and common MTHFR polymorphisms in relation to CIMP. Data from a population-based study of 951 cases (750 with tumor markers) and 1,205 controls were evaluated using multiple logistic regression models and generalized estimating equations. Reduced risk of methylated tumors was suggested in women with the upper tertile of folate intake (>/=0.42 mg/day) vs. the lower tertile: OR = 0.6, 95%CI = 0.3-1.2. In men, a significant 3-fold increased risk of CIMP+ tumor was observed for the upper tertile of folate (>/=0.75 mg/day) vs. the lower tertile (<0.44 mg/day): OR = 3.2, 95%CI = 1.5-6.7. These men consumed a greater proportion of folic acid fortified foods relative to natural, primarily plant-based sources (52% vs. 48%) than women with CIMP+ tumors (22% vs. 78%). MTHFR 1298A>C influenced folate in male CIMP+ risk (P interaction < 0.01). Our findings suggest folate supplementation effects may differ between genders, perhaps due to variation in MTHFR and/or endogenous/exogenous hormones, and may be important in the initiation and progression of methylated rectaltumors in men.	NB Gender difference: folate increases risk in men	Curtin (2011) Nutr Cancer 63: 357-66
Meta-analysis of cancer risk in folic acid	Meta-analysis	Several reports suggest that folate has a procarcinogenic effect. Folate has a unique role because its coenzymes are needed for de novo purine and	Rather an odd report. Uses Ebbing 2008 instead	{Baggott, 2011 #838}

supplementation trials		thymine nucleotide biosynthesis. Antifolates, such as methotrexate, are used in cancer treatment. Using a meta-analysis weighted for the duration of folic acid (pteroylglutamic acid) supplementation, we analyzed the cancer incidence of six previously published large prospective folic acid-supplementation trials in men and women. These articles were carefully selected from over 1100 identified using PubMed search. Our analyses suggest that cancer incidences were higher in the folic acid-supplemented groups than the non-folic acid-supplemented groups (relative risk=1.21 [95% confidence interval: 1.05-1.39]). Folic acid-supplementation trials should be performed with careful monitoring of cancer incidence. Solid monitoring systems to detect side effects, including increase in cancer risk, should be established before the initiation of folic acid supplementation trials.	of her combined analysis with longer follow-up (2009). Meta-analysis was weighted in relation to the length of the trials – the longer the trial, the greater the weighting.	
Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity	Systematic review	BACKGROUND/AIM: To define practical use and to specify the ideal method for monitoring the liver toxicity of MTX in the management of psoriasis. OBJECTIVE: To systematically review the literature regarding treatment modalities with methotrexate (MTX) in psoriasis, risk of MTX-mediated liver fibrosis and monitoring of hepatic toxicity. METHODS: A systematic literature search was carried out in Medline, Embase and Cochrane Library databases from 1980 to 2010 searching for randomized controlled trials and observational studies on methods of administering MTX in psoriasis and risk factors and assessment of liver toxicity. We limited the literature search to articles on human subjects over 19 years of age, articles in English or French on psoriasis and articles including psoriatic arthritis and original data. RESULTS: Among 949 references identified, 23 published studies were included. There were no studies focusing directly on the question of MTX treatment modalities. Treatment outcome appears to be dose dependent. A single study in rheumatoid arthritis showed the slightly superior efficacy of subcutaneous administration vs. oral dosing with a similar safety profile. Combination with folic acid may decrease the efficacy of MTX while improving tolerability. The extreme variability of the incidence of hepatic fibrosis in the literature does not allow the risk of hepatic fibrosis to be quantified. Type 2 diabetes and obesity, were associated with a significant increased risk of liver fibrosis. Hepatitis B and C and alcohol consumption were associated with a modest and non-significant increased risk of liver fibrosis. Procollagen III for detection of hepatic fibrosis dosing was the most extensively validated method to monitor liver fibrosis showing a sensitivity of 77.3% and a specificity of 91.5%. The Positive Predictive Value and Negative Predictive Value fluctuated depending on the prevalence of hepatic fibrosis. The sensitivities of the FibroTest and the fibroscan were of 83 and 50%, respectively, with specific features amounting to 61 and 88% respectively. CONCLUSIONS: Based on expert experience, the starting dose of MTX is between 5 and 10 mg/week for the first week. Fast dose escalation is recommended in order to obtain a therapeutic target dose of 15-25	Thorough review but nothing new on folate compared with Chladek Chladek et al. (2008) Eur J Clin Pharmacol 64: 347-55	Montaudie (2011) J Eur Acad Dermatol Venereol 25 Suppl 2: 12-8

		mg/week. The maximum recommended dose is 25 mg/week. A folic acid supplement is necessary. The initiation of treatment by oral administration is preferred. In cases where inadequate response is obtained or in the event of poor gastrointestinal tolerance, subcutaneous dosing can be proposed at the same dose. Published data do not confirm the incidence of hepatic fibrosis. Type 2 diabetes and obesity appear to be significant risk factors in fibrosis. A combination of FibroTests and fibroscans together with measurement of the type III serum procollagen aminopeptide seem to be ideal method for monitoring liver toxicity.		
Epigenetic influences that modulate infant growth, development and disease	Review	Significance: Epigenetic modifications are key processes in understanding normal human development and are largely responsible for the myriad of cell and tissue types that originate from a single celled fertilized ovum. The three most common processes involved in bringing about epigenetic changes are DNA methylation, histone modification and miRNA effects. There are critical periods in the development of the zygote, the embryo and the fetus where in the organism is most susceptible to epigenetic influences because of normal de-methylation and de novo methylation processes that occur in the womb. Recent Advances: A number of epigenetic modifications of normal growth patterns have been recognized leading to altered development and disease states in the mammalian fetus and infant. 'Fetal programming' due to these epigenetic changes has been implicated in pathogenesis of adult-onset disease such as hypertension, diabetes and cardiovascular disease. There may also be transgenerational effects of such epigenetic modifications. Critical Issues: The impact of environmental agents and endogenous factors such as stress at critical periods of infant development has immediate, life-long effects and even multi-generational effects. Both the timing and the degree of insult may be important. Understanding these influences may help prevent onset of disease and promote normal growth. Future Directions: Use of one-carbon metabolism modifying agents such as folic acid during critical periods of epigenetic modulation may have significant clinical impact. Their use as therapeutic agents in targeted epigenetic modulation of genes may be the new frontier for clinical therapeutics.		Hussain (2012) Antioxid Redox Signal
Cancer risk with folic acid supplements: a systematic review and meta-analysis	Systematic review and meta-analysis	Objective To explore if there is an increased cancer risk associated with folic acid supplements given orally. Design Systematic review and meta-analysis of controlled studies of folic acid supplementation in humans reporting cancer incidence and/or cancer mortality. Studies on folic acid fortification of foods were not included. Data sources Cochrane Library, Medline, Embase and Centre of Reviews and Dissemination, clinical trial registries and hand-searching of key journals. Results From 4104 potential references, 19 studies contributed data to our meta-analyses, including 12 randomised controlled trials (RCTs). Meta-analysis of the 10 RCTs reporting overall cancer incidence (N=38 233) gave an RR of developing cancer in patients randomised to folic acid supplements of 1.07 (95% CI	Important study that includes more trials than other meta-analyses. Importance of sub-groups, e.g. smokers. Prostate cancer convincing result: 1.24 (95% CI 1.03 to 1.49)	Wien (2012) BMJ Open 2: e000653

		1.00 to 1.14) compared to controls. Overall cancer incidence was not reported in the seven observational studies. Meta-analyses of six RCTs reporting prostate cancer incidence showed an RR of prostate cancer of 1.24 (95% CI 1.03 to 1.49) for the men receiving folic acid compared to controls. No significant difference in cancer incidence was shown between groups receiving folic acid and placebo/control group, for any other cancer type. Total cancer mortality was reported in six RCTs, and a meta-analysis of these did not show any significant difference in cancer mortality in folic acid supplemented groups compared to controls (RR 1.09, 95% CI 0.90 to 1.30). None of the observational studies addressed mortality. Conclusions A meta-analysis of 10 RCTs showed a borderline significant increase in frequency of overall cancer in the folic acid group compared to controls. Overall cancer incidence was not reported in the seven observational studies. Prostate cancer was the only cancer type found to be increased after folic acid supplementation (meta-analyses of six RCTs). Prospective studies of cancer development in populations where food is fortified with folic acid could indicate whether fortification similar to supplementation moderately increases prostate cancer risk.		

Table 5S. Other relevant reports on folic acid etc.

Title	Type of study	Abstract	Comment	Reference
Trends in blood folate and vitamin B-12 concentrations in the United States, 1988 2004	Observational population study	BACKGROUND: Monitoring the folate status of US population groups over time has been a public health priority for the past 2 decades, and the focus has been enhanced since the implementation of a folic acid fortification program in the mid-1990s. OBJECTIVE: We aimed to determine how population concentrations of serum and red blood cell (RBC) folate and serum vitamin B-12 have changed over the past 2 decades. DESIGN: Measurement of blood indicators of folate and vitamin B-12 status was conducted in approximately 23,000 participants in the prefortification third National Health and Nutrition Examination Survey (NHANES III; 1988-1994) and in approximately 8000 participants in 3 postfortification NHANES periods (together covering 1999-2004). RESULTS: Serum and RBC folate concentrations increased substantially (by 119-161% and 44-64%, respectively) in each age group in the first postfortification survey period and then declined slightly (by 5-13% and 6-9%, respectively) in most age groups between the first and third postfortification survey periods. Serum vitamin B-12 concentrations did not change appreciably. Prevalence estimates of low serum and RBC folate concentrations declined in women of childbearing age from before to after fortification (from 21% to <1% and from 38% to 5%, respectively) but remained unchanged thereafter. Prevalence estimates of high serum folate concentrations increased in children and older persons from before to after fortification (from 5% to 42% and from 7% to 38%, respectively) but decreased later after fortification. CONCLUSIONS: The decrease in folate concentrations observed longer after fortification is small compared with the increase soon after the introduction of fortification. The decrease is not at the low end of concentrations and therefore does not raise concerns about inadequate status	Note a large rise in blood folate after fortification and slight decrease a few years later	Pfeiffer (2007) Am J Clin Nutr 86: 718-27
Cost-effectiveness of a folic acid fortification program in Chile	Health economics	OBJECTIVE: Periconceptional intake of folic acid reduces the risk of neural tube defects (NTDs), a frequent birth defect that can cause significant infant mortality and disability. In Chile, fortification of wheat flour with folic acid has resulted in significant reduction in the risk of anencephaly and spina bifida. We investigated the cost-effectiveness implications of this policy. METHODS: We conducted an ex-post economic analysis of this intervention. Estimates of the effect of fortification in decreasing NTDs and deaths were derived from a prospective evaluation. The costs of fortification and provision of medical care to children with spina bifida in Chile were based on primary data collection. FINDINGS: The intervention costs per NTD case and infant death averted were I$ 1200 and 11,000, respectively. The cost per DALY averted was I$ 89, 0.8% of Chile's GDP per capita. Taking into account averted costs of care, fortification resulted in net cost savings of I$ 2.3 million. CONCLUSION: Fortification of wheat flour with folic acid is a cost-effective intervention in Chile, a middle income country in the post-epidemiological transition. This result supports the continuation of the Chile fortification program and constitutes valuable information for		Llanos (2007) Health Policy 83: 295-303

		policy makers in other countries to consider.		
Effect of a voluntary food fortification policy on folate, related B vitamin status, and homocysteine in healthy adults	Observational population study	BACKGROUND: Mandatory folic acid fortification of food is effective in reducing neural tube defects and may even reduce stroke-related mortality, but it remains controversial because of concerns about potential adverse effects. Thus, it is virtually nonexistent in Europe, albeit many countries allow food fortification on a voluntary basis. OBJECTIVE: The objective of the study was to examine the effect of a voluntary but liberal food fortification policy on dietary intake and biomarker status of folate and other homocysteine-related B vitamins in a healthy population. DESIGN: The study was a cross-sectional study. From a convenience sample of 662 adults in Northern Ireland, those who provided a fasting blood sample and dietary intake data were examined (n = 441, aged 18-92 y). Intakes of both natural food folate and folic acid from fortified foods were estimated; we used the latter to categorize participants by fortified food intake. RESULTS: Fortified foods were associated with significantly higher dietary intakes and biomarker status of folate, vitamin B-12, vitamin B-6, and riboflavin than were unfortified foods. There was no difference in natural food folate intake (range: 179-197 mug/d) between the fortified food categories. Red blood cell folate concentrations were 387 nmol/L higher and plasma total homocysteine concentrations were 2 mumol/L lower in the group with the highest fortified food intake (median intake: 208 mug/d folic acid) than in the nonconsumers of fortified foods (0 mug/d folic acid). CONCLUSIONS: These results show that voluntary food fortification is associated with a substantial increase in dietary intake and biomarker status of folate and metabolically related B vitamins with potential beneficial effects on health. However, those who do not consume fortified foods regularly may have insufficient B vitamin status to achieve the known and potential health benefits.		Hoey (2007) Am J Clin Nutr 86: 1405-13
Vitamin B12 and the risk of neural tube defects in a folic-acid-fortified population	Case-control	BACKGROUND: Low maternal vitamin B12 status may be a risk factor for neural tube defects (NTDs). Prior studies used relatively insensitive measures of B12, did not adjust for folate levels, and were conducted in countries without folic acid food fortification. In Canada, flour has been fortified with folic acid since mid-1997. METHODS: We completed a population-based case-control study in Ontario. We measured serum holotranscobalamin (holoTC), a sensitive indicator of B(12) status, at 15 to 20 weeks' gestation. There were 89 women with an NTD and 422 unaffected pregnant controls. A low serum holoTC was defined as less than 55.3 pmol/L, the bottom quartile value in the controls. RESULTS: The geometric mean serum holoTC levels were 67.8 pmol/L in cases and 81.2 pmol/L in controls. There was a trend of increasing risk with lower levels of holoTC, reaching an adjusted odds ratio of 2.9 (95% confidence interval = 1.2-6.9) when comparing the lowest versus highest quartile. CONCLUSIONS: There was almost a tripling in the risk for NTD in the presence of low maternal B(12) status, measured by holoTC. The benefits of adding synthetic B(12) to current recommendations for periconceptional folic acid tablet supplements or folic-acid-fortified foods need to be considered. It remains to be determined what fraction of NTD cases in a universally folate-fortified environment might be prevented by higher periconceptional intake of B(12).		Ray (2007) Epidemiology 18: 362-6
Folic acid metabolism in	Review	Following an introduction of the importance of folates and the rationale for seeking to estimate fractional folate absorption from foods (especially for countries not having a		Wright (2007) Br

human subjects revisited: potential implications for proposed mandatory folic acid fortification in the UK		mandatory folic acid fortification policy), scientific papers covering the mechanisms of folate absorption and initial biotransformation are discussed. There appears (post-1983) to be a consensus that physiological doses of folic acid undergo biotransformation in the absorptive cells of the upper small intestine to 5-methyltetrahydrofolic acid (as happens for all naturally-occurring reduced 1-carbon-substituted folates). This 'validates' short-term experimental protocols assessing 'relative' folate absorption in human subjects that use folic acid as the 'reference' dose. The underlying scientific premise on which this consensus is based is challenged on three grounds: (i) the apparent absence of a 5-methyltetrahydrofolic acid response in the human hepatic portal vein following absorption of folic acid, (ii) the low dihydrofolate reductase activity peculiar to man and (iii) the implications derived from recent stable-isotope studies of folate absorption. It is concluded that the historically accepted case for folic acid being a suitable 'reference folate' for studies of the 'relative absorption' of reduced folates in human subjects is invalid. It is hypothesised that the liver, and not the absorptive cells of the upper small intestine, is the initial site of folic acid metabolism in man and that this may have important implications for its use as a supplement or fortificant since human liver's low capacity for reduction may eventually give rise to saturation, resulting in significant (and potentially deleterious) unmetabolised folic acid entering the systemic circulation.		J Nutr 98: 667-75
Effect of folate oversupplementation on folate uptake by human intestinal and renal epithelial cells	Cell culture experiments	Background:Folic aid plays an essential role in cellular metabolism. Its deficiency can lead to neural tube defects. However, optimization of body folate homeostasis can reduce the incidence of neural tube defects and may decrease the risk of Alzheimer and cardiovascular diseases and cancer. Hence, food fortification and intake of supplemental folate are widespread. Objective:We examined the effects of long-term folate oversupplementation on the physiologic markers of intestinal and renal folate uptake processes. Design:Human-derived intestinal Caco-2 and renal HK-2 epithelial cells were maintained (5 generations) in a growth medium oversupplemented (100 {micro}mol folic acid/L) or maintained under sufficient conditions (0.25 and 9 {micro}mol folic acid/L). Results:Carrier-mediated uptake of 3H-folic acid (2 {micro}mol/L) at buffer pH 5.5 (but not buffer pH 7.4) by Caco-2 and HK-2 cells maintained under the folate-oversupplemented condition was significantly ($P < 0.01$) and specifically lower than in cells maintained under the folate-sufficient condition. This reduction in folic acid uptake was associated with a significant decrease in the protein and mRNA levels of the human reduced-folate carrier (hRFC) and a decrease in the activity of the hRFC promoter. It was also associated with a decrease in mRNA levels of the proton-coupled folate transporter/heme carrier protein 1 (PCFT/HCP1) and folate receptor (FR). Conclusions:Long-term oversupplementation with folate leads to a specific and significant down-regulation in intestinal and renal folate uptake, which is associated with a decrease in message levels of hRFC, PCFT/HCP1, and FR. This regulation appears to be mediated via a transcriptional mechanism, at least for the hRFC system.	Exposure to high folic acid levels down-regulates two key folate transporters	Ashokkumar (2007) Am J Clin Nutr 86: 159-166
Pre-conceptional vitamin/folic acid supplementation 2007:	Guidelines from Canadian Society of	Objective: To provide information regarding the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies, so that physicians, midwives, nurses, and other health care	Recommend 5mg/day for those who have had	Wilson (2007) J Obstet Gynaecol Can 29: 1003-13

The use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies	Obstetricians and Gynaecologists	workers can assist in the education of women in the pre-conception phase of their health care. Option: Supplementation with folic acid and vitamins is problematic, since 50% of pregnancies are unplanned, and women's health status may not be optimal when they conceive. Outcomes: Folic acid in combination with a multivitamin supplement has been associated with a decrease in specific birth defects. Evidence: Medline, PubMed, and Cochrane Database were searched for relevant English language articles published between 1985 and 2007. The previous Society of Obstetricians and Gynaecologists of Canada (SOGC) Policy Statement of November 1993 and statements from the American College of Obstetrics and Gynecology and Canadian College of Medical Geneticists were also reviewed in developing this clinical practice guideline. Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care. Benefits, Harms, and Costs: Promoting the use of folic acid and a multivitamin supplement among women of reproductive age will reduce the incidence of birth defects. The costs are those of daily vitamin supplementation and eating a healthy diet. Recommendations 1. Women in the reproductive age group should be advised about the benefits of folic acid in addition to a multivitamin supplement during wellness visits (birth control renewal, Pap testing, yearly examination) especially if pregnancy is contemplated. (III-A) 2. Women should be advised to maintain a healthy diet, as recommended in Eating Well With Canada's Food Guide (Health Canada). Foods containing excellent to good sources of folic acid are fortified grains, spinach, lentils, chick peas, asparagus, broccoli, peas, Brussels sprouts, corn, and oranges. However, it is unlikely that diet alone can provide levels similar to folate-multivitamin supplementation. (III-A) 3. Women taking a multivitamin containing folic acid should be advised not to take more than one daily dose of vitamin supplement, as indicated on the product label. (II-2-A) 4. Folic acid and multivitamin supplements should be widely available without financial or other barriers for women planning pregnancy to ensure the extra level of supplementation. (III-B) 5. Folic acid 5 mg supplementation will not mask vitamin B12 deficiency (pernicious anemia), and investigations (examination or laboratory) are not required prior to initiating supplementation. (II-2-A) 6. The recommended strategy to prevent recurrence of a congenital anomaly (anencephaly, myelomeningocele, meningocele, oral facial cleft, structural heart disease, limb defect, urinary tract anomaly, hydrocephalus) that has been reported to have a decreased incidence following preconception / first trimester folic acid +/- multivitamin oral supplementation is planned pregnancy +/- supplementation compliance. A folate-supplemented diet with additional daily supplementation of multivitamins with 5 mg folic acid should begin at least three months before conception and continue until 10 to 12 weeks post conception. From 12 weeks post-conception and continuing throughout pregnancy and the postpartum period (4-6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4-1.0 mg). (I-A) 7. The recommended strategy(ies) for primary prevention or to decrease the incidence of fetal congenital anomalies will include a number of options or treatment approaches depending on patient age, ethnicity, compliance, and genetic congenital anomaly risk status. * Option A: Patients with no personal health risks, planned pregnancy, and good compliance	previous babies with congenital malformations	

		require a good diet of folate-rich foods and daily supplementation with a multivitamin with folic acid (0.4-1.0 mg) for at least two to three months before conception and throughout pregnancy and the postpartum period (4-6 weeks and as long as breastfeeding continues). (II-2-A) * Option B: Patients with health risks, including epilepsy, insulin dependent diabetes, obesity with BMI >35 kg/m2, family history of neural tube defect, belonging to a high-risk ethnic group (e.g., Sikh) require increased dietary intake of folate-rich foods and daily supplementation, with multivitamins with 5 mg folic acid, beginning at least three months before conception and continuing until 10 to 12 weeks post conception. From 12 weeks post-conception and continuing throughout pregnancy and the postpartum period (4-6 weeks or as long as breastfeeding continues), supplementation should consist of a multivitamin with folic acid (0.4-1.0 mg). (II-2-A) * Option C: Patients who have a history of poor compliance with medications and additional lifestyle issues of variable diet, no consistent birth control, and possible teratogenic substance use (alcohol, tobacco, recreational non-prescription drugs) require counselling about the prevention of birth defects and health problems with folic acid and multivitamin supplementation. The higher dose folic acid strategy (5 mg) with multivitamin should be used, as it may obtain a more adequate serum red blood cell folate level with irregular vitamin / folic acid intake but with a minimal additional health risk. (III-B) 8.The Canadian Federal Government could consider an evaluation process for the benefit/risk of increasing the level of national folic acid flour fortification to 300 mg/100 g (present level 140 mg/100 g). (III-B) 9.The Canadian Federal Government could consider an evaluation process for the benefit/risk of additional flour fortification with multivitamins other than folic acid. (III-B) 10.The Society of Obstetricians and Gynaecologists of Canada will explore the possibility of a Canadian Consensus conference on the use of folic acid and multivitamins for the primary prevention of specific congenital anomalies. The conference would include Health Canada/Congenital Anomalies Surveillance, Canadian College of Medical Geneticists, Canadian Paediatric Society, Motherisk, and pharmaceutical industry representatives. Validation: This is a revision of a previous guideline and information from other consensus reviews from medical and government publications has been used.		
Integrated risk-benefit analyses: method development with folic acid as example	Theoretical analysis	With the introduction of novel and functional foods, there is increasing need for an integrated quantitative risk-benefit assessment of foods. Consensus about a quantitative risk-benefit assessment mirroring the risk assessment approach has been reached during a recent EFSA workshop. In line, we propose a risk-benefit model that consists of: (1) hazard and benefit identification, (2) hazard and benefit characterization through dose-response functions, (3) exposure assessment, and (4) risk-benefit integration. The DALY, which combines morbidity and mortality serves as common health measure. The overall health impact of bread fortified with folic acid in the Netherlands has been simulated. The case study showed how the risk-benefit approach may assist a policy maker in decisions on food fortification programs. It illustrates general problems regarding the data demands, the assumptions and uncertainties. A simple sensitivity analysis showed which assumptions were most crucial. Modest fortification (140 microg/100 g bread) seems reasonable to improve public health but the results hinge on the assumptions one makes for the association	Valuable discussion	Hoekstra (2008) Food Chem Toxicol 46: 893-909

		between colorectal cancer and high folate intake. A precautious policymaker may very well decide against folic acid fortification. The often debated increase in masked vitamin B12-deficiency appears negligible compared to the health gain resulting from prevented neural tube defects.		
Folate fortification and supplementation--are we there yet?	Population records	BACKGROUND: Folic acid fortification of flour has significantly decreased the incidence of neural tube defects (NTDs). We aimed at examining whether Ontario women of child-bearing age exhibit protective levels of RBC folate. METHODS: We reviewed laboratory databases on RBC folic acid from pre and post fortification years. The data included age, gender, RBC folate, hemoglobin, mean cell volume and pregnancy test. We examined a sub-set of females at ages 14-45 years who were non-anemic and normocytic. Complete protection against NTD was defined as RBC folate concentration above 900 nmol/L. RESULTS: In 2006, 40% of the women of child-bearing age and 36% of pregnant women, exhibited RBC folate levels below 900 nmol/L, rendering them sub-optimally protected against NTD. CONCLUSION: A considerable proportion of pregnant women is still at risk of having a baby with NTD. This should be remedied by increasing the mandatory concentrations of folic acid required in flour, complemented by public education and increasing the folic acid in prenatal supplements.	Define RBC folate as > 900 for adequate protection	Bar-Oz (2008) Reprod Toxicol 25: 408-12
Economic evaluation of folic acid food fortification in The Netherlands	Health economics	BACKGROUND: Folic acid intake before and during pregnancy reduces neural tube defects (NTD). Therefore, several countries have enriched bulk food with folic acid resulting in a 26-48% decrease in the prevalence of NTDs. In 2000, the Dutch Health Council advised against folic acid enrichment based on literature research; yet formal cost-effectiveness information was absent. We designed our study to estimate cost-effectiveness of folic acid food fortification in the Netherlands. METHOD: Prevalence of NTD at birth, life-time costs of care, and folic acid fortification costs were estimated using Dutch registrations, Dutch guidelines for costing, (inter)national literature and expert opinions. Both net cost per discounted life year gained and net cost per discounted quality adjusted life year (QALY) gained were estimated for the base case and sensitivity analyses. RESULTS: In the base case and most sensitivity analyses, folic acid enrichment was estimated to be cost-saving. Bulk food fortification with folic acid remains cost-effective as long as enrichment costs do not exceed euro5.5 million (threshold at euro20 000 per QALY). CONCLUSION: Our model suggests that folic acid fortification of bulk food to prevent cases of NTD in newborns might be a cost-saving intervention in the Netherlands. Additionally, besides the evidence that folic acid reduces the number of NTDs, there are indications that folic acid is associated with the prevention of other birth defects, cardiovascular diseases and cancer. Our model did not yet include these possibly beneficial effects.		Jentink (2008) Eur J Public Health 18: 270-4
Session 1: Public health nutrition. Folic acid food fortification: the Irish experience	Policy review	Adequate intake of folic acid by women during very early pregnancy can markedly reduce risk of the development of neural-tube defects (NTD). The effectiveness of advice to women to take folic acid supplements is limited, mainly because 50% of pregnancies are unplanned. However, mandatory folic acid food fortification programmes in North America have been very successful in reducing NTD rates. In Ireland higher rates of pregnancies are affected by NTD and the option of termination is illegal. Consequently, the much higher burden of disease makes primary		Flynn (2008) Proc Nutr Soc 67: 381-9

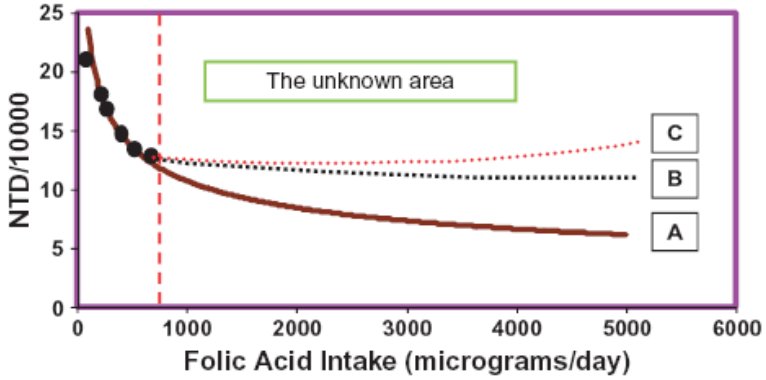
		prevention of NTD an important public health issue in Ireland. During 2006 a decision was taken in Ireland to initiate mandatory folic acid fortification of most bread to prevent NTD. Priority work was immediately undertaken to establish reliable and comprehensive baseline information on factors that will be affected by fortification. This information included data on: the national prevalence of pregnancies affected by NTD; the current extent of voluntary folic acid fortification of food on the Irish market and how it affects folic acid intakes; blood folate status indicators assessed for various subgroups of the Irish population. In addition, scientific developments that have arisen since 2006 relating to the risks and benefits of folic acid intake are under ongoing review. The present paper summarises the rationale for mandatory folic acid food fortification in Ireland and recent scientific developments relating to risks and benefits of folic acid intake. In this context, preliminary findings of baseline monitoring investigations in Ireland are considered.		
Trends in circulating concentrations of total homocysteine among US adolescents and adults: findings from the 1991-1994 and 1999-2004 National Health and Nutrition Examination Surveys	Observational, Population	Background: The National Health and Nutrition Examination Survey (NHANES) has monitored total homocysteine (tHcy) concentrations in a nationally-representative sample of the US population since 1991. Until recently, however, data could not be compared across survey periods because of changes in analytical methods and specimen matrices. Such an analysis of these data could supplement current knowledge regarding whether the US folic acid fortification program has modified national plasma tHcy concentrations. Methods: We examined tHcy data in the prefortification NHANES III survey (phase II, 1991-1994) and in 3 postfortification survey periods (1999-2000, 2001-2002, and 2003-2004). We applied method adjustment equations to the survey data based on method comparison studies of separate samples. Persons with chronic kidney disease were excluded from the analyses. Results: Mean plasma tHcy concentrations decreased by 8%, 9%, and 10% for adolescent, adult, and older men and by 6%, 3%, and 13% for women, respectively, from before to after fortification. Concentrations remained unchanged between the first and third postfortification survey periods. Prevalence estimates of increased plasma tHcy concentrations (>13 {micro}mol/L) for older men and women decreased from prefortification (32% and 20%, respectively) to postfortification (14% and 5%, respectively) but remained unchanged thereafter (16% and 14%, respectively [males] and 5% and 9%, respectively [females]). Conclusions: After adjusting for method changes, we quantified a prefortification to postfortification decrease in circulating tHcy concentrations of about 10% in a national sample of the US population. This change is similar to effects seen in intervention trials with folic acid and in smaller observational studies.		{Pfeiffer, 2008 #206}
Circulating folic acid in plasma: relation to folic acid fortification	Population study	BACKGROUND: The implementation of folic acid fortification in the United States has resulted in unprecedented amounts of this synthetic form of folate in the American diet. Folic acid in circulation may be a useful measure of physiologic exposure to synthetic folic acid, and there is a potential for elevated concentrations after fortification and the possibility of adverse effects. OBJECTIVE: We assessed the effect of folic acid fortification on circulating concentrations of folic acid and 5-methyltetrahydrofolate in the Framingham Offspring Cohort. DESIGN: This is a cross-sectional study that used plasma samples from fasting subjects before and after	Even in non-supplement users, free folic acid levels went up after fortification	Kalmbach (2008) Am J Clin Nutr 88: 763-8

		fortification. Samples were measured for folate distribution with the use of an affinity-HPLC method with electrochemical detection. RESULTS: Among nonsupplement users, the median concentration of folic acid in plasma increased from 0.25 to 0.50 nmol/L (P < 0.001) after fortification, and among supplement users the median increased from 0.54 to 0.68 nmol/L (P = 0.001). Among nonsupplement users, the prevalence of high circulating folic acid (>/=85th percentile) increased from 9.4% to 19.1% (P = 0.002) after fortification. Among supplement users, the prevalence of high circulating folic acid increased from 15.9% to 24.3% (P = 0.02). Folic acid intake and total plasma folate were positively and significantly related to high circulating folic acid after adjustment for potential confounding factors (P for trend < 0.001). CONCLUSIONS: Folic acid fortification has resulted in increased exposure to circulating folic acid. The biochemical and physiologic consequences of this are unknown, but these findings highlight the need to understand the effects of chronic exposure to circulating folic acid.		
A 19-base pair deletion polymorphism in dihydrofolate reductase is associated with increased unmetabolized folic acid in plasma and decreased red blood cell folate	Observational population	Dihydrofolate reductase (DHFR) catalyzes the reduction of folic acid to tetrahydrofolate (THF). A 19-bp noncoding deletion allele maps to intron 1, beginning 60 bases from the splice donor site, and has been implicated in neural tube defects and cancer, presumably by influencing folate metabolism. The functional impact of this polymorphism has not yet been demonstrated. The objective of this research was to determine the effects of the DHFR mutation with respect to folate status and assess influence of folic acid intake on these relations. The relationship between DHFR genotype and plasma concentrations of circulating folic acid, total folate, total homocysteine, and concentrations of RBC folate was determined in 1215 subjects from the Framingham Offspring Study. There was a significant interaction between DHFR genotype and folic acid intake with respect to the prevalence of high circulating unmetabolized folic acid (defined as >85th percentile). Folic acid intake of >or=500 microg/d increased the prevalence of high circulating unmetabolized folic acid in subjects with the deletion (del/del genotype (47.0%) compared with the wild type (WT)/del (21.4%) and wild type (WT)/WT genotypes (24.4%) (P for interaction = 0.03). Interaction between the DHFR polymorphism and folic acid intake was also seen with respect to RBC folate (P for interaction = 0.01). When folic acid intake was <250 microg/d, the del/del genotype was associated with significantly lower RBC folate (732.3 nmol/L) compared with the WT/WT genotype (844.4 nmol/L). Our results suggest the del/del polymorphism in DHFR is a functional polymorphism, because it limits assimilation of folic acid into cellular folate stores at high and low folic acid intakes.		Kalmbach (2008) J Nutr 138: 2323-7
Conclusions of a WHO technical consultation on folate and vitamin B12 deficiencies	Expert consensus	No abstract. Extract: The criteria for fortification strategies are 1) a high prevalence of inadequate folate and/or vitamin B12 intakes; 2) evidence of deficiency; 3) a high burden of deficiency-related disease such as NTD; 4) absence of circumstances that would make targeted supplementation likely to be successful; and 5) a widely available and highly consumed food vehicle that can be produced centrally.		de Benoist (2008) Food Nutr Bull 29 S238-S244
Fortification of selected foodstuffs with folic acid	Survey of opinions	BACKGROUND: The UK Food Standards Agency Board identified four options to increase folate intake in women of reproductive age in order to reduce the risk of		Tedstone (2008) J Public Health

in the UK: consumer research carried out to inform policy recommendations		neural tube defect (NTD) affected pregnancies; these ranged from continuing with current policy, to mandatory fortification of bread or flour with folic acid. In order to appraise these options, the agency carried out a consultation, and also commissioned four pieces of research. This paper provides detailed information about two of the research studies, which used qualitative research approaches to gather consumer evidence. METHODS: Study 1: This was carried out with people from a wide range of demographic backgrounds. A 'reconvened group' methodology was used, with five groups convened twice, in five geographical locations. In addition paired, in depth face-to-face interviews were conducted with female black and ethnic minority consumers. Study 2: This was carried out with young mothers living in deprived communities. The approach used for this study was in depth face-to-face interviews (n = 24). In addition, discussions were held in seven friendship groups. RESULTS: Study 1: only a minority of participants knew about a link between spina bifida and folic acid, and these tended to be women with young families. After the provision of some information about the causes and impacts of NTDs, the majority were in favour of action to tackle the issue. Support for mandatory fortification increased considerably during the study, and at the final discussion, this option was most preferred. Study 2: In this group, there was a fatalistic approach to pregnancy and to health. The women were less likely to change established habits if this required effort, money or doing something unfamiliar. They tended to actively avoid thinking about risks, by rationalizing them. Mandatory fortification was preferred by the majority of respondents. CONCLUSIONS: In this research, mandatory fortification was the preferred option. There were outstanding concerns about risk, and the maintenance of consumer choice, which would need to be addressed in policy recommendations.		(Oxf) 30: 23-9
Folate and clefts of the lip and palate--a U.K.-based case-control study: Part II: Biochemical and genetic analysis	Retrospective case-control study	OBJECTIVE: To investigate associations between nonsyndromic oral clefts and biochemical measures of folate status and the MTHFR C677T variant in the United Kingdom, where there has been no folic acid fortification program. METHOD: Dietary details were obtained from the mothers of 112 cases of cleft lip with or without cleft palate (CL+/-P), 78 cleft palate only (CP) cases, and 248 unaffected infants. Infant and parental MTHFR C677T genotype was determined. Red blood cell (RBC) and serum folate and homocysteine levels were assessed in 12-month postpartum blood samples from a subset of mothers. The data were analyzed by logistic and log-linear regression methods. RESULTS: There was an inverse association between CL+/-P and maternal MTHFR CT (odds ratio [OR] = 0.5, 95% confidence interval [CI] = 0.31-0.95) and TT (OR = 0.6, 95% CI = 0.21-1.50) genotypes, with similar risk estimates for CP. There was no clear association with infant MTHFR genotype. Higher levels of maternal postpartum RBC and serum folate were associated with a lower risk for CL+/-P and an increased risk for CP. Higher levels of serum homocysteine were associated with a slightly increased risk for both CL+/-P and CP. CONCLUSION: While the inverse relation between the mother's having the MTHFR C677T variant and both CL+/-P and CP suggests perturbation of maternal folate metabolism is of etiological importance, contrasting relations between maternal postpartum levels of RBC and serum folate by type of cleft are difficult to explain.	Note converse result with blood folate: high folate associated with less Cleft Lip (with or without Cleft Palate) but with more pure Cleft Palate.	Little (2008) Cleft Palate Craniofac J 45: 428-38

Economic evaluation of a neural tube defect recurrence-prevention program	Health economics	BACKGROUND: Women with a pregnancy affected by a neural tube defect (NTD) are encouraged to take folic acid prior to a subsequent pregnancy, but it is unknown whether organized attempts to identify and counsel such women to prevent recurrent NTDs are cost effective. METHODS: Data from the South Carolina recurrence-prevention program for October 2001-September 2002 were analyzed between October 2002 and December 2003 to calculate costs. Cost-effectiveness modeling of the program during 1992-2006 was conducted during 2007. Results were calculated for three scenarios based on recurrence risk, supplement use, and the effectiveness of folic acid in preventing recurrences. For each scenario, quality-adjusted life years (QALYs) were calculated separately using prevented NTD-affected live births; prevented NTD-affected births (including fetal deaths); and all prevented NTD-affected pregnancies. RESULTS: The prevention program cost approximately $155,000 per year in 2003 dollars to protect 35 pregnancies and prevent approximately one NTD. The direct costs associated with an NTD depend on type and outcome, but are approximately $560,000 in 2003 dollars for a live birth with spina bifida. The base-case cost-effectiveness ratio was $39,600 per QALY gained from avoided NTD-affected live births and stillbirths, and $14,700 per QALY gained from the avoidance of all NTD-affected pregnancies. The baseline NTD recurrence risk and the use of folic acid supplements by women who are at high risk for an NTD-affected pregnancy were influential parameters. CONCLUSIONS: The South Carolina NTD recurrence-prevention program appears comparable in cost effectiveness to other preventive services. Other states might consider including NTD recurrence prevention in birth defect-prevention programs.	Use of supplements is cost-effective for prevention of recurrence	Grosse (2008) Am J Prev Med 35: 572-7
Examination of selected national policies towards mandatory folic acid fortification	Review of policies	The purpose of this paper is to present an examination of the contrasting policies towards mandatory folic acid fortification in six countries from different regions of the world. Three questions are addressed: 1) What is the policy of the country? 2) Why was the policy adopted? 3) What lessons have been learned? Policy contrasts among countries were assessed as reflecting different interpretations of the potential risks and benefits associated with folic acid fortification. Although commonalities were identified, it was considered unlikely that there could be a standard policy response for all countries. Instead, a country-by-country policy response based on national circumstances is indicated.		Lawrence (2009) Nutr Rev 67 Suppl 1: S73-8
A strategic approach to the unfinished fortification agenda: feasibility, costs, and cost-effectiveness analysis of fortification programs in 48 countries	Review	BACKGROUND: Food fortification is a promising strategy for combating micronutrient deficiencies, which plague one-third of the world's population. Which foods to fortify, with which micronutrients, and in which countries remain essential questions that to date have not been addressed at the global level. OBJECTIVE: To provide a tool for international agencies to identify and organize the next phase of the unfinished global fortification agenda by prioritizing roughly 250 potential interventions in 48 priority countries. By explicitly defining the structure and operations of the fortification interventions in a detailed and transparent manner, and incorporating a substantial amount of country-specific data, the study also provides a potentially useful starting point for policy discussions in each of the 48 countries, which--it is hoped--will help to catalyze the development of public-private partnerships and accelerate the introduction of fortification and reduction of micronutrient deficiencies. METHODS:	Comprehensive overview of general fortification, just folic acid	Fiedler (2009) Food Nutr Bull 30: 283-316

		Forty-eight high-priority countries were identified, and the feasibility of fortifying vegetable oil and sugar with vitamin A and fortifying wheat flour and maize flour with two alternative multiple micronutrient formulations was assessed. One hundred twenty-two country-, food-, and fortification formulation-specific interventions were assessed to be feasible, and the costs of each intervention were estimated. Assuming a 30% reduction in the micronutrient deficiencies of the persons consuming the food, the number of disability-adjusted life years (DALYs) saved by each of the programs was estimated. RESULTS: The cost per DALY saved was calculated for each of the 122 interventions, and the interventions were rank-ordered by cost-effectiveness. It is estimated that the 60 most cost-effective interventions would carry a 10-year price tag of US$1 billion and have costs per DALY saved ranging from US$1 to US$134. The single "best bet" intervention--i.e., the most cost-effective intervention--in each of the 48 countries was identified. CONCLUSIONS: This study provides a detailed, transparent, evidence-based approach to defining and estimating the costs and cost-effectiveness of the unfinished global fortification agenda in the 48 priority countries. Other considerations in designing a strategic approach to the unfinished global fortification agenda are also discussed.		
Nutritional interpretation of folic acid interventions	Review	Folate is an essential micronutrient, and its nutritional inadequacy is widespread; hence, programs to increase its intake are necessary. However, many concerns about possible adverse effects due to excesses have been raised. Serum folate levels are directly correlated with intake and, when low, are associated with neural tube defects (NTD), high blood homocysteine levels, and megaloblastic anemia. Serum folate cutoff points have been identified for each abnormality, and all can be associated with intakes related to the current recommended dietary parameters. Likewise, high intakes that overwhelm the physiological capacity to process folic acid into biologically active folate derivatives are near the recommended tolerable upper intake level. Although we do not know with certainty the minimum efficacious dose that prevents all folate-dependent NTD, it may actually be much lower than the current recommendation, especially when provided through food fortification; supplemental intakes around 100 microg/day appear to be appropriate.	Thoughtful. Useful figures. Reminds about Kirke 1992 where low doses seemed to be sufficient	Dary (2009) Nutr Rev 67: 235-44

				
Intake of selected nutrients from foods, from fortification and from supplements in various European countries	Dietary surveys	BACKGROUND: Recent European Union regulation requires setting of maximum amount of micronutrients in dietary supplements or foods taking into account the tolerable upper intake level (ULs) established by scientific risk assessment and population reference intakes. OBJECTIVE: To collect and evaluate recently available data on intakes of selected vitamins and minerals from conventional foods, food supplements and fortified foods in adults and children. Intake of calcium, copper, iodine, iron, magnesium, phosphorus, selenium, zinc, folic acid, niacin and total vitamin A/retinol, B6, D and E was derived from nationally representative surveys in Denmark, Germany, Finland, Ireland, Italy, the Netherlands, Poland, Spain and the United Kingdom. Intake of high consumers, defined as the 95th percentile of each nutrient, was compared to the UL. RESULTS: For most nutrients, adults and children generally consume considerably less than the UL with exceptions being retinol, zinc, iodine, copper and magnesium. The major contributor to intakes for all nutrients and in all countries is from foods in the base diet. The patterns of food supplements and voluntary fortification vary widely among countries with food supplements being responsible for the largest differences in total intakes. In the present study, for those countries with data on fortified foods, fortified foods do not significantly contribute to higher intakes for any nutrient. Total nutrient intake expressed as percentage of the UL is generally higher in children than in adults. CONCLUSION: The risk of excessive intakes is relatively low for the majority of nutrients with a few exceptions. Children are the most vulnerable group as they are more likely to exhibit high intakes relative to the UL. There is a need to develop improved methods for estimating intakes of micronutrients from fortified foods and food supplements in future dietary surveys.	Note that children tend to have higher intakes	Flynn (2009) Food Nutr Res 53 (Supplement 1): 1-51
The extremely slow and	Experimental	Numerous clinical trials using folic acid for prevention of cardiovascular disease, stroke, cognitive decline, and neural tube defects have been completed or are	Important since it	{{Bailey, 2009

variable activity of dihydrofolate reductase in human liver and its implications for high folic acid intake	study	underway. Yet, all functions of folate are performed by tetrahydrofolate and its one-carbon derivatives. Folic acid is a synthetic oxidized form not significantly found in fresh natural foods; to be used it must be converted to tetrahydrofolate by dihydrofolate reductase (DHFR). Increasing evidence suggests that this process may be slow in humans. Here we show, using a sensitive assay we developed, that the reduction of folic acid by DHFR per gram of human liver (n = 6) obtained from organ donors or directly from surgery is, on average, less than 2% of that in rat liver at physiological pH. Moreover, in contrast to rats, there was almost a 5-fold variation of DHFR activity among the human samples. This limited ability to activate the synthetic vitamer raises issues about clinical trials using high levels of folic acid. The extremely low rate of conversion of folic acid suggests that the benefit of its use in high doses will be limited by saturation of DHFR, especially in individuals possessing lower than average activity. These results are also consistent with the reports of unmetabolized folic acid in plasma and urine.	shows that individual variations may be large in folic acid metabolism	#622}
How much folate is in Canadian fortified products 10 years after mandated fortification?	Food analysis	OBJECTIVE: In 1998, the Canadian government mandated folic acid fortification of white flour and enriched grain products to lower the prevalence of neural tube defects. There is now growing concern over the potential harmful effects of too much folic acid on some segments of the population. Given that the actual amount of folate in Canadian foods is unknown, the objective of this study was to measure the folate content in selected fortified foods. METHODS: Using data from the 2001 Food Expenditure Survey and the ACNielsen Company, 95 of the most commonly purchased folic acid-fortified foods in Canada were identified. Folate concentrations in these foods were determined using tri-enzyme digestion followed by microbiological assay. Analyzed values were compared to those in the Canadian Nutrient File (2007b, CNF) and to label values. RESULTS: The analyzed folate content of foods was, on average, 151% +/- 63 of the CNF values. Analyzed values as a percent of CNF values ranged from 116% in the "rolls and buns" category to 188% in "ready-to-eat cereals". Analyzed values were higher than label values for "breads", "rolls and buns" and "ready-to-eat cereals" (141%, 118% and 237%, respectively [p < 0.05]). CONCLUSIONS: Ten years after folic acid fortification of the food supply, neither the CNF nor label values accurately reflect actual amounts of folate in foods. Further, overage differences by food category hinder the development of future strategies designed to strike the right balance between health benefits and risks; monitoring of fortified foods for their nutrient content is required.		Shakur (2009) Can J Public Health 100: 281-4
Health Canada's proposed discretionary fortification policy is misaligned with the nutritional needs of Canadians	Population study	Health Canada has proposed new fortification policies that will allow manufacturers to add vitamins and minerals to a wide variety of foods at their discretion and increase nutrient additions to breakfast cereals. Our objective was to examine the potential impact of these policies on nutrient inadequacies and excesses in the Canadian population. Using dietary intake data from the Canadian Community Health Survey, Cycle 2.2 (2004), usual intake distributions from food were estimated for vitamins A and C, folate, niacin, calcium, and magnesium for all age/sex groups. The prevalence of individuals with inadequate nutrient intake and the proportion of individuals with intakes above the tolerable upper intake level (UL) were assessed where possible, assuming full implementation of the proposed policies. To approximate a "mature		Sacco (2009) J Nutr 139: 1980-6

		market" scenario, consumption patterns of fortified foods in the United States were estimated and applied to Canadian intake data. Full implementation resulted in marked reductions in inadequate intakes of vitamin A, vitamin C, magnesium, and folate, and improvements in calcium intakes for some age/sex groups. However, it caused intakes of folate, niacin, vitamin A, and calcium to rise above the UL, particularly among younger age groups. Although increased food fortification may reduce the apparent prevalence of inadequate intakes for some nutrients, there is no evidence of inadequacies for niacin or several other nutrients slated for addition. Our modeling suggests that Health Canada's proposed policies are misaligned with the nutritional needs of the population, because they are not rooted in an assessment of current nutrient intake patterns.		
Maternal MTHFR 677C>T genotype and dietary intake of folate and vitamin B(12): their impact on child neurodevelopment	Observational study	Using the Bayley test, the mental and psychomotor development in a cohort of 253 children were evaluated. Maternal dietary intake of vitamin B(12) and folate was assessed from a semiquantitative questionnaire administered during the first trimester of pregnancy. Maternal genotypes of MTHFR (677C>T and 1298A>C), were ascertained by PCR-RFLP. The 677T and 1298C variant alleles were present in 59% and 10% of participants, respectively. A dietary deficiency of vitamin B(12) was negatively associated with mental development (beta = -1.6; 95% CI = -2.8 to -0.3). In contrast, dietary intake of folate (< 400 mg/day) reduced the mental development index only among children of mothers who were carriers of the TT genotype (beta = -1.8; 95% CI = -3.6 to -0.04; P for interaction = 0.07). Vitamin B(12) and folate supplementation during pregnancy could have a favorable impact on the mental development of children during their first year of life, mainly in populations that are genetically susceptible.		{del Rio Garcia, 2009 #694}
Folate intake and the risk of colorectal cancer in a Korean population	Observational population study	BACKGROUND: Folate, a water-soluble B vitamin and one of the major micronutrients in vegetables, is known as an essential factor for the de novo biosynthesis of purines and thymidylate, and it plays an important role in DNA synthesis and replication. Thus, folate deficiency results in ineffective DNA synthesis, and has been shown to induce the initiation and progression of colorectal cancer (CRC). Recently, the incidence of CRC in Korea has increased markedly in both men and women; this trend may be related to the adoption of a more 'westernized' lifestyle, including dietary habits. OBJECTIVE: A hospital-based case-control study was conducted to examine the relationship between folate intake and the risk of CRC within a Korean population. METHODS: A total of 596 cases and 509 controls, aged 30-79 years, were recruited from two university hospitals. Site- and sex-specific odds ratios (ORs) were estimated using logistic regression models. RESULTS: Cases were more frequently found to have a family history of CRC among first-degree relatives, to consume more alcohol, to be more likely current smokers and less likely to participate in vigorous physical activity than the controls. In the overall data for men and women combined, multivariate ORs (95% confidence interval (CI), P for trend) comparing the highest vs the lowest quartile of dietary folate intake were: 0.47 (0.32-0.69, <0.001) for CRC, 0.42 (0.26-0.69, <0.001) for colon cancer and 0.48 (0.28-0.81, 0.007) for rectal cancer. An inverse association was also found in women with dietary folate intake: 0.36 (0.20-0.64, <0.001) for CRC, 0.34 (0.16-0.70, 0.001)	Subgroup effect: women protected but not men. NB when supplements included, no protection in colon cancer but still for rectal in women: source effect	Kim (2009) Eur J Clin Nutr 63: 1057-64

		for colon cancer and 0.30 (0.12-0.74, 0.026) for rectal cancer, but not in men. In addition, the total folate intake of women was strongly associated with a reduced risk of rectal cancer (OR, 0.38; 95% CI, 0.17-0.88; P for trend=0.04). CONCLUSION: We found a statistically significant relationship between higher dietary folate intake and reduced risk of CRC, colon cancer and rectal cancer in women. A significant association is indicated between higher total folate intake and reduced risk of rectal cancer in women.		
Dietary reference values of individual micronutrients and nutriomes for genome damage prevention: current status and a road map to the future	Review	Damage to the genome is recognized as a fundamental cause of developmental and degenerative diseases. Several micronutrients play an important role in protecting against DNA damage events generated through endogenous and exogenous factors by acting as cofactors or substrates for enzymes that detoxify genotoxins as well as enzymes involved in DNA repair, methylation, and synthesis. In addition, it is evident that either micronutrient deficiency or micronutrient excess can modify genome stability and that these effects may also depend on nutrient-nutrient and nutrient-gene interaction, which is affected by genotype. These observations have led to the emerging science of genome health nutrigenomics, which is based on the principle that DNA damage is a fundamental cause of disease that can be diagnosed and nutritionally prevented on an individual, genetic subgroup, or population basis. In this article, the following topics are discussed: 1) biomarkers used to study genome damage in humans and their validation, 2) evidence for the association of genome damage with developmental and degenerative disease, 3) current knowledge of micronutrients required for the maintenance of genome stability in humans, 4) the effect of nutrient-nutrient and nutrient-genotype interaction on DNA damage, and 5) strategies to determine dietary reference values of single micronutrients and micronutrient combinations (nutriomes) on the basis of DNA damage prevention. This article also identifies important knowledge gaps and future research directions required to shed light on these issues. The ultimate goal is to match the nutriome to the genome to optimize genome maintenance and to prevent pathologic amounts of DNA damage.	Dose-response relationships emphasized for folate and other micronutrients	Fenech (2010) Am J Clin Nutr 91: 1438S-1454S
Lower maternal folate status in early pregnancy is associated with childhood hyperactivity and peer problems in offspring	Population observational study	BACKGROUND: Maternal nutrition during pregnancy has been linked with fetal brain development and psychopathology in the offspring. We examined for associations of maternal folate status and dietary intake during pregnancy with brain growth and childhood behavioural difficulties in the offspring. METHODS: In a prospective cohort study, maternal red blood cell folate (RCF) was measured at 14 weeks of pregnancy and total folate intake (TFI) from food and supplements was assessed in early and late pregnancy. The offspring's head circumference and body weight were measured at birth and in infancy, and 100 mothers reported on children's behavioural difficulties at a mean age of 8.75 years using the Strengths and Difficulties Questionnaire. RESULTS: Lower maternal RCF and TFI in early pregnancy were associated with higher childhood hyperactivity (RCF: beta = -.24; p = .013; TFI: beta = -.24; p = .022) and peer problems scores (RCF: beta = -.28; p = .004; TFI: beta = -.28; p = .009) in the offspring. Maternal gestational RCF was positively associated with head circumference at birth (adjusted for gestational age), and mediation analyses showed significant inverse indirect associations of RCF with hyperactivity/inattention and peer	Median folate at 95 gestational day was 1053 nmol/L, suggesting that the women had been taking folic acid. Only give regression data so difficult to work out what 'low folate' status means	Schlotz (2010) J Child Psychol Psychiatry 51: 594-602

		problems via fetal brain growth. Adjustment for mother's smoking and drinking alcohol during pregnancy did not change the results. CONCLUSIONS: Although the associations are small and residual confounding is possible, our data provide preliminary support for the hypothesis that lower folate status in early pregnancy might impair fetal brain development and affect hyperactivity/inattention and peer problems in childhood.		
Folic acid source, usual intake, and folate and vitamin B-12 status in US adults: National Health and Nutrition Examination Survey (NHANES) 2003-2006		BACKGROUND: US adults have access to multiple sources of folic acid. The contribution of these sources to usual intakes above the tolerable upper level (UL) (1000 mug/d) and to folate and vitamin B-12 status is unknown. OBJECTIVE: The objective was to estimate usual folic acid intake above the UL and adjusted serum and red blood cell folate, vitamin B-12, methylmalonic acid, and homocysteine concentrations among US adults by 3 major folic acid intake sources-enriched cereal-grain products (ECGP), ready-to-eat cereals (RTE), and supplements (SUP)-categorized into 4 mutually exclusive consumption groups. DESIGN: We used data from the National Health and Nutrition Examination Survey (NHANES) 2003-2006 (n = 8258). RESULTS: Overall, 2.7% (95% CI: 1.9%, 3.5%) of adults consumed more than the UL of folic acid. The proportions of those who consumed folic acid from ECGP only, ECGP+RTE, ECGP+SUP, and ECGP+RTE+SUP were 42%, 18%, 25%, and 15%, respectively. Of 60% of adults who did not consume supplements containing folic acid (ECGP only and ECGP+RTE), 0% had intakes that exceeded the UL. Of 34% and 6% of adults who consumed supplements with an average of </=400 and >400 mug folic acid/d, <1% and 47.8% (95% CI: 39.6%, 56.0%), respectively, had intakes that exceeded the UL. Consumption of RTE and/or supplements with folic acid was associated with higher folate and vitamin B-12 and lower homocysteine concentrations, and consumption of supplements with vitamin B-12 was associated with lower methylmalonic acid concentrations (P < 0.001). CONCLUSION: At current fortification levels, US adults who do not consume supplements or who consume an average of </=400 mug folic acid/d from supplements are unlikely to exceed the UL in intake for folic acid.		Yang (2010) Am J Clin Nutr 91: 64-72
Getting folic acid nutrition right	Editorial	No Abstract. Extract: "…the Food and Drug Administration (FDA) models of exposure, which preceded the 1996 mandate that enriched flour be fortified with 140 micorg folic acid per 100 g flour to prevent neural tube defect births, got the folic acid dose right. This mandate increased folic acid exposure in women of childbearing age without excessive exposure to those beneficiaries and others in the population. The documentation in these 2 articles of the remarkable predictive value of those models over a decade ago is testimony to the value of prefortification modelling…"	Discusses articles by Yang (above) and Bailey (Table 4)	Rosenberg (2010) Am J Clin Nutr 91: 3-4
Cost-effectiveness of mandatory folate fortification v. other options for the prevention of neural tube defects: results from Australia and New Zealand	Health economics analysis	OBJECTIVE: To provide input to Australian and New Zealand government decision making regarding an optimal strategy to reduce the rate of neural tube defects (NTD). DESIGN: Standard comparative health economic evaluation techniques were employed for a set of intervention options for promoting folate/folic acid consumption in women capable of or planning a pregnancy. Evidence of effectiveness was informed by the international literature and costs were derived for Australia and New Zealand. RESULTS: Population-wide campaigns to promote supplement use and mandatory fortification were the most effective at reducing NTD, at an estimated 36	Excellent. Point out that standard folic supplement in NZ contains 0.8 mg	Dalziel (2010) Public Health Nutr 13: 566-78

		and 31 fewer cases per annum respectively for Australia and New Zealand, representing an 8 % reduction in the current annual NTD rate. Population-wide and targeted approaches to increase supplement use were cost-effective, at less than $AU 12,500 per disability-adjusted life year (DALY) averted ($US 9893, pound 5074), as was extending voluntary fortification. Mandatory fortification was not cost-effective for New Zealand at $AU 138,500 per DALY ($US 109 609, pound 56,216), with results uncertain for Australia, given widely varying cost estimates. Promoting a folate-rich diet was least cost-effective, with benefits restricted to impact on NTD. CONCLUSIONS: Several options for reducing NTD appear to fall well within accepted societal cost-effectiveness norms. All estimates are subject to considerable uncertainty, exacerbated by possible interactions between interventions, including impacts on currently effective strategies. The Australian and New Zealand governments have decided to proceed with mandatory fortification; it is hoped they will support a rigorous evaluation which will contribute to the evidence base.		
Folate bioavailability: implications for establishing dietary recommendations and optimizing status	Review	The addition of folic acid to the US food supply, along with the critical role of folate in certain health outcomes, has intensified worldwide interest in the bioavailability of folate. Bioavailability is a function of absorptive and postabsorptive processes, which in turn are influenced by diet, individuality, and complex diet-host interactions. As such, it is unlikely that a single bioavailability figure will accurately reflect food folate bioavailability from every diet for every person. Although there is broad agreement that naturally occurring food folate is not as bioavailable as folic acid, questions remain as to the extent of these differences, particularly within the context of a whole diet. This article 1) summarizes and integrates bioavailability estimates derived from studies that use whole-diet approaches; 2) highlights the influences of genetics, ethnicity-race, and sex as postabsorptive bioavailability modifiers; and 3) discusses the adequacy of the US folate Recommended Dietary Allowance in achieving folate sufficiency in select subpopulations.	Usual folate intake in non-fortified countries of about 250 microgram DFE per day is not sufficient to optimize tHcy, especially in MTHFR-TT. Need about 660 DFE, mainly from fortified foods to lower tHcy.near to normal	Caudill (2010) Am J Clin Nutr 91: 1455S-1460S
Total folate and folic acid intakes from foods and dietary supplements of US children aged 1-13 y	Population study	Background: Total folate intake includes naturally occurring food folate and folic acid from fortified foods and dietary supplements. Recent reports have focused on total folate intakes of persons aged >14 y. Information on total folate intakes of young children, however, is limited. Objective: The objective was to compute total folate and total folic acid intakes of US children aged 1-13 y by using a statistical method that adjusts for within-person variability and to compare these intakes with the Dietary Reference Intake guidelines for adequacy and excess. Design: Data from the 2003-2006 National Health and Nutrition Examination Survey, a nationally representative cross-sectional survey, were analyzed. Total folate intakes were derived by combining intakes of food folate (naturally occurring and folic acid from fortified foods) on the basis of 24-h dietary recall results and folic acid intakes from dietary supplements on the basis of a 30-d questionnaire. Results: More than 95% of US		Bailey (2010) Am J Clin Nutr 92: 353-358

		children consumed at least the Estimated Average Requirement (EAR) for folate from foods alone. More than one-third (35%) of US children aged 1-13 y used dietary supplements, and 28% used dietary supplements containing folic acid. Supplement users had significantly higher total folate and folic acid intakes than did nonusers. More than half (53%) of dietary supplement users exceeded the Tolerable Upper Intake Level (UL) for total folic acid (fortified food + supplements) as compared with 5% of nonusers. Conclusions: Total folate intakes of most US children aged 1-13 y meet the EAR. Children who used dietary supplements had significantly higher total folate intakes and exceeded the UL by >50%.		
Micronutrient intake and breast cancer characteristics among postmenopausal women	Observational large prospective population cohort study	Few studies on micronutrients and postmenopausal breast cancer have examined the association with breast cancer characteristics. The aim of this study was to investigate the associations between vitamin C, vitamin E, folate and beta-carotene from diet and supplements and risk of postmenopausal breast cancer subtypes defined by histology (ductal/lobular), estrogen receptor (ER) and progesterone receptor (PGR) status. In a prospective cohort study of 26,224 postmenopausal women information on diet, supplements and lifestyle was collected through questionnaires. One thousand seventy-two cases were identified during follow-up. Incidence rate ratios of total breast cancers and breast cancer subtypes related to micronutrient intake were calculated using Cox proportional hazard analyses. This study found no association between overall breast cancer and any micronutrients, while some effects were shown when stratifying by breast cancer subtypes: dietary but not supplemental beta-carotene showed a protective effect against lobular breast cancer [incidence rate ratio (IRR): 0.72; 95% confidence interval (CI): 0.57-0.91]. Dietary vitamin E was associated with decreased risk of ER and PGR positive breast cancer (IRR: 0.50; 95% CI: 0.25-0.98) and dietary folate was associated with increased risk of ER and PGR positive breast cancer (IRR: 1.27; 95% CI: 1.03-1.95). This study found no effect of micronutrients on overall risk of postmenopausal breast cancer, but indicated possible effects of micronutrients in subgroups of breast cancer, with a potential beneficial effect of dietary beta-carotene in lobular breast cancer and dietary vitamin E in ER + PGR+ breast cancer and a potential harmful effect of dietary folate in ER+ PGR+ breast cancer.	Subgroups showed increased risk.	Roswall (2010) Eur J Cancer Prev 19: 360-5
Micronutrient intake and risk of colon and rectal cancer in a Danish cohort	Large prospective population cohort study	BACKGROUND: Micronutrients may protect against colorectal cancer. Especially folate has been considered potentially preventive. However, studies on folate and colorectal cancer have found contradicting results; dietary folate seems preventive, whereas folic acid in supplements and fortification may increase the risk. OBJECTIVE: To evaluate the association between intake of vitamins C, E, folate and beta-carotene and colorectal cancer risk, focusing on possibly different effects of dietary, supplemental and total intake, and on potential effect modification by lifestyle factors. DESIGN: In a prospective cohort study of 56,332 participants aged 50-64 years, information on diet, supplements and lifestyle was collected through questionnaires. 465 Colon and 283 rectal cancer cases were identified during follow-up. Incidence rate ratios of colon and rectal cancers related to micronutrient intake were calculated using Cox proportional hazard analyses. RESULTS: The present study found a protective effect of dietary but not supplemental folate on colon cancer.	Subgroup: alcohol consumers only. NB source effect: those taking supplementary folic acid were not protected	Roswall (2010) Cancer Epidemiol 34: 40-6

		No association with any other micronutrient was found. Rectal cancer did not seem associated with any micronutrient. For both colon and rectal cancer, we found an interaction between dietary folate and alcohol intake, with a significant, preventive effect among those consuming above 10g alcohol/day only. CONCLUSIONS: This study adds further weight to the evidence that dietary folate protects against colon cancer, and specifies that there is a source-specific effect, with no preventive effect of supplemental folic acid. Further studies should thus take source into account. Vitamins C, E and beta-carotene showed no relation with colorectal cancer.		
Source-specific effects of micronutrients in lung cancer prevention	Large prospective cohort population study	The role of micronutrients in lung cancer prevention is controversial, as observational and experimental studies have generated contradicting results. These discrepancies between studies may be due to different effects of micronutrients depending on source (diet or supplements). The objective of this study was to evaluate the association between vitamin C, E, folate and beta-carotene and lung cancer risk while focusing on source-specific effects of dietary and supplemental intake. The association was evaluated in a cohort of 55,557 Danes who completed a food frequency questionnaire including information on consumption of vitamin C, E, folate and beta-carotene from diet and supplements. Incidence rate ratios of lung cancer were calculated using Cox proportional hazards models. During a median follow-up of 10.6 years, 721 incident lung cancer cases were diagnosed. We found a significant protective effect of dietary vitamin E intake and a significantly higher lung cancer risk with supplemental beta-carotene and dietary folate intake. All three micronutrients exhibited significant source-specific effects. The harmful effect of dietary folate is, however, most likely to be due to uncontrolled confounding. Our results indicate source-specific effects of vitamin E and beta-carotene in lung cancer prevention with a preventive effect of dietary vitamin E and a harmful effect of supplemental beta-carotene. Future studies on micronutrients and lung cancer should take source into account.	Source effects, with only dietary folate being associated with increased risk, not supplements. But they consider the increased risk with folate intake was due to confounding – mainly because it had not been reported before!	Roswall (2010) Lung Cancer 67: 275-81
Uracil misincorporation into DNA and folic acid supplementation	Clinical trial	BACKGROUND: Folate deficiency decreases thymidylate synthesis from deoxyuridylate, which results in an imbalance of deoxyribonucleotide that may lead to excessive uracil misincorporation (UrMis) into DNA during replication and repair. OBJECTIVE: We evaluated the relation between UrMis in different tissues and the effect of folate supplementation on UrMis. DESIGN: We analyzed UrMis concentrations in rectal mucosa (n = 92) and white blood cells (WBCs; n = 60) among individuals randomly assigned to receive supplementation with 1 mg folate/d or placebo, who were then evaluated for colorectal adenoma recurrence. RESULTS: As expected, total homocysteine was significantly lower among the study participants who received active folate treatment (Wilcoxon's P = 0.003) than among those in the placebo group. The median UrMis concentration in rectal mucosa and WBCs among individuals treated with folate was not significantly lower than that in those who received placebo (Wilcoxon's P = 0.17). UrMis concentrations in both rectal mucosa and WBCs did not correlate significantly with folate measured in plasma and red blood cells. UrMis in rectal mucosa was marginally associated with an increased risk of adenoma recurrence (odds ratio per SD: 1.43; 95% CI: 0.91, 2.25). CONCLUSIONS: UrMis measurements in WBCs are not a robust surrogate for UrMis		Hazra (2010) Am J Clin Nutr 91: 160-165

		measurements in the rectal mucosa (Spearman correlation coefficient = 0.23, P = 0.08). Furthermore, folate supplementation in an already replete population (half treated with folic acid supplements and all exposed to folic acid fortification of the food supply) was not significantly associated with reduced UrMis in rectal mucosa cells or WBCs. Large-scale studies are needed to evaluate whether excessive UrMis concentrations are an important risk factor for colorectal neoplasia. This trial was registered at clinicaltrials.gov as NCT00272324.		
Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies	Meta-analysis	BACKGROUND & AIMS: The association between fruit and vegetable intake and colorectal cancer risk has been investigated by many studies but is controversial because of inconsistent results and weak observed associations. We summarized the evidence from cohort studies in categorical, linear, and nonlinear, dose-response meta-analyses. METHODS: We searched PubMed for studies of fruit and vegetable intake and colorectal cancer risk that were published until the end of May 2010. We included 19 prospective studies that reported relative risk estimates and 95% confidence intervals (CIs) of colorectal cancer-associated with fruit and vegetable intake. Random effects models were used to estimate summary relative risks. RESULTS: The summary relative risk for the highest vs the lowest intake was 0.92 (95% CI: 0.86-0.99) for fruit and vegetables combined, 0.90 (95% CI: 0.83-0.98) for fruit, and 0.91 (95% CI: 0.86-0.96) for vegetables (P for heterogeneity=.24, .05, and .54, respectively). The inverse associations appeared to be restricted to colon cancer. In linear dose-response analysis, only intake of vegetables was significantly associated with colorectal cancer risk (summary relative risk=0.98; 95% CI: 0.97-0.99), per 100 g/d. However, significant inverse associations emerged in nonlinear models for fruits (Pnonlinearity<.001) and vegetables (Pnonlinearity=.001). The greatest risk reduction was observed when intake increased from very low levels of intake. There was generally little evidence of heterogeneity in the analyses and there was no evidence of small-study bias. CONCLUSIONS: Based on meta-analysis of prospective studies, there is a weak but statistically significant nonlinear inverse association between fruit and vegetable intake and colorectal cancer risk.	Superb analysis, shows importance of non-linear approach. Only those with low intake benefitted. See discussion in Editorial by Lee & Chan where they relate to folate studies Lee (2011) Gastroenterology 141: 16-20	Aune (2011) Gastroenterology 141: 106-18
High intake of folate from food sources is associated with reduced risk of esophageal cancer in an Australian population	Observational population studies	Folate plays a key role in DNA synthesis and methylation. Limited evidence suggests high intake may reduce risks of esophageal cancer overall; however, associations with esophageal cancer subtypes and Barrett's esophagus (BE), a precancerous lesion, remain unexplored. We evaluated the relation between intake of folate, B vitamins, and methyl-group donors (methionine, choline, betaine) from foods and supplements, polymorphisms in key folate-metabolizing genes, and risk of BE, esophageal adenocarcinoma (EAC), and esophageal squamous cell carcinoma (ESCC) in 2 population-based case-control studies in Australia. BE patients without (n = 266) or with (n = 101) dysplasia were compared with population controls (n = 577); similarly, EAC (n = 636) or ESCC (n = 245) patients were compared with population controls (n = 1507) using multivariable adjusted logistic regression. Increasing intake of folate from foods was associated with reduced EAC risk (P-trend = 0.01) and mitigated the increased risks of ESCC associated with smoking and alcohol consumption. In contrast, high intake of folic acid from supplements was associated with a significantly elevated risk of BE with dysplasia. High intakes of	Misleading title. See abstract for increased risk of Barrett's esophagous with dysplasia associated with folic acid from supplements. Source effect.	Ibiebele (2011) J Nutr 141: 274-283

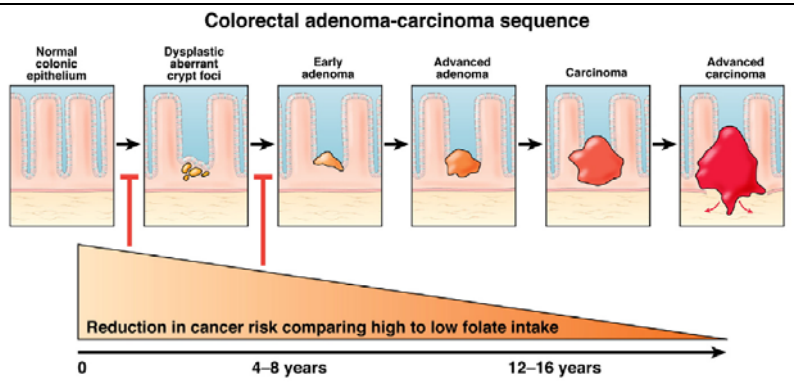
		riboflavin and methionine from food were associated with increased EAC risk, whereas increasing betaine intake was associated with reduced risks of BE without (P-trend = 0.004) or with dysplasia (P-trend = 0.02). Supplemental thiamin, riboflavin, niacin, and vitamin B-12 were associated with increased EAC risk. There were no consistent associations between genetic polymorphisms studied and BE or EAC risk. High intake of folate-containing foods may reduce risk of EAC, but our data raise the possibility that folic acid supplementation may increase risks of BE with dysplasia and EAC.		
Folic acid supplementation before and during pregnancy in the Newborn Epigenetics Study (NEST)	Case study	Folic acid (FA) added to foods during fortification is 70-85% bioavailable compared to 50% of folate occurring naturally in foods. Thus, if FA supplements also are taken during pregnancy, both mother and fetus can be exposed to FA exceeding the Institute of Medicine's recommended tolerable upper limit (TUL) of 1,000 micrograms per day (ug/d) for adult pregnant women. The primary objective is to estimate the proportion of women taking folic acid (FA) doses exceeding the TUL before and during pregnancy, and to identify correlates of high FA use. METHODS: During 2005-2008, pre-pregnancy and pregnancy-related data on dietary supplementation were obtained by interviewing 539 pregnant women enrolled at two obstetrics-care facilities in Durham County, North Carolina. RESULTS: Before pregnancy, 51% of women reported FA supplementation and 66% reported this supplementation during pregnancy. Before pregnancy, 11.9% (95% CI=9.2%-14.6%) of women reported supplementation with FA doses above the TUL of 1,000ug/day, and a similar proportion reported this intake prenatally. Before pregnancy, Caucasian women were more likely to take FA doses above the TUL (OR=2.99; 95%=1.28-7.00), compared to African American women, while women with chronic conditions were less likely to take FA doses above the TUL (OR=0.48; 95%CI=0.21-0.97). Compared to African American women, Caucasian women were also more likely to report FA intake in doses exceeding the TUL during pregnancy (OR=5.09; 95%CI=2.07-12.49). CONCLUSIONS: Fifty-one percent of women reported some FA intake before and 66% during pregnancy, respectively, and more than one in ten women took FA supplements in doses that exceeded the TUL. Caucasian women were more likely to report high FA intake. A study is ongoing to identify possible genetic and non-genotoxic effects of these high doses.		Hoyo (2011) BMC Public Health 11: 46
Folic acid and human reproduction-ten important issues for clinicians	Review	This article presents data on the current best evidence-based clinical practices and controversies surrounding folic acid supplementation/fortification for the prevention of neural tube defects (NTDs) during early pregnancy. Formatted as a series of ten clinical questions, answers and extensive discussion are provided for each point. We assess the history and evidence behind supplementation and fortification, racial/ethnic disparities in NTDs on a global scale, and present information on risk factors for NTDs other than dietary folic acid deficiency. Also discussed are public health challenges, including disparities in NTD rates, population-wide monitoring of NTDs, and tracking safety data in the post-fortification era. Emerging data are also reviewed regarding the role folic acid may play in malignant processes, cardiovascular disease, male fertility, and other medical conditions.	Thoughtful and balanced	Dunlap (2011) J Exp Clin Assist Reprod 8: 2
High intake of folic acid	Animal study	BACKGROUND: Folic acid fortification and supplementation has increased folate	Discuss possible	Pickell (2011)

disrupts embryonic development in mice		intake and blood folate concentrations and successfully reduced the incidence of neural tube defects. However, the developmental consequences of high folate intake are unknown. This study investigated the impact of high folate intake, alone or with methylenetetrahydrofolate reductase (MTHFR) deficiency, on embryonic and placental development in mice. METHODS: Mthfr +/+ or +/- pregnant mice on a control diet (CD; recommended intake of folic acid for rodents) or folic acid-supplemented diet (FASD; 20-fold higher than the recommended intake) were examined for embryonic loss, delay, and defects at 10.5 and 14.5 days post coitum (dpc); 10.5-dpc placenta, and 14.5-dpc embryo hearts were studied histologically. RESULTS: Total plasma folate was 10-fold higher in FASD compared to CD mice; plasma homocysteine levels were not affected by diet. At 10.5 dpc, the FASD was associated with embryonic delay and growth retardation, and may confer susceptibility to embryonic defects. The FASD did not adversely affect 10.5-dpc placental development. At 14.5 dpc, embryos from the FASD Mthfr +/+ group were delayed and the FASD was associated with thinner ventricular walls in embryonic hearts. There was a significant interaction between maternal MTHFR deficiency and a high folate diet for several developmental outcomes. CONCLUSIONS: Our study suggests that high folate intake may have adverse effects on fetal mouse development and that maternal MTHFR deficiency may improve or rescue some of the adverse outcomes. These findings underscore the need for additional studies on the potential negative impact of high folate intake during pregnancy.	implications for humans. Point out that placenta transports folate into embryo so concentration will be higher than in mother.Some recommendations have suggested taking amonuts 15 times the usual 0.4 mg Wilson et al. (2007) J Obstet Gynaecol Can 29: 1003-13.	Birth Defects Res A Clin Mol Teratol 91: 8-19
Folate, Vitamin B12, Vitamin B6 and homocysteine: impact on pregnancy outcome	Prospective study	Good clinical practice recommends folic acid supplementation 1 month prior to pregnancy and during the first trimester to prevent congenital malformations. However, high rates of fetal growth and development in later pregnancy may increase the demand for folate. Folate and vitamins B12 and B6 are required for DNA synthesis and cell growth, and are involved in homocysteine metabolism. The primary aim of this study was to determine if maternal folate, vitamin B12, vitamin B6 and homocysteine concentrations at 18-20 weeks gestation are associated with subsequent adverse pregnancy outcomes, including pre-eclampsia and intrauterine growth restriction (IUGR). The secondary aim was to investigate maternal B vitamin concentrations with DNA damage markers in maternal lymphocytes. A prospective observational study was conducted at the Women's and Children's Hospital, Adelaide, South Australia. One hundred and thirty-seven subjects were identified prior to 20 weeks gestation as at high or low risk for subsequent adverse pregnancy outcome by senior obstetricians. Clinical status, dietary information, circulating micronutrients and genome damage biomarkers were assessed at 18-20 weeks gestation. Women who developed IUGR had reduced red blood cell (RBC) folate ($P < 0.001$) and increased plasma homocysteine concentrations ($P < 0.001$) compared with controls. Maternal DNA damage, represented by micronucleus frequency and nucleoplasmic bridges in lymphocytes, was positively correlated with homocysteine ($r = 0.179$, $P = 0.038$ and $r = 0.171$, $P = 0.047$, respectively). Multivariate regression analysis revealed RBC folate was a strong predictor of IUGR ($P = 0.006$). This study suggests that low maternal RBC folate and high homocysteine values in mid pregnancy are associated with subsequent reduced fetal growth.		Furness (2011) Matern Child Nutr

Maternal red blood cell folate concentration at 10-12 weeks gestation and pregnancy outcome	Prospective	Objective: To determine if maternal circulating red blood cell (RBC) folate concentration in early pregnancy is associated with late gestation pregnancy complications including small for gestational age (SGA) infants, preeclampsia and preterm birth in a socioeconomically disadvantaged population. Method: This was a retrospective case control study, conducted at Lyell McEwin Health Service, South Australia, including 400 primiparous women. RBC folate and demographic data were collected at 10-12 weeks gestation. Pregnancy outcome data were obtained from patient case notes. Results: Patients who were folate deficient were more likely to develop pregnancy complications, specifically SGA (OR 6.9, 95% CI 2-24.3) and preterm birth (OR 5.4 95% CI 1.4-21.2). Those who were folate insufficient were also at increased risk of SGA (OR 3.0, 95% CI 1.3-7.7). No association between folate and preeclampsia was found. Women who were supplementing with folic acid delivered infants who were 179g heavier (5.5% increased birth weight, P=0.003) and 4.5 days later, compared to those who did not supplement. Furthermore, low RBC folate was associated with cigarette smoking (P<0.001). Conclusions: Maternal RBC folate concentration in early pregnancy is associated with SGA and preterm birth, but not with preeclampsia.		Furness (2011) J Matern Fetal Neonatal Med
A sustained dietary change increases epigenetic variation in isogenic mice	Dietary supplementation in mice over 6 generations	Epigenetic changes can be induced by adverse environmental exposures, such as nutritional imbalance, but little is known about the nature or extent of these changes. Here we have explored the epigenomic effects of a sustained nutritional change, excess dietary methyl donors, by assessing genomic CpG methylation patterns in isogenic mice exposed for one or six generations. We find stochastic variation in methylation levels at many loci; exposure to methyl donors increases the magnitude of this variation and the number of variable loci. Several gene ontology categories are significantly overrepresented in genes proximal to these methylation-variable loci, suggesting that certain pathways are susceptible to environmental influence on their epigenetic states. Long-term exposure to the diet (six generations) results in a larger number of loci exhibiting epigenetic variability, suggesting that some of the induced changes are heritable. This finding presents the possibility that epigenetic variation within populations can be induced by environmental change, providing a vehicle for disease predisposition and possibly a substrate for natural selection.	Diet massively enriched in folic, B12, choline, betaine etc.	Li (2011) PLoS Genet 7: e1001380
Folate (vitamin B9) and vitamin B12 and their function in the maintenance of nuclear and mitochondrial genome integrity	Review	Folate plays a critical role in the prevention of uracil incorporation into DNA and hypomethylation of DNA. This activity is compromised when vitamin B12 concentration is low because methionine synthase activity is reduced, lowering the concentration of S-adenosyl methionine (SAM) which in turn may diminish DNA methylation and cause folate to become unavailable for the conversion of dUMP to dTMP. The most plausible explanation for the chromosome-breaking effect of low folate is excessive uracil misincorporation into DNA, a mutagenic lesion that leads to strand breaks in DNA during repair. Both in vitro and in vivo studies with human cells clearly show that folate deficiency causes expression of chromosomal fragile sites, chromosome breaks, excessive uracil in DNA, micronucleus formation, DNA hypomethylation and mitochondrial DNA deletions. In vivo studies show that folate and/or vitamin B12 deficiency and elevated plasma homocysteine (a metabolic indicator of folate deficiency) are significantly correlated with increased micronucleus	Important dose-response relationships	Fenech (2011) Mutat Res

		formation and reduced telomere length respectively. In vitro experiments indicate that genomic instability in human cells is minimised when folic acid concentration in culture medium is greater than 100nmol/L. Intervention studies in humans show (a) that DNA hypomethylation, chromosome breaks, uracil incorporation and micronucleus formation are minimised when red cell folate concentration is greater than 700nmol/L and (b) micronucleus formation is minimised when plasma concentration of vitamin B12 is greater than 300pmol/L and plasma homocysteine is less than 7.5mumol/L. These concentrations are achievable at intake levels at or above current recommended dietary intakes of folate (i.e. >400mug/day) and vitamin B12 (i.e. >2mug/day) depending on an individual's capacity to absorb and metabolise these vitamins which may vary due to genetic and epigenetic differences.		
A dose-finding trial of the effect of long-term folic acid intervention: implications for food fortification policy	Clinical trial	BACKGROUND: The lowest dose of folic acid required to achieve effective reductions in homocysteine is controversial but important for food fortification policy given recent concerns about the potential adverse effects of overexposure to this vitamin. OBJECTIVE: We compared the effectiveness of 0.2 mg folic acid/d with that of 0.4 and 0.8 mg/d at lowering homocysteine concentrations over a 6-mo period. DESIGN: A randomized dose-finding trial with folic acid was conducted. Of 203 participants screened, 101 patients with ischemic heart disease and 71 healthy volunteers completed the study. Participants were randomly assigned to receive placebo or folic acid at doses of 0.2, 0.4, or 0.8 mg/d for 26 wk; subsamples of patients with ischemic heart disease were also examined at 6 or 12 wk. RESULTS: Participants with higher baseline homocysteine concentrations had the greatest reductions in homocysteine in response to folic acid doses of 0.2 mg (-20.6%), 0.4 mg (-20.7%), and 0.8 mg (-27.8%); in those with lower baseline homocysteine concentrations, the responses were -8.2%, -8.9%, and -8.3%, respectively. No significant differences in homocysteine responses to the different doses were observed. In the patient group sampled at intervals during the intervention, the maximal homocysteine response appeared to be achieved by 6 wk in the 0.8-mg/d group and by 12 wk in the 0.4-mg/d group. However, the homocysteine response was suboptimal in the 0.2-mg/d group at both 6 and 12 wk compared with that at 26 wk. CONCLUSIONS: A folic acid dose as low as 0.2 mg/d can, if administered for 6 mo, effectively lower homocysteine concentrations. Higher doses may not be necessary because they result in no further significant lowering, whereas doses even lower than 0.2 mg/d may be effective in the longer term. Previous trials probably overestimated the folic acid dose required because of a treatment duration that was too short.	Although they say that this level of intake is associated with the greatest reduction in NTDs, they do not actually compare the serum folate levels in their 1997 Lancet paper with those attained here.	Tighe (2011) Am J Clin Nutr 93: 11-8
New insights on the lowest dose for mandatory folic acid fortification?	Prospective cohort	No abstract. Editorial on paper by Tighe et al. Extract: “In conclusion, an ongoing, uncontrolled population-based experiment has already indicated that folic acid ‘‘supplementation’’ at a level of’0.2 mg/d is likely to lower NTD incidence. Whether lower fortification levels are as effective or safer is currently still unknown. Folate status is low among young women of childbearing age in many developing and emerging countries, where it contributes to maternal and childhood mortality. In those countries, folic acid fortification of flour or other staple foods may be the best approach to reach the groups at risk. In the developed countries where mandatory folic acid fortification is not yet in place, targeted		Verhoef (2011) Am J Clin Nutr 93: 1-2

		supplementation of women of childbearing age has become ever so important."		
Effect modification by population dietary folate on the association between MTHFR genotype, homocysteine, and stroke risk: a meta-analysis of genetic studies and randomised trials	Meta-analysis of trials	The MTHFR 677C-->T polymorphism has been associated with raised homocysteine concentration and increased risk of stroke. A previous overview showed that the effects were greatest in regions with low dietary folate consumption, but differentiation between the effect of folate and small-study bias was difficult. A meta-analysis of randomised trials of homocysteine-lowering interventions showed no reduction in coronary heart disease events or stroke, but the trials were generally set in populations with high folate consumption. We aimed to reduce the effect of small-study bias and investigate whether folate status modifies the association between MTHFR 677C-->T and stroke in a genetic analysis and meta-analysis of randomised controlled trials. METHODS: We established a collaboration of genetic studies consisting of 237 datasets including 59 995 individuals with data for homocysteine and 20 885 stroke events. We compared the genetic findings with a meta-analysis of 13 randomised trials of homocysteine-lowering treatments and stroke risk (45 549 individuals, 2314 stroke events, 269 transient ischaemic attacks). FINDINGS: The effect of the MTHFR 677C-->T variant on homocysteine concentration was larger in low folate regions (Asia; difference between individuals with TT versus CC genotype, 3.12 mumol/L, 95% CI 2.23 to 4.01) than in areas with folate fortification (America, Australia, and New Zealand, high; 0.13 mumol/L, -0.85 to 1.11). The odds ratio (OR) for stroke was also higher in Asia (1.68, 95% CI 1.44 to 1.97) than in America, Australia, and New Zealand, high (1.03, 0.84 to 1.25). Most randomised trials took place in regions with high or increasing population folate concentrations. The summary relative risk (RR) of stroke in trials of homocysteine-lowering interventions (0.94, 95% CI 0.85 to 1.04) was similar to that predicted for the same extent of homocysteine reduction in large genetic studies in populations with similar folate status (predicted RR 1.00, 95% CI 0.90 to 1.11). Although the predicted effect of homocysteine reduction from large genetic studies in low folate regions (Asia) was larger (RR 0.78, 95% CI 0.68 to 0.90), no trial has evaluated the effect of lowering of homocysteine on stroke risk exclusively in a low folate region. INTERPRETATION: In regions with increasing levels or established policies of population folate supplementation, evidence from genetic studies and randomised trials is concordant in suggesting an absence of benefit from lowering of homocysteine for prevention of stroke. Further large-scale genetic studies of the association between MTHFR 677C-->T and stroke in low folate settings are needed to distinguish effect modification by folate from small-study bias. If future randomised trials of homocysteine-lowering interventions for stroke prevention are undertaken, they should take place in regions with low folate consumption.	Subgroups again	Holmes (2011) Lancet
Fruit, vegetables, and folate: cultivating the evidence for cancer prevention	Editorial	No abstract. Comment on Stevens paper. paper on folate and Aune on fruit and veg. Stress importance of non-linear analysis. Timing is everything!	Useful figure that needs modifying	Lee et al. (2011) Gastroenterology 141: 16-20

				
Folate intake and risk of colorectal cancer and adenoma: modification by time	Prospective population study	Experimental and observational studies have suggested that folate may play dual roles in colorectal cancer risk depending on the timing and dose. OBJECTIVE: We examined the latency between folate intake and the incidence of colorectal cancer. DESIGN: We prospectively examined associations between folate intake assessed every 2 to 4 y by using validated food-frequency questionnaires and risk of colorectal cancer and adenoma in the Nurses' Health Study and Health Professionals Follow-Up Study, which included 2299 incident colorectal cancers and 5655 colorectal adenomas from 1980 to 2004. RESULTS: There was an association between total folate intake 12-16 y before diagnosis and lower risk of colorectal cancer (relative risk: 0.69; 95% CI: 0.51, 0.94; >/=800 compared with <250 mug folate/d), but there was no association between intake in the recent past and colorectal cancer risk. Long- and short-term intakes of total folate were associated with a lower risk of colorectal adenoma, with a strong association with intake 4-8 y before diagnosis (odds ratio: 0.68; 95% CI: 0.60, 0.78; >/=800 compared with <250 mug folate/d). The current use of multivitamins for >15 y, but not a shorter duration of use, was associated with lower risk of colorectal cancer; and a shorter duration of use was related to lower risk of adenoma. We did not observe an adverse effect of total folate or synthetic folic acid on risk of colorectal cancer or adenoma even during the folic acid fortification era. CONCLUSION: Folate intake is inversely associated with risk of colorectal cancer only during early preadenoma stages.		Lee (2011) Am J Clin Nutr
Foods, fortificants, and supplements: where do Americans get their nutrients?	Review	Limited data are available on the source of usual nutrient intakes in the United States. This analysis aimed to assess contributions of micronutrients to usual intakes derived from all sources (naturally occurring, fortified and enriched, and dietary supplements) and to compare usual intakes to the Dietary Reference Intake for U.S. residents aged >/=2 y according to NHANES 2003-2006 (n = 16,110). We used the National Cancer Institute method to assess usual intakes of 19 micronutrients by source. Only a small percentage of the population had total usual intakes (from dietary intakes and supplements) below the estimated average requirement (EAR) for the following: vitamin B-6 (8%), folate (8%), zinc (8%), thiamin, riboflavin, niacin, vitamin B-12,		Fulgoni (2011) J Nutr 141: 1847-54

		phosphorus, iron, copper, and selenium (<6% for all). However, more of the population had total usual intakes below the EAR for vitamins A, C, D, and E (34, 25, 70, and 60%, respectively), calcium (38%), and magnesium (45%). Only 3 and 35% had total usual intakes of potassium and vitamin K, respectively, greater than the adequate intake. Enrichment and/or fortification largely contributed to intakes of vitamins A, C, and D, thiamin, iron, and folate. Dietary supplements further reduced the percentage of the population consuming less than the EAR for all nutrients. The percentage of the population with total intakes greater than the tolerable upper intake level (UL) was very low for most nutrients, whereas 10.3 and 8.4% of the population had intakes greater than the UL for niacin and zinc, respectively. Without enrichment and/or fortification and supplementation, many Americans did not achieve the recommended micronutrient intake levels set forth in the Dietary Reference Intake.		
Contributions of enriched cereal-grain products, ready-to-eat cereals, and supplements to folic acid and vitamin B12 usual intake and folate and vitamin B12 status in US children: National Health and Nutrition Examination Survey(NHANES)2003-06	Population study	US children consume folic acid from multiple sources. These sources may contribute differently to usual intakes above the age-specific tolerable upper intake level (UL) for folic acid and to folate and vitamin B-12 status. OBJECTIVE: We estimated usual daily folic acid intakes above the UL and adjusted serum and red blood cell folate, serum vitamin B-12, homocysteine, and methylmalonic acid (MMA) concentrations in US children by age group and by the following 3 major folic acid intake sources: enriched cereal-grain products (ECGP), ready-to-eat cereals (RTE), and supplements containing folic acid (SUP). DESIGN: We analyzed data in 4 groups of children aged 1-3, 4-8, 9-13, and 14-18 y from the National Health and Nutrition Examination Survey (NHANES), 2003-2006 (n = 7161). RESULTS: A total of 19-48% of children consumed folic acid from ECGP only. Intakes above the UL varied from 0-0.1% of children who consumed ECGP only to 15-78% of children who consumed ECGP+RTE+SUP. In children aged 1-8 y, 99-100% of those who consumed >/=200 mug folic acid/d from supplements exceeded their UL. Although <0.5% of children had folate deficiency or low vitamin B-12 status, the consumption of RTE or SUP with folic acid was associated with higher mean folate and vitamin B-12 concentrations and, in some older children, with lower homocysteine and MMA concentrations. CONCLUSIONS: Our data suggest that the majority of US children consume more than one source of folic acid. Postfortification, the consumption of RTE or SUP increases usual daily intakes and blood concentrations of folate and vitamin B-12.	Supplements are the main reason why childred often exceed the safe upper limit	Yeung (2011) Am J Clin Nutr 93: 172-85
Women's compliance with current folic acid recommendations and achievement of optimal vitamin status for preventing neural tube defects	Cohort study	The timing of folic acid supplement usage is critical to preventing pregnancies affected by neural tube defects (NTDs) because the neural tube closes by Day 28 post-conception. We investigated compliance of pregnant women with current folic acid recommendations (400 microg/day from preconception to 12 weeks) in relation to achieving a folate status associated with lowest risk of NTDs. METHODS: From a sample of 296 women with singleton uncomplicated pregnancies attending an antenatal clinic in Northern Ireland, those who reported taking folic acid in the first trimester (n = 226) were investigated. Samples were taken at 14 weeks gestation to measure serum concentrations of folate and vitamin B12 (related to folate and an independent predictor of NTD), and dietary B-vitamin intake and folic acid usage were investigated. RESULTS: Although the majority of the overall sample (84%) reported taking folic acid supplements in the first trimester, only 19% had started	Also give serum folate levels. Note low B12 status and they speculate about role of B12	McNulty (2011) Hum Reprod 26: 1530-6

		before conception, as recommended. Multigravidae compared with primigravidae women were less likely to have followed the recommendations correctly (P= 0.001). At 14 weeks, red cell folate (considered a reliable biomarker of previous 3 months, covering time of neural tube closure) was correlated (r = 0.320, P < 0.001) with the reported duration of folic acid usage, and was lower (P< 0.0001) in women who started folic acid after conception. CONCLUSIONS: Red cell folate concentrations in women not complying with recommendations were suboptimal in relation to NTD risk. The findings generally support the recent official recommendation to the Chief Medical Officer for mandatory fortification of food with folic acid in the UK.		
Maternal and infant nutritional supplementation practices in Ireland: implications for clinicians and policymakers	Prospective cohort	This prospective Irish observational study examined maternal and infant nutritional supplement use. From an initial sample of 539 mothers recruited from the Coombe Women and Infants University Hospital in Dublin (during 2004-2006), 450 eligible mothers were followed up at 6 weeks and 6 months postpartum. Only 200 women (44.4%) complied with peri-conceptional folic acid at the recommended time with strong social patterning associated with its uptake. Almost 10% of the sample (n = 44) consumed a combined multivitamin and mineral supplement during pregnancy. A vitamin D-containing supplement was provided to only 5 (1.1%) and 15 (3.3%) infants at 6 weeks and 6 months, respectively. A national guideline that advises on adequate and safe use of both vitamin and multivitamin supplements during pregnancy with particular reference to vitamin A and D is warranted. Given the re-emergence of rickets in Ireland, and the reported morbidities associated with vitamin D insufficiency, promoting and monitoring compliance with 200 IU [5 microg] daily vitamin D supplements to all infants particularly those from higher risk groups from birth to 1 year, should be a public health priority.		Tarrant (2011) Ir Med J 104: 173-7
Why do Canadian women fail to achieve optimal pre-conceptional folic acid supplementation? An observational study	Population survey	Objectives: To determine the factors that put Canadian women at risk for not supplementing with folic acid (FA) in the three months before conception, as recommended for the prevention of infant neural tube defects. Methods: This study used data from the Canadian Maternity Experiences Survey. We used Poisson regression analysis with a robust variance to determine which factors were associated with women not supplementing with FA in the three months prior to pregnancy as compared with women who did supplement. Results: Of the 6421 women surveyed, 57.7% were supplementing with FA pre-conceptionally. The risk factors associated with a lack of FA supplementation pre-conceptionally were maternal age <19 (prevalence ratio [PR] = 0.50; 95% CI 0.36 to 0.69) or 20 to 24 (PR = 0.75; 95% CI 0.67 to 0.84); education below high school level (PR = 0.73; 95% CI 0.61 to 0.87), at high school level (PR = 0.77; 95% CI 0.71 to 0.83), or at post-secondary level other than university (PR = 0.93; 95% CI 0.88 to 0.97); being at or below the low-income cut-off (PR = 0.74; 95% CI 0.67 to 0.81); smoking before pregnancy (PR = 0.79; 95% CI 0.73 to 0.86); being non-fluent in the language of the health care provider (PR = 0.66; 95% CI 0.49 to 0.88); being obese (BMI >/= 30) (PR = 0.91; 95% CI 0.85 to 0.98); being unemployed (PR = 0.94; 95% CI 0.89 to 1.00); and being born outside of Canada (PR = 0.79; 95% CI 0.74 to 0.84). Conclusion: Young maternal age, low education, low income, smoking, language barriers, obesity, unemployment, and being born outside Canada are risk factors for suboptimal or lack		Miller (2011) J Obstet Gynaecol Can 33: 1116-23

		of FA supplementation pre-conceptionally.		
The combined oral contraceptive pill containing drospirenone and ethinyl estradiol plus levomefolate calcium	Review	Neural tube defects are the second most common congenital anomaly in the United States, although their incidence may be decreased by periconception folic acid supplementation. A new oral contraceptive containing drospirenone and ethinyl estradiol plus levomefolate calcium was formulated to decrease the risk of neural tube defects in pregnancies conceived while taking or shortly after discontinuing this pill. Areas covered: Because of its novelty, very few studies have been performed to evaluate the efficacy, side effects and safety related to contraception, premenstrual dysphoric disorder and acne; therefore, literature evaluating similar contraceptives without levomefolate is reviewed. Additionally, we review studies evaluating the addition of levomefolate calcium to oral contraceptives containing 3 mg drospirenone and either 20 or 30 mug ethinyl estradiol. To date, no study has been performed to evaluate the effect this new oral contraceptive has on reducing the incidence of neural tube defects. Expert opinion: This new pill has similar contraceptive efficacy, side effect, safety and benefits profile to other drospirenone-containing contraceptives. While also approved to prevent neural tube defects, no studies validate this claim and physician time is better spent counseling women, regardless of contraceptive choice, on the importance of folic acid supplementation during the child-bearing years.		Rapkin (2011) Expert Opin Pharmacother 12: 2403-10
The process of setting micronutrient recommendations: a cross-European comparison of nutrition-related scientific advisory bodies	Review of policy practice	OBJECTIVE: To examine the workings of the nutrition-related scientific advisory bodies in Europe, paying particular attention to the internal and external contexts within which they operate. DESIGN: Desk research based on two data collection strategies: a questionnaire completed by key informants in the field of micronutrient recommendations and a case study that focused on mandatory folic acid (FA) fortification. SETTING: Questionnaire-based data were collected across thirty-five European countries. The FA fortification case study was conducted in the UK, Norway, Denmark, Germany, Spain, Czech Republic and Hungary. RESULTS: Varied bodies are responsible for setting micronutrient recommendations, each with different statutory and legal models of operation. Transparency is highest where there are standing scientific advisory committees (SAC). Where the standing SAC is created, the range of expertise and the terms of reference for the SAC are determined by the government. Where there is no dedicated SAC, the impetus for the development of micronutrient recommendations and the associated policies comes from interested specialists in the area. This is typically linked with an ad hoc selection of a problem area to consider, lack of openness and transparency in the decisions and over-reliance on international recommendations. CONCLUSIONS: Even when there is consensus about the science behind micronutrient recommendations, there is a range of other influences that will affect decisions about the policy approaches to nutrition-related public health. This indicates the need to document the evidence that is drawn upon in the decisions about nutrition policy related to micronutrient intake.		Timotijevic (2011) Public Health Nutr 14: 716-28
Low maternal vitamin B12 is a risk factor for neural tube defects: a meta-	Meta-analysis	The objective of this study was to assess whether low level of maternal vitamin B12 is associated with an increased risk of fetal neural tube defects (NTDs), in order to contribute to research on further reduction of NTDs under a background of mandatory folic acid (FA) fortification. Methods. A meta-analysis was conducted. We retrieved	Important that B12 is considered as well as folate	Wang (2011) J Matern Fetal Neonatal Med

analysis		and evaluated the studies published on the risk of low level of maternal vitamin B(12) for NTDs. The homogeneity of the studies was examined using the forest graph. Meta-analysis was applied to calculate the odds ratio (OR) of fetal NTDs in relation to low maternal B(12) and its 95% confidence interval (CI). Results. We identified nine published articles including 567cases and 1566 controls in the meta-analysis. All the studies selected were homogeneous according to the forest graph (chi(2) = 15.05, P < 0.1). The estimated OR value of fetal NTDs in relation to low maternal B(12) was 2.41 (95% CI: 1.90-3.06). Conclusion. Low maternal B(12) status could be an important risk factor for the development of fetal NTDs. The addition of synthetic B(12) to current recommendations for periconceptional FA tablet supplements or FA-fortified foods should be considered.		
Comparison of standardised dietary folate intake across ten countries participating in the European Prospective Investigation into Cancer and Nutrition	Population study	Folate plays an important role in the synthesis and methylation of DNA as a cofactor in one-carbon metabolism. Inadequate folate intake has been linked to adverse health events. However, comparable information on dietary folate intake across European countries has never been reported. The objective of the present study was to describe the dietary folate intake and its food sources in ten countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. A cross-sectional analysis was conducted in 36 034 participants (aged 35-74 years) who completed a single 24 h dietary recall using a computerised interview software program, EPIC-Soft(R) (International Agency for Research on Cancer, Lyon). Dietary folate intake was estimated using the standardised EPIC Nutrient DataBase, adjusted for age, energy intake, weight and height and weighted by season and day of recall. Adjusted mean dietary folate intake in most centres ranged from 250 to 350 mug/d in men and 200 to 300 mug/d in women. Folate intake tended to be lower among current smokers and heavier alcohol drinkers and to increase with educational level, especially in women. Supplement users (any types) were likely to report higher dietary folate intake in most centres. Vegetables, cereals and fruits, nuts and seeds were the main contributors to folate intake. Nonetheless, the type and pattern of consumption of these main food items varied across the centres. These first comparisons of standardised dietary folate intakes across different European populations show moderate regional differences (except the UK health conscious group), and variation by sex, educational level, smoking and alcohol-drinking status, and supplement use.		Young Park (2011) Br J Nutr 1-18
Economic burden of neural tube defects and impact of prevention with folic acid: a literature review	Review	Neural tube defects (NTDs) are the second most common group of serious birth defects. Although folic acid has been shown to reduce effectively the risk of NTDs and measures have been taken to increase the awareness, knowledge, and consumption of folic acid, the full potential of folic acid to reduce the risk of NTDs has not been realized in most countries. To understand the economic burden of NTDs and the economic impact of preventing NTDs with folic acid, a systematic review was performed on relevant studies. A total of 14 cost of illness studies and 10 economic evaluations on prevention of NTDs with folic acid were identified. Consistent findings were reported across all of the cost of illness studies. The lifetime direct medical cost for patients with NTDs is significant, with the majority of cost being for inpatient care, for treatment at initial diagnosis in childhood, and for comorbidities in adult life. The	Do not consider cost of any adverse effects of fortification	Yi (2011) Eur J Pediatr 170: 1391-400

		lifetime indirect cost for patients with spina bifida is even greater due to increased morbidity and premature mortality. Caregiver time costs are also significant. The results from the economic evaluations demonstrate that folic acid fortification in food and preconception folic acid consumption are cost-effective ways to reduce the incidence and prevalence of NTDs. This review highlights the significant cost burden that NTDs pose to healthcare systems, various healthcare payers, and society and concludes that the benefits of prevention of NTDs with folic acid far outweigh the cost. Further intervention with folic acid is justified in countries where the full potential of folic acid to reduce the risk of NTDs has not been realized.		
Long-term effect of low-dose folic acid intake: potential effect of mandatory fortification on the prevention of neural tube defects	Clinical Trial	BACKGROUND: Understanding the full effect of chronic low-dose folic acid is important in interpreting the effect of the mandatory folic acid fortification program in North America. OBJECTIVE: We aimed to describe the rate of attainment and steady state (plateau) of red blood cell (RBC) folate in response to long-term intake of 140 mug (designed to mimic fortification) and 400 mug (recommended dose for the primary prevention of neural tube defects) folic acid/d in reproductive-aged women living in a country with minimal fortification. DESIGN: On the basis of pharmacokinetics principles, it was recently proposed that a steady state should be reached after 40 wk. Thus, 144 women aged 18-40 y were randomly assigned to receive a daily folic acid supplement of 140 (n = 49) or 400 (n = 48) mug or placebo (n = 47) for 40 wk. RBC folate was measured at baseline and at 6, 12, 29, and 40 wk. RESULTS: After 40 wk, RBC folate did not reach a plateau in either treatment group. Kinetic modeling of the data indicated that RBC folate would approximately double from 779 to 1356 nmol/L in response to 140 mug folic acid/d with only approximately 50% of model-estimated steady state conditions achieved at 40 wk. An average RBC folate concentration of 1068 nmol/L after 12 wk of supplementation with 400 mug folic acid/d was readily achieved at 36 wk after continuous intake of 140 mug/d. CONCLUSION: Our model shows the considerable length of time required to attain the full effect of low-dose folic acid, which suggests that 140 mug folic acid/d could be as effective as 400 mug folic acid/d taken during the periconceptional period if given sufficient time.	Conclude that it may not be necessary for women to take 0.4 mg supplements since fortification will do the job, if at the level of 140 microg per day	Houghton (2011) Am J Clin Nutr 94: 136-41
Genetic and environmental determinants of plasma total homocysteine levels: impact of population-wide folate fortification	Population study	OBJECTIVES: Folate metabolism is an important target for drug therapy. Drug-induced inhibition of folate metabolism often causes an elevation of plasma total homocysteine (tHcy). Plasma tHcy levels are influenced by several nongenetic (e.g. folate intake, age, smoking) as well as genetic factors. Over the last decade, several countries have implemented a nationwide folate fortification program of all grain products. This investigation sought to determine the impact of folate fortification on the relative contribution of environmental and genetic factors to the variability of plasma tHcy. METHODS: Two cohorts were compared in this study, one from the United States (with folate fortification, n=281) and one from Austria (without folate fortification, n=139). Several environmental factors as well as previously identified gene variants important for tHcy levels (MTHFR C677T, MTHFR A1298C, MTRR A66G) were examined for their ability to predict plasma tHcy in a multiple linear regression model. RESULTS: Nongenetic, environmental factors had a comparable influence on plasma tHcy between the two cohorts (R: approximately 0.19). However,	Subgroups	Nagele (2011) Pharmacogenet Genomics 21: 426-31

		after adjusting for other covariates, the tested gene variants had a substantially smaller impact among patients from the folate-fortified cohort (R=0.021) compared with the nonfolate-fortified cohort (R=0.095). The MTHFR C677T polymorphism was the single most important genetic factor. Male sex, smoking, and folate levels were important predictors for nonfolate-fortified patients; age was for folate-fortified patients. CONCLUSION: Population wide folate fortification had a significant effect on the variability of plasma tHcy and reduced the influence of genetic factors, most importantly the MTHFR 677TT genotype, and may be an important confounder for a personalized drug therapy.		
The basis of differential responses to folic acid supplementation	Intervention study in twins	BACKGROUND/AIMS: Elevated levels of total homocysteine (tHcy) are associated with an increased risk of many common diseases. Supplementation with folic acid has been shown to significantly reduce tHcy levels. We used the classical twin model to partition the variability in changes in plasma tHcy levels through folic acid supplementation into genetic, environmental, and confounding epidemiological factors. METHODS: We carried out an intervention study of folic acid using 101 healthy, female, identical and non-identical twins aged 50-80 years. Each twin was administered folic acid (0.8 mg/day) for 6 weeks. Total plasma folate, cobalamin and tHcy were measured at both baseline and after dosing. We calculated the heritability and tested for associations between the MTHFR C677T functional variant and response to folic acid supplementation. RESULTS: Supplementation with folic acid led to a significant reduction in tHcy levels. The mean tHcy changed from 12.14 to 10.42 mumol/l after supplementation ($p < 10(-5)$). Moreover, the change in tHcy levels was highly heritable (64%), not associated with the C677T functional variant at MTHFR and not confounded by age, BMI or diet. CONCLUSIONS: Our results highlight the need to identify genetic factors associated with biomarkers of response to folate supplementation.	Subgroups due to genetic factors	{Cotlarciuc, 2011 #911}
Effect on risk of anencephaly of gene-nutrient interactions between methylenetetrahydrofolate reductase C677T polymorphism and maternal folate, vitamin B12 and homocysteine profile	Case-control study	OBJECTIVE: To evaluate the effects on anencephaly risk of the interaction between the maternal profile of folate, vitamin B12 and homocysteine and the 677C-->T polymorphism in the gene encoding methylenetetrahydrofolate reductase (MTHFR). DESIGN: Case-control study paired (1:1) on maternity clinic, date of birth and state of residence. Cases of anencephaly were identified using the Registry of the Mexican Neural Tube Defect Epidemiological Surveillance System. Case and control mothers were selected from the same maternity departments. All mothers completed a structured questionnaire and blood samples were obtained to determine the MTHFR 677C-->T polymorphism and biochemical profile. SETTING: Mexico, Puebla and Guerrero states, Mexico. SUBJECTS: A total of 151 mothers of cases and controls were enrolled from March 2000 to February 2001. We had complete information on biochemical profile and MTHFR C677T polymorphism for ninety-eight mothers of cases and ninety-one mothers of controls. RESULTS: The adjusted models show that the risk of anencephaly in mothers with 677TT genotype was reduced by 18 % (OR = 0.82; 95 % CI 0.72, 0.94) for each 1 ng/ml increment in serum folate. In terms of tertiles, mothers with 677TT genotype with serum folate levels in the upper tertile (>14.1 ng/ml) had a 95 % lower risk to have a child with anencephaly than mothers with serum folate levels in the first and second tertiles (P trend = 0.012).	Importance of subgroups again	Lacasana (2012) Public Health Nutr 1-10

		CONCLUSIONS: Our data agree with the hypothesis of a gene-nutrient interaction between MTHFR 677C-->T polymorphism and folate status. We observed a protective effect on anencephaly risk only in mothers with 677TT genotype as serum folate levels increased.		
Dietary intake of folate and alcohol, MTHFR C677T polymorphism, and colorectal cancer risk in Korea	Observational population study	BACKGROUND: The incidence of colorectal cancer (CRC) is increasing sharply in Korea, and evidence has suggested the role of dietary methyl supply and related polymorphisms on colorectal carcinogenesis. OBJECTIVE: We investigated the association between folate and alcohol intake, methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, and CRC risk in Koreans. DESIGN: A total of 787 cases and 656 controls were recruited from 2 university hospitals. Multiple logistic regression models were used to estimate ORs and corresponding 95% CIs. RESULTS: MTHFR 677T homozygotes were at a lower risk of CRC (OR: 0.60; 95% CI: 0.46, 0.78 for TT compared with CC/CT). High folate intake was associated with reduced CRC risk (OR: 0.64; 95% CI: 0.49, 0.84 for high compared with low intake), and high alcohol consumption was associated with increased risk of CRC (OR: 1.76; 95% CI: 1.26, 2.46 for high compared with low intake). When data were stratified by the amount of dietary methyl (combined intake of folate and alcohol), those with low-methyl diets had higher risk of CRC (OR: 2.32; 95% CI: 1.18, 4.56) than did those with high-methyl diets among CC/CT carriers, whereas the amount of dietary methyl did not affect the CRC risk among carriers with the TT homozygous variant. This association was stronger in patients with colon cancer than in patients with rectal cancer. CONCLUSION: We found that the effect of dietary methyl supply on colorectal carcinogenesis may differ according to MTHFR C677T genotype and the subsite of origin in a Korean population.	Complex story of subgroups. Note in contrast to breast cancer, a lower risk of CRC in those with TT and reduced risk in CC and CT of higher folate intake	Kim (2012) Am J Clin Nutr