National Toxicology Program
U.S. Department of Health and Human Services

SUPPLEMENTARY MATERIAL: STUDY SUMMARIES

HYPERSENSITIVITY-RELATED OUTCOMES

IDENTIFYING RESEARCH NEEDS FOR ASSESSING SAFE USE OF HIGH INTAKES OF FOLIC ACID

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Office of Health Assessment and Translation
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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1. CRIDER, 2013

Full citation: Crider KS, Cordero AM, Qi YP, Mulinare J, Dowling NF, Berry RJ. 2013. Prenatal folic acid and risk of asthma in children: a systematic review and meta-analysis. Am J Clin Nutr 98(5): 1272-1281.
Funding: Supported by the CDC and in part by an appointment to the Research Participation Program at the CDC administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the CDC.

1.1. Prenatal folic acid and risk of asthma in children

Protocol: Prenatal folic acid and risk of asthma in children	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (18). See "supplemental data – protocol" under "Supplemental data" in the online issue for our protocol. With the assistance of a research librarian, we searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Medline (http://www.ncbi.nlm.nih.gov/), Embase (http://www.embase.com), Cumulative Index to Nursing and Allied Health Literature (http://www.ebscohost.com/academic/cinahl-plus-with-full-text), Cochrane (http://www.thecochranelibrary.com/view/0/index.html), Web of Science (http://thomsonreuters.com/web-of-science/), Population Information Online (http://www.popline.org/), and Education Resources Information Center (http://eric.ed.gov/) for the period from the inception of the database through February 2013 by using the term folic acid and its variants (folate, folacin, and vitamin B-9) combined with terms specific to allergic and respiratory outcomes (eg, asthma, respiratory, wheeze, reactive airway, atopy, and allergy) and their associated Medical Subject Headings. To ensure maximum sensitivity, no language or other limits were set. See "supplemental data – search strategies" under "Supplemental data" in the online issue for full search strategies for each database. We scanned reference lists of all included studies as well as those of relevant systematic review articles returned in the search, and articles with potentially relevant titles were pulled for screening against inclusion criteria.	**Inclusion Criteria:** have an exposure timing during the periconceptional period or during pregnancy, include an evaluation of the direct association between folic acid exposure and one of the outcomes of interest, provide results on at least one allergic or respiratory outcome, randomized controlled trial, cohort, case-control, or cross-sectional study, report the exposure of natural food folate intake, folic acid intake from fortified foods, total folate intake from foods (eg, dietary folate equivalents), folic acid intake from supplements, or maternal or cord blood serum, plasma, or red blood cell folate concentrations **Exclusion Criteria:** "heterogeneity of exposure and outcome" excluded 9 of the 14 studies that met the inclusion criteria
Starting date:	**Ending date:** 2013-02-01
Total references from search: 1154	**References Included:** 14

Additional Notes:

1.2. Result(s)

1.2.A Periconceptional and first trimester folic acid supplement use and asthma in childhood

Studies (3), Total Subjects (4823)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Periconceptional and first trimester folic acid supplement use	asthma	1.01	(0.78, 1.3)	I2=0.00%, p=0.74

Notes: Estimate p=0.95,

1.2.B Periconceptional and first trimester folic acid supplement use and asthma or wheeze in childhood

Studies (5), Total Subjects (45642)

Exposure	Assessed Outcome	relative risk	95% CI (low, high)	Test of Heterogeneity
Periconceptional and first trimester folic acid supplement use	asthma or wheeze	1.05	(1.02, 1.09)	I2=0.00%, p=0.68

Notes: Estimate p<0.01

1.3. Statistical Method(s)

Results: Periconceptional and first trimester folic acid supplement use and asthma in childhood; Periconceptional and first trimester folic acid supplement use and asthma or wheeze in childhood

Adjustment factors:

Statistical metric description: We performed meta-analyses on articles with similar exposures and outcomes with Comprehensive Meta-Analysis Software (version 2; Biostat). Only the subset of studies of periconceptional folic acid exposure (month before and through the first trimester) and risk of asthma or wheezing was large enough to perform a meta-analysis of risk (criteria defined as > or = 3 studies of sufficient quality). We measured the summary effect size for asthma alone and performed a sensitivity analysis with asthma combined with wheezing, which is sometimes used as a proxy for asthma. We combined the data from cohort studies and nested-case control studies by using ORs to approximate RRs. We used a random-effects model in our analyses. The risk estimate with the greatest control for confounders from each study was used in all analyses; see Supplemental Table 1 under “Supplemental data” in the online issue for a list of confounders adjusted for in each study. When risk estimates were provided for multiple exposure time points within the periconceptional period, exposure timing was prioritized in the following order for inclusion in the quantitative analysis (or meta-analysis) , to prioritize exposure time periods closest to the DNA methylation programing in the early embryo:

periconceptional, prepregnancy, and first trimester. Statistical heterogeneity was tested with the Q statistic and evaluated by using the I2 statistic (19), which provides an estimate of the proportion of the variance that is not attributable to random error. Heterogeneity was considered to be substantial if I2 was greater than the conventional value of 50%. Publication bias was assessed by a visual inspection of funnel plots. The trim-and-fill analysis of Duval and Tweedie (20) was used to investigate the potential influence that unpublished studies could have on the summary estimates. P , 0.05 was considered statistically significant in all analyses.

2. AISEN, 2008

Full citation: Aisen PS, Schneider LS, Sano M, Diaz-Arrastia R, van Dyck CH, Weiner MF, Bottiglieri T, Jin S, Stokes KT, Thomas RG, Thal LJ. 2008. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA 300(15): 1774-1783.

Funding: This study was supported by grant U01-AG10483 from the National Institute on Aging (NIA), as well as grants from the General Clinical Research Center Program of the National Center for Research Resources, National Institutes of Health. Folic acid and vitamins B6 and B12 were donated by Roche Inc.

ALZHEIMER DISEASE COOPERATIVE STUDY (ADCS) HIGH-DOSE SUPPLEMENT TRIAL

Age: 76.3 (mean)	**Study design:** Controlled trial (**n =** 409)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United States **Region:** 40 sites across US **State:**
Inclusion criteria: medically stable, Mini-Mental State Examination (MMSE) score between 14 to 26, older than 50 years of age, participants with mild to moderate Alzheimer's	**Exclusion critieria:** Low levels of B12 or folate, renal insufficiency, use of anticholinergic drugs, sedatives, anti-Parkinsonian drug or any other experimental drug for Alzheimer's within the past 2 months

2.1. Exposure: Multi-B vitamin supplement

Method	Description	Analysis
supplement intake	5mg/d of folic acid,1mg/d of vitamin B12 (cyanocobalamin) and 25 mg/day vitamin B6 (pyridoxine hydrochloride)	intervention

Outcomes

	Outcome	Diagnostic Description
A	Upper respiratory tract infection (URTI) (not reported)	not mentioned how diagnosed

Results

2.1.A Upper respiratory tract infection (URTI)

Population: ADCS, multivitamin supplement trial adverse events
Exposure: Multi-B vitamin supplement
Outcome: Upper respiratory tract infection (URTI)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	166	-	

Group	N	other 95% CI (low, high)	*p*-value
multi-B vitamin supplement	240	-	0.19

Statistical Method(s)

Endpoints: Upper respiratory tract infection (URTI)
Adjustment factors:
Statistical metric: other
Statistical metric description: Fisher exact test, unadjusted for multiple comparisons

3. BEKKERS, 2012

Full citation: Bekkers MB, Elstgeest LE, Scholtens S, Haveman-Nies A, de Jongste JC, Kerkhof M, Koppelman GH, Gehring U, Smit HA, Wijga AH. 2012. Maternal use of folic acid supplements during pregnancy, and childhood respiratory health and atopy. Eur Respir J 39(6): 1468-1474.

Funding: Research relating to this manuscript was funded by the Netherlands Organization for Health Research and Development, the Netherlands Organization for Scientific Research, the Netherlands Asthma Fund, the Netherlands Ministry of Spatial Planning, Housing and the Environment, and the Netherlands Ministry of Health, Welfare and Sport.

PIAMA BIRTH COHORT, 1996-1997

Age: children were followed up to 8 years of age	**Study design:** Prospective (**n =** 3786)
Gender: Male and Female **Ethnicities:** White, Other	**Country:** Netherlands **Region:** North, Central, West **State:**
Inclusion criteria: none	**Exclusion critieria:** missing data on health outcomes, missing exposure information

3.1. Exposure: Folic acid containing supplements during pregnancy

Method	Description	Analysis
questionnaire	Expectant mothers were asked whether or not they used specific vitamin or mineral supplements during pregnancy, including folic acid, pre-natal vitamins (multivitamin supplements especially for pregnant females), multivitamins and vitamin B complex supplements.	Four exposure groups of maternal use of folic acid-containing supplements (FACSs) were defined as children whose mothers had used: 1) folic acid-only supplements ("folic acid"); 2) pre-natal vitamin supplements ("pre-natal vitamin"), but not folic acid only; 3) multivitamin or vitamin B complex supplements ("multivitamin or vitamin B complex") but not folic acid-only or pre-natal vitamins; and 4) no folic acid-only, no pre-natal and no multivitamin/vitamin B supplements at all ("no FACSs"). By "FACSs", we mean all folic acid-containing supplements: folic acid only, pre-natal vitamins, and multivitamin/vitamin B complex supplements. 80% of the questionnaires were completed between the 30th and 36th weeks of pregnancy (median 33 weeks of gestation). Use of FACSs by these mothers and by mothers who completed the questionnaire before the 30th week or after the 36th week was similar.

Outcomes

	Outcome	Diagnostic Description
A	Asthma symptoms (self-reported)	at least one attack of wheeze, and/or at least one attack of dyspnoea, and/or prescription of inhalation steroids for respiratory or lung problems by a medical doctor (at 3–8 yrs)
B	Bronchial hyperresponsiveness (BHR) (medical professional or test)	At the age of 8 yrs, all children still in the study were invited for a hospital-based examination, including blood sampling and a lung function test. Bronchial hyperresponsiveness (BHR) measurements were obtained from 938 children, and BHR was defined as a decrease of >/=20% in forced expiratory volume in 1 s at a cumulative dose of </=0.61 mg methacholine bromide. NOTE: By the design of the PIAMA study, children of allergic mothers were over-represented in the subgroup of children invited for the hospital-based examination. As a result, the prevalence of maternal allergy was higher (65%) in the group of children with data on sensitization and BHR than in the baseline PIAMA population (31%).
C	Eczema (self-reported)	an itchy rash that came and went on typical eczema sites (the folds of the elbows or behind the knees, around ears or eyes or in front of the ankles)

	Outcome	Diagnostic Description
D	Frequent asthma symptoms (self-reported)	at least four attacks of wheeze, and/or dyspnoea, and/or prescription of inhalation steroids for respiratory or lung problems by a medical doctor (at 3–8 yrs)
E	Frequent respiratory tract infection (fRTI) (self-reported)	parental report of at least three respiratory tract infections (bronchitis, pneumonia, flu/serious cold, middle ear infection, sinusitis or inflammation of the throat)
F	Lower respiratory tract infection (LRTI) (self-reported)	parental report of a doctor diagnosed bronchitis and/or pneumonia
G	Sensitisation at 8 yrs (medical professional or test)	Blood samples were obtained at age 8 yrs and specific immunoglobulin (Ig)E to common allergens was measured for 1,713 children. Sensitisation: serum IgE > or = 0.70 IU/mL NOTE: By the design of the PIAMA study, children of allergic mothers were over-represented in the subgroup of children invited for the hospital-based examination. As a result, the prevalence of maternal allergy was higher (65%) in the group of children with data on sensitization and BHR than in the baseline PIAMA population (31%).
H	Upper respiratory tract infection (URTI) (self-reported)	parental report of a doctor-diagnosed flu/serious cold, and/or inflammation of the throat, and/or middle ear infection
I	Wheeze (self-reported)	at least one attack of wheeze (at 1–8yrs)

Results

3.1.A Asthma symptoms

Population: PIAMA birth cohort, 1996-1997
Exposure: Folic acid containing supplements during pregnancy
Outcome: Asthma symptoms
Statistical metric: adjusted prevalence ratio

Group	N	adjPR 95% CI (low, high)	*p*-value
No folic acid use	1302	1.0	
Folic acid-only supplements	1998	1.03 (0.92, 1.16)	
Pre-natal vitamin supplements	287	1.0 (0.81, 1.23)	
Multivitamin or vitamin B complex supplements	199	1.02 (0.8, 1.29)	

3.1.B Bronchial hyperresponsiveness (BHR)

Population: PIAMA birth cohort, 1996-1997
Exposure: Folic acid containing supplements during pregnancy
Outcome: Bronchial hyperresponsiveness (BHR)
Statistical metric: adjusted prevalence ratio

Group	N	adjPR 95% CI (low, high)	*p*-value
No folic acid use	1302	1.0	
Folic acid-only supplements	1998	0.97 (0.82, 1.15)	
Pre-natal vitamin supplements	287	0.98 (0.72, 1.34)	
Multivitamin or vitamin B complex supplements	199	0.94 (0.65, 1.36)	

3.1.C Eczema

Population: PIAMA birth cohort, 1996-1997
Exposure: Folic acid containing supplements during pregnancy
Outcome: Eczema
Statistical metric: adjusted prevalence ratio

Group	N	adjPR 95% CI (low, high)	*p*-value
No folic acid use	1302	1.0	
Folic acid-only supplements	1998	0.98 (0.87, 1.09)	
Pre-natal vitamin supplements	287	1.07 (0.89, 1.29)	
Multivitamin or vitamin B complex supplements	199	1.04 (0.83, 1.3)	

3.1.D Frequent asthma symptoms

Population: PIAMA birth cohort, 1996-1997
Exposure: Folic acid containing supplements during pregnancy
Outcome: Frequent asthma symptoms
Statistical metric: prevalence ratio

Group	N	PR 95% CI (low, high)	*p*-value
No folic acid use	1302	1.0	
Folic acid-only supplements	1998	0.88 (0.71, 1.09)	
Pre-natal vitamin supplements	287	0.88 (0.6, 1.31)	
Multivitamin or vitamin B complex supplements	199	1.03 (0.66, 1.61)	

3.1.E Frequent respiratory tract infection (fRTI)

Population: PIAMA birth cohort, 1996-1997
Exposure: Folic acid containing supplements during pregnancy
Outcome: Frequent respiratory tract infection (fRTI)
Statistical metric: adjusted prevalence ratio

Group	N	adjPR 95% CI (low, high)	*p*-value
No folic acid use	1302	1.0	
Folic acid-only supplements	1998	1.01 (0.89, 1.13)	
Pre-natal vitamin supplements	287	1.11 (0.89, 1.39)	
Multivitamin or vitamin B complex supplements	199	1.13 (0.9, 1.43)	

3.1.F Lower respiratory tract infection (LRTI)

Population: PIAMA birth cohort, 1996-1997
Exposure: Folic acid containing supplements during pregnancy
Outcome: Lower respiratory tract infection (LRTI)
Statistical metric: adjusted prevalence ratio

Group	N	adjPR 95% CI (low, high)	*p*-value
No folic acid use	1302	1.0	
Folic acid-only supplements	1998	0.94 (0.83, 1.06)	
Pre-natal vitamin supplements	287	0.99 (0.79, 1.24)	

Group	N	adjPR 95% CI (low, high)	*p*-value
Multivitamin or vitamin B complex supplements	199	0.88 (0.66, 1.18)	

3.1.G Sensitisation at 8 yrs

Population: PIAMA birth cohort, 1996-1997
Exposure: Folic acid containing supplements during pregnancy
Outcome: Sensitisation at 8 yrs
Statistical metric: adjusted prevalence ratio

Group	N	adjPR 95% CI (low, high)	*p*-value
No folic acid use	1302	1.0	
Folic acid-only supplements	1998	0.86 (0.73, 1.01)	
Pre-natal vitamin supplements	287	0.94 (0.71, 1.24)	
Multivitamin or vitamin B complex supplements	199	0.7 (0.46, 1.05)	

3.1.H Upper respiratory tract infection (URTI)

Population: PIAMA birth cohort, 1996-1997
Exposure: Folic acid containing supplements during pregnancy
Outcome: Upper respiratory tract infection (URTI)
Statistical metric: adjusted prevalence ratio

Group	N	adjPR 95% CI (low, high)	*p*-value
No folic acid use	1302	1.0	
Folic acid-only supplements	1998	1.04 (1.0, 1.09)	0.05
Pre-natal vitamin supplements	287	1.07 (0.98, 1.17)	
Multivitamin or vitamin B complex supplements	199	1.03 (0.93, 1.14)	

3.1.I Wheeze

Population: PIAMA birth cohort, 1996-1997
Exposure: Folic acid containing supplements during pregnancy
Outcome: Wheeze
Statistical metric: adjusted prevalence ratio

Group	N	adjPR 95% CI (low, high)	*p*-value
No folic acid use	1302	1.0	
Folic acid-only supplements	1998	1.07 (0.96, 1.2)	
Pre-natal vitamin supplements	287	1.04 (0.85, 1.27)	
Multivitamin or vitamin B complex supplements	199	1.05 (0.83, 1.34)	

Statistical Method(s)

Endpoints: Wheeze; Frequent respiratory tract infection (fRTI); Upper respiratory tract infection (URTI); Lower respiratory tract infection (LRTI)
Adjustment factors: maternal allergy, maternal education, maternal smoking during pregnancy, number older siblings

Statistical metric: adjusted prevalence ratio
Statistical metric description: Longitudinally, generalised estimating equations (GEEs) with a log link function were used to obtain prevalence ratios (PRs). GEEs take into account the correlation between repeated measurements in the same individual. An m-dependent correlation structure was used: m=7 for the other outcome measures. An interaction term with age was included in the GEE model to allow the association between maternal use of supplements and the outcomes to vary with age. The PRs were the prevalence of respiratory outcomes in the exposed groups (folic acid only, pre-natal vitamins, and multivitamins or vitamin B complex) versus the prevalence of respiratory outcomes in the unexposed group (no FACSs). We also performed these analyses with exposure to any folic acid (three exposed groups together) versus no FACSs. In addition, we divided the children into three groups according to maternal folic acid use in trimesters. Because maternal allergy was considered to be a potential effect modifier, the analyses were repeated, stratified on maternal allergy, and interaction between maternal allergy and maternal use of supplements was tested. Maternal education, maternal allergy, maternal smoking during pregnancy and number of older siblings were included in the statistical models as confounders as the combination of these variables changed some of the associations by >5%. Furthermore, the prevalence of these variables differed substantially between the four exposure groups.

Endpoints: Frequent asthma symptoms
Adjustment factors:
Statistical metric: prevalence ratio
Statistical metric description: Longitudinally, generalised estimating equations (GEEs) with a log link function were used to obtain prevalence ratios (PRs). GEEs take into account the correlation between repeated measurements in the same individual. An m-dependent correlation structure was used: m=7 for the other outcome measures. An interaction term with age was included in the GEE model to allow the association between maternal use of supplements and the outcomes to vary with age. The PRs were the prevalence of respiratory outcomes in the exposed groups (folic acid only, pre-natal vitamins, and multivitamins or vitamin B complex) versus the prevalence of respiratory outcomes in the unexposed group (no FACSs). We also performed these analyses with exposure to any folic acid (three exposed groups together) versus no FACSs. In addition, we divided the children into three groups according to maternal folic acid use in trimesters. Because maternal allergy was considered to be a potential effect modifier, the analyses were repeated, stratified on maternal allergy, and interaction between maternal allergy and maternal use of supplements was tested. Maternal education, maternal allergy, maternal smoking during pregnancy and number of older siblings were included in the statistical models as confounders as the combination of these variables changed some of the associations by >5%. Furthermore, the prevalence of these variables differed substantially between the four exposure groups. The analyses with frequent asthma symptoms were performed in a group of children with frequent asthma symptoms and children without asthma symptoms. No multivariable analyses could be performed with frequent asthma symptoms because of the small numbers of children with a positive score on this outcome.

Endpoints: Eczema
Adjustment factors: maternal allergy, maternal education, maternal smoking during pregnancy, number older siblings
Statistical metric: adjusted prevalence ratio
Statistical metric description: Longitudinally, generalised estimating equations (GEEs) with a log link function were used to obtain prevalence ratios (PRs). GEEs take into account the correlation between repeated measurements in the same individual. An m-dependent correlation structure was used: m=7 for the other outcome measures. An interaction term with age was included in the GEE model to allow

the association between maternal use of supplements and the outcomes to vary with age. The PRs were the prevalence of outcomes in the exposed groups (folic acid only, pre-natal vitamins, and multivitamins or vitamin B complex) versus the prevalence of outcomes in the unexposed group (no FACSs). We also performed these analyses with exposure to any folic acid (three exposed groups together) versus no FACSs. In addition, we divided the children into three groups according to maternal folic acid use in trimesters. Because maternal allergy was considered to be a potential effect modifier, the analyses were repeated, stratified on maternal allergy, and interaction between maternal allergy and maternal use of supplements was tested. Maternal education, maternal allergy, maternal smoking during pregnancy and number of older siblings were included in the statistical models as confounders as the combination of these variables changed some of the associations by >5%. Furthermore, the prevalence of these variables differed substantially between the four exposure groups.

Endpoints: Asthma symptoms
Adjustment factors: maternal allergy, maternal education, maternal smoking during pregnancy, number older siblings
Statistical metric: adjusted prevalence ratio
Statistical metric description: Longitudinally, generalised estimating equations (GEEs) with a log link function were used to obtain prevalence ratios (PRs). GEEs take into account the correlation between repeated measurements in the same individual. An m-dependent correlation structure was used: m=5 for the outcome measure (frequent) asthma symptoms. An interaction term with age was included in the GEE model to allow the association between maternal use of supplements and the outcomes to vary with age. The PRs were the prevalence of respiratory outcomes in the exposed groups (folic acid only, pre-natal vitamins, and multivitamins or vitamin B complex) versus the prevalence of respiratory outcomes in the unexposed group (no FACSs). We also performed these analyses with exposure to any folic acid (three exposed groups together) versus no FACSs. In addition, we divided the children into three groups according to maternal folic acid use in trimesters. Because maternal allergy was considered to be a potential effect modifier, the analyses were repeated, stratified on maternal allergy, and interaction between maternal allergy and maternal use of supplements was tested. Maternal education, maternal allergy, maternal smoking during pregnancy and number of older siblings were included in the statistical models as confounders as the combination of these variables changed some of the associations by >5%. Furthermore, the prevalence of these variables differed substantially between the four exposure groups.

Endpoints: Bronchial hyperresponsiveness (BHR); Sensitisation at 8 yrs
Adjustment factors: maternal allergy, maternal education, maternal smoking during pregnancy, number older siblings
Statistical metric: adjusted prevalence ratio
Statistical metric description: Log binomial regression analyses were used to obtain PRs for the associations between maternal use of FACSs and sensitisation to allergens and BHR at 8 yrs of age. The PRs were the prevalence of outcomes in the exposed groups (folic acid only, pre-natal vitamins, and multivitamins or vitamin B complex) versus the prevalence of outcomes in the unexposed group (no FACSs). We also performed these analyses with exposure to any folic acid (three exposed groups together) versus no FACSs. In addition, we divided the children into three groups according to maternal folic acid use in trimesters. Because maternal allergy was considered to be a potential effect modifier, the analyses were repeated, stratified on maternal allergy, and interaction between maternal allergy and maternal use of supplements was tested. Maternal education, maternal allergy, maternal smoking during pregnancy and number of older siblings were included in the statistical models as confounders as

the combination of these variables changed some of the associations by >5%. Furthermore, the prevalence of these variables differed substantially between the four exposure groups.

4. BINKLEY, 2011

Full citation: Binkley KE, Leaver C, Ray JG. 2011. Antenatal risk factors for peanut allergy in children. Allergy Asthma Clin Immunol 7: 17.

Funding: Supported by a grant-in-aid from the Division of Allergy and Clinical Immunology, St. Michael's Hospital, Toronto, Ontario, Canada

ANAPHYLAXIS CANADA REGISTRY, 2008

Age: not reported	**Study design:** Case-control (**n =** 1413)
Gender: Not reported **Ethnicities:** Unknown/Unspecified	**Country:** Canada **Region:** national **State:**
Inclusion criteria: Anaphylaxis Canada Member Survey 2007, parent or guardian of a child with a life threatening allergy	**Exclusion critieria:**

4.1. Exposure: maternal folic acid supplementation

Method	Description	Analysis
questionnaire	A self-administered, web-based questionnaire was sent to all Anaphylaxis Canada Member Survey 2007 respondents questioning folic acid supplementation before and after conception. Those with more than one child with an allergy were instructed to answer about the pregnancy when eldest child with an allergy was carried. Participants were asked to respond Yes, No, or Do not know to the following two questions: 1. At the time that the child with allergy was conceived (at the time that you actually became pregnant) was the mother of the child with allergy taking a multivitamin supplement containing folic acid or a folic acid supplement? 2. If the mother of the child was NOT taking a multivitamin supplement containing folic acid or folic acid supplement at the time that the child was conceived, did the mother start taking a supplement one once she suspected or knew that she was pregnant?	All study participants were previously registered with Anaphylaxis Canada. Groups were determined based on yes/no responses to 2 questions regarding folic acid supplementation and pregnancy. Case group comprised of parents or caregivers of a child with a peanut allergy.

Outcomes

	Outcome	Diagnostic Description
A	peanut allergy (self-reported)	Those with more than one child with an allergy were asked to respond to details in regards to their first live born child with an allergy. Peanut allergy was based on inclusion in a pre-existing database of anaphylactic patients and previously self-reported having a child with a peanut allergy.

Results

4.1.A peanut allergy

Population: Anaphylaxis Canada Registry, Member Survey 2007
Exposure: maternal folic acid supplementation
Outcome: peanut allergy
Statistical metric: crude odds ratio

Group	N	OR 95% CI (low, high)	*p*-value
Initiated a folic acid supplement before conception	817	1.48 (0.99, 2.2)	

Group	N	OR 95% CI (low, high)	*p*-value
Initiated a folic acid supplement after conception	536	0.78 (0.27, 2.24)	
Took a folic acid supplement throughout pregnancy	1232	0.53 (0.19, 1.48)	

Statistical Method(s)

Endpoints: peanut allergy
Adjustment factors:
Statistical metric: crude odds ratio
Statistical metric description: The risk of each exposure variable in pregnancy was examined in association with case status of a peanut allergy vs. control status of a shellfish allergy, and expressed as an odds ratio (OR) and 95% confidence interval (CI).

5. BOGDEN, 1994

Full citation: Bogden JD, Bendich A, Kemp FW, Bruening KS, Shurnick JH, Denny T, Baker H, Louria DB. 1994. Daily micronutrient supplements enhance delayed-hypersensitivity skin test responses in older people. Am J Clin Nutr 60(3): 437-447.

Funding: Supported by grants from Hoffmann-La Roche Inc. and the New Jersey State Commission on Cancer Research.

12 MONTH NUTRITIONAL INTERVENTION IN THE ELDERLY

Age: 69.2 (mean), from 59.0-85.0 years	**Study design:** Controlled trial (**n =** 56)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United States **Region:** **State:** New Jersey
Inclusion criteria: healthy, independently living senior citizens	**Exclusion critieria:** alcoholism or drug abuse, any past or current malignancy except basal or squamous cell skin cancers, current infectious or inflammatory disease, dementia, malnutrition as determined by clinical judgment or a recent weight loss of >/= 10 kg, use of medications known to influence the immune system (steroids, estrogens, cyclosporin, and antineoplastic agents), vitamin supplement use in the past 3 months

5.1. Exposure: Micronutrient supplementation for 12 months

Method	Description	Analysis
treatment intervention	Theragran M micronutrient supplement including 0.4 mg/day (or 400 ug/day) of folic acid given for one year, plus other micronutrients. Theragran M supplement contained: Vitamin A (1000 RE, ug), beta-Carotene (0.75 mg), Vitamin C (90 mg), Vitamin E (20 alpha-TE, mg), Vitamin D (10 ug), Thiamin mononitrate (3 mg), Riboflavin (3.4 mg), Niacin (30 mg), Vitamin B-6 (3 mg), VitaminB-12 (9 ug), Folic acid (0.4 mg), Pantothenic acid (10 mg), Biotin (35 ug), Zinc (15 mg), Iodine (150 ug), Iron (27 mg), Copper (2 mg), Selenium (10 ug), Manganese (5 mg), Chromium (15 ug), Molybdenum (15 ug), Magnesium (100 mg), Calcium (40 mg), Phosphorus (31 mg)	Dietary assessment and blood concentrations also measured

Outcomes

	Outcome	Diagnostic Description
A	Delayed-Hypersensitivity Skin Test, number of Positive Responses (medical professional or test)	DHST responses to seven recall antigens were assessed by using the Merieux Multitest CMI skin test antigen applicator as well as control injection. Then at 0, 6 or 12 months, subjects returned 48 +/- 2 hours later for duplicate independent readings of skin test responses to the 7 recall antigens used Reactions were assessed 48 ± 2 h after injection by measuring mean induration diameter (mm). Induration of >/= 2 mm was considered a positive reaction. Data are reported as the number of positive responses to the seven antigens administered and the sum of induration for positive responses
B	Delayed-Hypersensitivity Skin Test, Total Induration (medical professional or test)	DHST responses to seven recall antigens were assessed by using the Merieux Multitest CMI skin test antigen applicator as well as control injection. Then at 0, 6 or 12 months, subjects returned 48 +/- 2 hours later for duplicate independent readings of skin test responses to the 7 recall antigens used. Reactions were assessed 48 ± 2 h after injection by measuring mean induration diameter (mm). Induration of >/= 2 mm was considered a positive reaction. Data are reported as the number of positive responses to the seven antigens administered and the sum of induration for positive responses.

Results

5.1.A Delayed-Hypersensitivity Skin Test, number of Positive Responses

Population: Elderly Population, NJ, USA
Exposure: Micronutrient supplementation for 12 months

Outcome: Delayed-Hypersensitivity Skin Test, number of Positive Responses
Statistical metric: Wilcoxon Test

Group	N	Wilcoxon Test 95% CI (low, high)	*p*-value
Placebo, 0 months - all	26	-	
Placebo, 6 months - all	26	-	
Placebo, 12 months - all	26	-	
Micronutrient, 0 months - all	29	-	
Micronutrient, 6 months - all	29	-	0.05
Micronutrient, 12 months - all	29	-	0.05
Placebo, 0 months - female	19	-	
Placebo, 6 months - female	19	-	
Placebo, 12 months - female	19	-	
Micronutrient, 0 months - female	18	-	
Micronutrient, 6 months - female	18	-	0.05
Micronutrient, 12 months - female	18	-	0.05
Placebo, 0 months - male	7	-	
Placebo, 6 months - male	7	-	
Placebo, 12 months - male	7	-	
Micronutrient, 0 months - male	11	-	
Micronutrient, 6 months - male	11	-	0.05
Micronutrient, 12 months - male	11	-	0.05

5.1.B Delayed-Hypersensitivity Skin Test, Total Induration

Population: Elderly Population, NJ, USA
Exposure: Micronutrient supplementation for 12 months
Outcome: Delayed-Hypersensitivity Skin Test, Total Induration
Statistical metric: Wilcoxon Test

Group	N	Wilcoxon Test 95% CI (low, high)	*p*-value
Placebo, 0 months - all	26	-	
Placebo, 6 months - all	26	-	
Placebo, 12 months - all	26	-	
Micronutrient, 0 months - all	29	-	
Micronutrient, 6 months - all	29	-	0.05
Micronutrient, 12 months - all	29	-	0.05
Placebo, 0 months - female	19	-	
Placebo, 6 months - female	19	-	
Placebo, 12 months - female	19	-	
Micronutrient, 0 months - female	18	-	
Micronutrient, 6 months - female	18	-	0.05
Micronutrient, 12 months - female	18	-	0.05
Placebo, 0 months - male	7	-	
Placebo, 6 months - male	7	-	
Placebo, 12 months - male	7	-	
Micronutrient, 0 months - male	11	-	
Micronutrient, 6 months - male	11	-	
Micronutrient, 12 months - male	11	-	

Statistical Method(s)

Endpoints: Delayed-Hypersensitivity Skin Test, Total Induration; Delayed-Hypersensitivity Skin Test, number of Positive Responses
Adjustment factors:
Statistical metric: Wilcoxon Test
Statistical metric description: Within-group DHST results (induration and number of positive responses) were compared with pretreatment values by using paired a' tests and the Wilcoxon signed-rank test.

6. CHRISTIAN, 2008

Full citation: Christian P, Darmstadt GL, Wu L, Khatry SK, Leclerq SC, Katz J, West KP, Jr., Adhikari RK. 2008. The effect of maternal micronutrient supplementation on early neonatal morbidity in rural Nepal: a randomised, controlled, community trial. Arch Dis Child 93(8): 660-664.

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PREGNANT WOMEN IN RURAL NEPAL

Age: 6 weeks of age	**Study design:** Controlled trial (**n =** 3927)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Nepal **Region:** **State:** District of Sarlahi
Inclusion criteria: Birth assessment data available, Live births, urine-based b-hCG test, reported being amenstrual in the past 30 days	**Exclusion critieria:**

6.1. Exposure: Maternal Supplementation with Folic Acid during Pregnancy and until 3 months Postpartum

Method	Description	Analysis
treatment regimen	Exposure as supplemental treatment as either (1) 400 ug folic acid, (2) folic acid plus 60 mg iron, (3) folic acid plus iron plus 30 mg zinc, and (4) multiple micronutrients (folic acid,iron, zinc, 10 mg vitamin D, 10 mg vitamin E, 1.6 mg vitamin B-1, 1.8 mg vitamin B-2, 20 mg niacin, 2.2 mg vitamin B-6, 2.6 mg vitamin B-12, 100 mg vitamin C, 65 mg vitamin K, 2 mg copper and 100 mg magnesium) all given with 1000 mg retinol equivalents (RE) vitamin A, and all compared to vitamin A alone as the control, on birth weight and infant survival. Supplementation began in the week following the detection of pregnancy and continued during pregnancy through to 3 months postpartum.	delivery of supplements twice a week by female workers to mothers

Outcomes

	Outcome	Diagnostic Description
A	Acute lower respiratory infection (ALRI) until 6 weeks (medical professional or test)	Determined during birth assessments; acute lower respiratory infection (ALRI) defined as: Respiratory rate >60 and chest indrawing on at least 2 days. Trained workers showed video training of rapid breathing and chest indrawing; symptoms of acute lower respiratory infection (and other morbidity) assessed until 6 weeks of age.

Results

6.1.A Acute lower respiratory infection (ALRI) until 6 weeks

Population: Newborns of supplemented mothers in rural Nepal
Exposure: Maternal Supplementation with Folic Acid during Pregnancy and until 3 months Postpartum
Outcome: Acute lower respiratory infection (ALRI) until 6 weeks
Statistical metric: crude odds ratio

Group	N	OR 95% CI (low, high)	*p*-value
Control	-	1.0	
Folic Acid	-	0.38 (0.08, 1.82)	0.23
Iron plus Folic Acid	-	0.94 (0.3, 2.9)	0.91
Iron plus Folic Acid plus zinc	-	0.51 (0.1, 2.52)	0.41
Multiple micronutrients	-	0.49 (0.13, 1.87)	0.3

Statistical Method(s)

Endpoints: Acute lower respiratory infection (ALRI) until 6 weeks
Adjustment factors: cluster randomization
Statistical metric: crude odds ratio
Statistical metric description: Data from the 10-day morbidity and birth assessments were examined as percentages. The effect of micronutrient supplementation on 10-day morbidity was analysed using the generalised estimating equations (GEE) logistic regression model with supplementation group as an indicator variable and the control group as the reference, and each of the morbidities as the outcome.14 GEE analysis was used to adjust for cluster randomisation. Similar analyses were conducted using morbidity data collected at 6 weeks of age.

7. DOBÓ, 1998

Full citation: Dobó M and Czeizel AE. 1998. Long-term somatic and mental development of children after periconceptional multivitamin supplementation. Eur J Pediatr 157(9): 719-723.

Funding: none reported

HUNGARIAN OPTIMAL FAMILY PLANNING PROGRAMME (HOFPP), 1984-1992

Age: 2.0-6.0 years	**Study design:** Controlled trial (**n =** 625)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Hungary **Region:** national **State:**
Inclusion criteria: children who completed 2nd year of life between certain months/years, children who participated in the short-term follow up study, children whose mothers had full periconceptual supplementation, children whose mothers participated in OFPP	**Exclusion critieria:** death, declined to participate, incomplete examination, lost to follow up, severe congenital anomalies

7.1. Exposure: Maternal periconceptual Multivitamin vs Trace Elements supplementation

Method	Description	Analysis
treatment	randomly assigned to multivitamin (MV) or trace element (TE) once per day for at least one month prior to planned conception and at least until the date of the second missed menstrual period	by 1) questioning, 2) charted intake of supplements, 3) counting of unused tablets

Outcomes

	Outcome	Diagnostic Description
A	Acute infections of ear (otitis) at 2 yrs (medical professional or test)	Review and evaluation of available medical documents concerning particularly diseases, operations, etc. and a general pediatric exam at age 2.
B	Acute infections of ear (otitis) at 6 yrs (medical professional or test)	Review and evaluation of available medical documents concerning particularly diseases, operations, etc. and a general pediatric exam at age 6.
C	Acute Respiratory Infections (ARI) at 2 yrs (medical professional or test)	Review and evaluation of available medical documents concerning particularly diseases, operations, etc. and a general pediatric exam at age 2.
D	Acute Respiratory Infections (ARI) at 6 yrs (medical professional or test)	Review and evaluation of available medical documents concerning particularly diseases, operations, etc. and a general pediatric exam at age 6.
E	Allergies at 2 yrs	Review and evaluation of available medical documents concerning

	Outcome	Diagnostic Description
	(medical professional or test)	particularly diseases, operations, etc. and a general pediatric exam at age 2: allergy diagnosis included asthma bronchiale, bronchitis obstructive, pseudocroup, and food allergies
F	Allergies at 6 yrs (medical professional or test)	Review and evaluation of available medical documents concerning particularly diseases, operations, etc. and a general pediatric exam at age 6: allergy diagnosis included asthma bronchiale, bronchitis obstructive, pseudocroup, and food allergies
G	Atopic dermatitis at 2 yrs (medical professional or test)	Review and evaluation of available medical documents concerning particularly diseases, operations, etc. and a general pediatric exam at age 2.
H	Atopic dermatitis at 6 yrs (medical professional or test)	Review and evaluation of available medical documents concerning particularly diseases, operations, etc. and a general pediatric exam at age 6.

Results

7.1.A Acute infections of ear (otitis) at 2 yrs

Population: Hungarian Optimal Family Planning Programme (HOFPP), 1984-1992
Exposure: Maternal periconceptual Multivitamin vs Trace Elements supplementation
Outcome: Acute infections of ear (otitis) at 2 yrs
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Trace Elements	200	-	
Multivitamin	200	-	

7.1.B Acute infections of ear (otitis) at 6 yrs

Population: Hungarian Optimal Family Planning Programme (HOFPP), 1984-1992
Exposure: Maternal periconceptual Multivitamin vs Trace Elements supplementation
Outcome: Acute infections of ear (otitis) at 6 yrs
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Trace Elements	200	-	
Multivitamin	200	-	

7.1.C Acute Respiratory Infections (ARI) at 2 yrs

Population: Hungarian Optimal Family Planning Programme (HOFPP), 1984-1992
Exposure: Maternal periconceptual Multivitamin vs Trace Elements supplementation
Outcome: Acute Respiratory Infections (ARI) at 2 yrs
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Trace Elements	200	-	
Multivitamin	200	-	

7.1.D Acute Respiratory Infections (ARI) at 6 yrs

Population: Hungarian Optimal Family Planning Programme (HOFPP), 1984-1992
Exposure: Maternal periconceptual Multivitamin vs Trace Elements supplementation

Outcome: Acute Respiratory Infections (ARI) at 6 yrs
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Trace Elements	200	-	
Multivitamin	200	-	

7.1.E Allergies at 2 yrs

Population: Hungarian Optimal Family Planning Programme (HOFPP), 1984-1992
Exposure: Maternal periconceptual Multivitamin vs Trace Elements supplementation
Outcome: Allergies at 2 yrs
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value

7.1.F Allergies at 6 yrs

Population: Hungarian Optimal Family Planning Programme (HOFPP), 1984-1992
Exposure: Maternal periconceptual Multivitamin vs Trace Elements supplementation
Outcome: Allergies at 6 yrs
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Trace Elements	200	-	
Multivitamin	200	-	

7.1.G Atopic dermatitis at 2 yrs

Population: Hungarian Optimal Family Planning Programme (HOFPP), 1984-1992
Exposure: Maternal periconceptual Multivitamin vs Trace Elements supplementation
Outcome: Atopic dermatitis at 2 yrs
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Trace Elements	200	-	
Multivitamin	200	-	

7.1.H Atopic dermatitis at 6 yrs

Population: Hungarian Optimal Family Planning Programme (HOFPP), 1984-1992
Exposure: Maternal periconceptual Multivitamin vs Trace Elements supplementation
Outcome: Atopic dermatitis at 6 yrs
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Trace Elements	200	-	
Multivitamin	200	-	

Statistical Method(s)

Endpoints: Allergies at 2 yrs; Acute infections of ear (otitis) at 6 yrs; Acute Respiratory Infections (ARI) at 2 yrs; Acute Respiratory Infections (ARI) at 6 yrs; Atopic dermatitis at 6 yrs; Acute infections of ear

(otitis) at 2 yrs; Allergies at 6 yrs; Atopic dermatitis at 2 yrs
Adjustment factors:
Statistical metric: other
Statistical metric description: Statistical evaluation consisted of the two tailed Chi-squared test and Mann-Whitney U test.

8. DUNSTAN, 2012

Full citation: Dunstan JA, West C, McCarthy S, Metcalfe J, Meldrum S, Oddy WH, Tulic MK, D'Vaz N, Prescott SL. 2012. The relationship between maternal folate status in pregnancy, cord blood folate levels, and allergic outcomes in early childhood. Allergy 67(1): 50-57.

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PREGNANT WOMEN IN WESTERN AUSTRALIA

Age: All outcomes assessed at 1 year of age	**Study design:** Prospective (**n** = 484)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Australia **Region:** **State:** Western Australia
Inclusion criteria: full-term pregnancy, mother healthy, mother non-smoker, uncomplicated pregnancy	**Exclusion critieria:** missing infant measures

8.1. Exposure: Cord blood folate

Method	Description	Analysis
serum	Cord blood was collected at delivery, serum folate measured	Folate in serum was measured using a competitive immunoassay (Immulite 2000; Siemans Medical Solutions Diagnostics, Flanders, NJ, USA).

Outcomes

	Outcome	Diagnostic Description
A	Allergic sensitization (medical professional or test)	Allergic sensitization was assessed by SPT at 1 year of age using common allergen extracts (milk, peanut, house dust mite, cat, grass, mold; Hollister-Stier Laboratories, Spokane, WA, USA), and whole egg. A wheal diameter of ‡2 mm was considered positive.
B	Allergic sensitization to food allergens (medical professional or test)	Allergic sensitization was assessed by SPT at 1 year of age using common food allergen extracts (milk, peanut; Hollister-Stier Laboratories, Spokane, WA, USA), and whole egg. A wheal diameter of ‡2 mm was considered positive.
C	Any allergic disease (medical professional or test)	physician diagnosis of IgE-mediated food allergy, eczema, or asthma
D	Eczema (medical professional or test)	A physician diagnosis of eczema was made in infants with typical skin lesions.
E	Food reactions (self-reported)	history of immediate symptoms following contact and/or ingestion; NOTE: described as Food allergy in Table 4 and food reaction in Table 3, using food reaction for consistency.
F	IgE mediated food allergy (medical professional or test)	history of immediate symptoms following contact and/or ingestion and a positive SPT to the implicated food

	Outcome	Diagnostic Description
G	Recurrent wheeze (self-reported)	A diagnosis of history of recurrent wheeze was >2 episodes of wheezing before 12 months of age.

Results

8.1.A Allergic sensitization

Population: Pregnant women in Western Australia
Exposure: Cord blood folate
Outcome: Allergic sensitization
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<50.3 nmol/l)	70	2.7 (1.1, 7.0)	0.05
Tertile 2 (50.3-75.1 nmol/l)	73	1.0 (1.0, 1.0)	
Tertile 3 (>75.1 nmol/l)	73	3.3 (1.3, 8.0)	0.05

8.1.B Allergic sensitization to food allergens

Population: Pregnant women in Western Australia
Exposure: Cord blood folate
Outcome: Allergic sensitization to food allergens
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<50.3 nmol/l)	70	2.2 (0.9, 5.6)	
Tertile 2 (50.3-75.1 nmol/l)	73	1.0	
Tertile 3 (>75.1 nmol/l)	73	1.1 (0.5, 2.4)	

8.1.C Any allergic disease

Population: Pregnant women in Western Australia
Exposure: Cord blood folate
Outcome: Any allergic disease
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<50.3 nmol/l)	81	1.4 (0.7, 2.9)	
Tertile 2 (50.3-75.1 nmol/l)	72	1.0	
Tertile 3 (>75.1 nmol/l)	76	1.8 (0.9, 3.6)	

8.1.D Eczema

Population: Pregnant women in Western Australia
Exposure: Cord blood folate
Outcome: Eczema
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<50.3 nmol/l)	81	0.9 (0.3, 2.4)	
Tertile 2 (50.3-75.1 nmol/l)	71	1.0	
Tertile 3 (>75.1 nmol/l)	74	0.8 (0.3, 2.2)	

8.1.E Food reactions

Population: Pregnant women in Western Australia
Exposure: Cord blood folate
Outcome: Food reactions
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<50.3 nmol/l)	71	1.5 (0.5, 4.4)	
Tertile 2 (50.3-75.1 nmol/l)	58	1.0	
Tertile 3 (>75.1 nmol/l)	62	2.3 (0.9, 6.5)	

8.1.F IgE mediated food allergy

Population: Pregnant women in Western Australia
Exposure: Cord blood folate
Outcome: IgE mediated food allergy
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<50.3 nmol/l)	79	1.7 (0.5, 5.6)	
Tertile 2 (50.3-75.1 nmol/l)	71	1.0	
Tertile 3 (>75.1 nmol/l)	74	2.6 (0.9, 8.1)	

8.1.G Recurrent wheeze

Population: Pregnant women in Western Australia
Exposure: Cord blood folate
Outcome: Recurrent wheeze
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<50.3 nmol/l)	77	0.8 (0.3, 2.1)	
Tertile 2 (50.3-75.1 nmol/l)	65	1.0	
Tertile 3 (>75.1 nmol/l)	67	0.9 (0.3, 2.4)	

Statistical Method(s)

Endpoints: Eczema; Any allergic disease; Recurrent wheeze; Food reactions; IgE mediated food allergy; Allergic sensitization to food allergens; Allergic sensitization
Adjustment factors: infant postnatal diet, maternal allergy
Statistical metric: adjusted odds ratio
Statistical metric description: Folate data were not generally normally distributed and were expressed as median and interquartile range (IQR). Differences between groups and between related samples were determined by appropriate tests for nonparametric lognormal according to the data distribution. Associations between normally and lognormally distributed variables were evaluated in linear models (Pearson's correlation and linear regression). Logistic regression was used to evaluate the effect of folate on binary allergic outcomes after adjusting for caloric intake or potential confounder variables (including maternal allergy, postnatal diet/feeding practices, exposure to pets, childcare, or older siblings). Folate variables were also categorized (to dummy variables based on tertiles) to determine effects of folate amounts on allergic outcomes compared with the defined reference category. Tertiles

were assigned a consecutive integer to assess the trends of association between folate status and clinical outcome in logistic regression models.

8.2. Exposure: Maternal folic acid intake from supplements in pregnancy

Method	Description	Analysis
questionnaire	semi-quantitative food frequency questionnaires (SQFFQ) in the third trimester (after 28 weeks gestation)	Converted into daily folic acid intake (microgram/day) using dosage information provided on the packaging NOTE: description of conversion to µg DFE is inconsistent with tables which use mg. Assuming tables should say µg and corrected in data entry.

Outcomes

	Outcome	Diagnostic Description
A	Allergic sensitization (medical professional or test)	Allergic sensitization was assessed by SPT at 1 year of age using common allergen extracts (milk, peanut, house dust mite, cat, grass, mold; Hollister-Stier Laboratories, Spokane, WA, USA), and whole egg. A wheal diameter of ‡2 mm was considered positive.
B	Allergic sensitization to food allergens (medical professional or test)	Allergic sensitization was assessed by SPT at 1 year of age using common food allergen extracts (milk, peanut; Hollister-Stier Laboratories, Spokane, WA, USA), and whole egg. A wheal diameter of ‡2 mm was considered positive.
C	Any allergic disease (medical professional or test)	physician diagnosis of IgE-mediated food allergy, eczema, or asthma
D	Eczema (medical professional or test)	A physician diagnosis of eczema was made in infants with typical skin lesions.
E	Food reactions (medical professional or test)	history of immediate symptoms following contact and/or ingestion
F	IgE mediated food allergy (medical professional or test)	history of immediate symptoms following contact and/or ingestion and a positive SPT to the implicated food
G	Recurrent wheeze (self-reported)	A diagnosis of history of recurrent wheeze was >2 episodes of wheezing before 12 months of age.

Results

8.2.A Allergic sensitization

Population: Pregnant women in Western Australia
Exposure: Maternal folic acid intake from supplements in pregnancy
Outcome: Allergic sensitization
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<200 µg/day)	155	1.0	
Tertile 2 (200-499 µg/day)	173	1.3 (0.8, 2.3)	
Tertile 3 (500+ µg/day)	134	1.2 (0.7, 2.1)	

8.2.B Allergic sensitization to food allergens

Population: Pregnant women in Western Australia
Exposure: Maternal folic acid intake from supplements in pregnancy
Outcome: Allergic sensitization to food allergens
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<200 µg/day)	155	1.0	
Tertile 2 (200-499 µg/day)	173	1.3 (0.7, 2.3)	
Tertile 3 (500+ µg/day)	134	1.1 (0.6, 2.0)	

8.2.C Any allergic disease

Population: Pregnant women in Western Australia
Exposure: Maternal folic acid intake from supplements in pregnancy
Outcome: Any allergic disease
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<200 µg/day)	160	1.0	
Tertile 2 (200-499 µg/day)	181	1.3 (0.8, 2.1)	
Tertile 3 (500+ µg/day)	138	1.4 (0.9, 2.4)	

8.2.D Eczema

Population: Pregnant women in Western Australia
Exposure: Maternal folic acid intake from supplements in pregnancy
Outcome: Eczema
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<200 µg/day)	161	1.0	
Tertile 2 (200-499 µg/day)	177	1.5 (1.0, 2.5)	0.05
Tertile 3 (500+ µg/day)	134	1.7 (1.0, 2.8)	0.05

8.2.E Food reactions

Population: Pregnant women in Western Australia
Exposure: Maternal folic acid intake from supplements in pregnancy
Outcome: Food reactions
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<200 µg/day)	141	1.0	
Tertile 2 (200-499 µg/day)	142	1.7 (0.9, 3.3)	
Tertile 3 (500+ µg/day)	120	1.2 (0.6, 2.3)	

8.2.F IgE mediated food allergy

Population: Pregnant women in Western Australia
Exposure: Maternal folic acid intake from supplements in pregnancy
Outcome: IgE mediated food allergy
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<200 µg/day)	158	1.0	
Tertile 2 (200-499 µg/day)	177	1.4 (0.7, 3.0)	
Tertile 3 (500+ µg/day)	134	1.1 (0.5, 2.4)	

8.2.G Recurrent wheeze

Population: Pregnant women in Western Australia
Exposure: Maternal folic acid intake from supplements in pregnancy
Outcome: Recurrent wheeze
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (<200 µg/day)	159	1.0	
Tertile 2 (200-499 µg/day)	179	0.8 (0.4, 1.7)	
Tertile 3 (500+ µg/day)	136	1.1 (0.6, 2.3)	

Statistical Method(s)

Endpoints: Any allergic disease; Recurrent wheeze; Allergic sensitization to food allergens; Allergic sensitization; Eczema; Food reactions; IgE mediated food allergy
Adjustment factors: infant postnatal diet, maternal allergy
Statistical metric: adjusted odds ratio
Statistical metric description: Folate data were not generally normally distributed and were expressed as median and interquartile range (IQR). Differences between groups and between related samples were determined by appropriate tests for nonparametric lognormal according to the data distribution. Associations between normally and lognormally distributed variables were evaluated in linear models (Pearson's correlation and linear regression). Logistic regression was used to evaluate the effect of folate on binary allergic outcomes after adjusting for caloric intake or potential confounder variables (including maternal allergy, postnatal diet/feeding practices, exposure to pets, childcare, or older siblings). Folate variables were also categorized (to dummy variables based on tertiles) to determine effects of folate amounts on allergic outcomes compared with the defined reference category. Tertiles were assigned a consecutive integer to assess the trends of association between folate status and clinical outcome in logistic regression models.

9. FARRES, 2011

Full citation: Farres MN, Shahin RY, Melek NA, El-Kabarity RH, Arafa NA. 2011. Study of Folate Status Among Egyptian Asthmatics. Internal Medicine 50(3): 205-211.

Funding: none reported

EGYPTIAN ASTHMATICS, 2009-2010

Age: 32.2 (mean)	**Study design:** Case-control (**n =** 180)
Gender: Male and Female **Ethnicities:**	**Country:** Egypt **Region:** **State:**
Inclusion criteria: no folate supplementation at time of recruitment, no history of alcohol intake	**Exclusion critieria:** current or past immunotherapy, intake of drugs which affect folate levels i.e. methotrexate, sulfonamides, and trimethoprim, presence of other associated allergic diseases or major systemic diseases, smoking

9.1. Exposure: Serum Folate by Quartile

Method	Description	Analysis
serum assay	Serum folate levels were measured using a chemiluminescent competitive immunoassay method (Immulite 1,000 Analyzer, Diagnostic Product Corp., Los Angeles, CA, USA) according to the manufacturer's instructions.	Folate analyzed by quartile

Outcomes

	Outcome	Diagnostic Description
A	Asthma (medical professional or test)	Atopic status was determined by (skin-prick test) SPT reaction to a large panel of the most common locally encountered allergens.
B	Total Serum IgE (medical professional or test)	Serum total IgE levels were measured by the ImmunoCAP system.. The normal limit of total IgE was 100 IU/mL

Results

9.1.A Asthma

Population: Egyptian Asthmatics, 2009-2010
Exposure: Serum Folate by Quartile
Outcome: Asthma
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1 (1.58 - 6.82)	-	1.0	
Q2 (6.83 - 10.81)	-	0.72 (0.26, 2.02)	0.533

Group	N	adjOR 95% CI (low, high)	*p*-value
Q3 (10.82 - 13.23)	-	1.01 (0.36, 2.84)	0.981
Q4 (13.24 - 18.57)	-	0.77 (0.28, 2.11)	0.613

9.1.B Total Serum IgE

Population: Egyptian Asthmatics, 2009-2010
Exposure: Serum Folate by Quartile
Outcome: Total Serum IgE
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1 (1.58 - 6.82)	-	1.0	
Q2 (6.83 - 10.81)	-	0.47 (0.2, 1.11)	0.085
Q3 (10.82 - 13.23)	-	0.32 (0.14, 0.76)	0.009
Q4 (13.24 - 18.57)	-	0.31 (0.13, 0.74)	0.008

Statistical Method(s)

Endpoints: Asthma; Total Serum IgE
Adjustment factors: age, sex
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic regression models were performed using quartiles of folate levels as a categorical variable, and adjusting for age and sex. A p-value of less than 0.05 was considered significant.

9.2. Exposure: Serum folate, Case vs Control

Method	Description	Analysis
assay	Serum folate levels were measured using a chemiluminescent competitive immunoassay method (Immulite 1,000 Analyzer, Diagnostic Product Corp., Los Angeles, CA, USA) according to the manufacturer's instructions.	none described

Outcomes

	Outcome	Diagnostic Description
A	Atopic/non-atopic asthmatics vs control (medical professional or test)	Atopic status was determined by SPT reaction to a large panel of the most common locally encountered allergens
B	Forced expiratory volume in 1s (FEV1) (medical professional or test)	Forced expiratory volume in 1s (FEV1): Spirometry was performed at a specialized pulmonary functions laboratory using the Flowmate V Plus spirometer (Spirometrics, Gray, ME, USA). All tests were performed in the sitting position, and the best of three consecutive readings was recorded.
C	Number of Positive Skin Test Reactions, asthmatics only	Skin prick test (SPT): Histamine (0.1%) in phosphate-buffered saline and physiologic saline were used as positive and negative controls,

	Outcome	Diagnostic Description
	(medical professional or test)	respectively. Briefly, the skin of the anterior surface of the right forearm was cleaned, and drops of each allergen extract were carefully applied approximately 3 cm apart. The epidermis was pricked carefully through each allergen extract drop, without causing any bleeding. After 20 minutes, the mean wheal diameter was calculated by adding the largest diameter to the diameter perpendicular to it, and dividing the result by two. The SPT was considered valid if the difference in mean wheal diameter between the positive and negative controls was at least 1 mm. A mean wheal diameter of at least 3 mm greater than the negative control was considered positive
D	Total Serum IgE (medical professional or test)	Serum total IgE levels were measured by the ImmunoCAP system.. The normal limit of total IgE was 100 IU/mL

Results

9.2.A Atopic/non-atopic asthmatics vs control

Population: Egyptian Asthmatics, 2009-2010
Exposure: Serum folate, Case vs Control
Outcome: Atopic/non-atopic asthmatics vs control
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Serum Folate levels	-	-	0.001

9.2.B Forced expiratory volume in 1s (FEV1)

Population: Egyptian Asthmatics, 2009-2010
Exposure: Serum folate, Case vs Control
Outcome: Forced expiratory volume in 1s (FEV1)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum Folate levels	-	-	

9.2.C Number of Positive Skin Test Reactions, asthmatics only

Population: Egyptian Asthmatics, 2009-2010
Exposure: Serum folate, Case vs Control
Outcome: Number of Positive Skin Test Reactions, asthmatics only
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum Folate levels	-	-	

9.2.D Total Serum IgE

Population: Egyptian Asthmatics, 2009-2010
Exposure: Serum folate, Case vs Control
Outcome: Total Serum IgE
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum Folate levels	-	-	

Statistical Method(s)

Endpoints: Number of Positive Skin Test Reactions, asthmatics only
Adjustment factors:
Statistical metric: correlation
Statistical metric description: Parametric data were analyzed using Student's t-test and one way analysis of variance (ANOVA) for the comparison of two and three groups, respectively.

Endpoints: Total Serum IgE
Adjustment factors: age, sex
Statistical metric: correlation
Statistical metric description: To assess the strength of the relationship between serum folate levels and other quantitative variables, Spearman's correlation coefficient was performed

Endpoints: Atopic/non-atopic asthmatics vs control
Adjustment factors:
Statistical metric: other
Statistical metric description: Data expressed as median and interquartile range (IQR) for non-parametric data... Non-parametric data were analyzed using the Mann-Whitney U and Kruskal-Wallis tests to compare two and three groups, respectively

Endpoints: Forced expiratory volume in 1s (FEV1)
Adjustment factors:
Statistical metric: correlation
Statistical metric description: Parametric data were analyzed using Student's t-test and one-way analysis of variance (ANOVA) for the comparison of two and three groups, respectively.

10. GARIBALLA, 2007

Full citation: Gariballa S, Forster S. 2007. Associations between underlying disease and nutritional status following acute illness in older people. Clin Nutr 26(4): 466-473.

Funding: This study was funded by The Health Foundation project grant.

UNITED KINGDOM HOSPITALIZED PATIENTS

Age: 77.0 (mean)	**Study design:** Controlled trial (**n =** 445)
Gender: Male and Female **Ethnicities:**	**Country:** United Kingdom **Region:** **State:**
Inclusion criteria: able to give written consent, able to swallow, medically stable, older than 65	**Exclusion critieria:** diagnosed moderate to severe dementia and malignancy, gastric surgery, in coma, living in institution, malabsorption, morbid obesity (body mass index (BMI) >/= 40, patients already on supplements, severe medical or psychiatric illness including those with liver and kidney disease, uncontrolled heart failure

10.1. Exposure: Nutritional Supplementation for 6 weeks

Method	Description	Analysis
serum	2x 200 mL each of oral nutritional supplement daily containing 100% of reference nutrient intakes for "healthy old person" for vitamins and minerals-- continued for 6 weeks Red cell folate (and plasma vitamin B12) were measured on the Architect (Abbott Laboratories) using chemiluminescent microparticle immunoassay technology.	The inter-assay coefficients of variation (c.v.) for red cell folate (normal reference range >320 nmol/L) was 12.6%

Outcomes

	Outcome	Diagnostic Description
A	Chest Infection (not reported)	n/a

Results

10.1.A Chest Infection

Population: United Kingdom Hospitalized Patients, folate intervention
Exposure: Nutritional Supplementation for 6 weeks
Outcome: Chest Infection
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	-	-	
Supplementation	-	-	

Statistical Method(s)

Endpoints: Chest Infection
Adjustment factors: baseline nutritional status
Statistical metric: other
Statistical metric description: treatment effect; Nutritional status at 6 weeks was analyzed using an analysis of covariance model, with baseline value and treatment group as co-variates

11. GARIBALLA, 2013

Full citation: Gariballa S, Afandi B, Haltem MA, Yassin J, Alessa A. 2013. Effect of antioxidants and B-group vitamins on risk of infections in patients with type 2 diabetes mellitus. Nutrients 5(3): 711-724.

Funding: none reported

TYPE 2 DIABETES POPULATION IN UNITED ARAB EMIRATES (UAE)

Age: 51.0 (mean)	**Study design:** Controlled trial (**n =** 85)
Gender: Male and Female **Ethnicities:**	**Country:** United Arab Emirates **Region:** **State:**
Inclusion criteria: age 18 and over, with type 2 diabetes	**Exclusion critieria:** participants taking dietary supplements, participants unable to give informed written consent, participants with severe chronic clinical or psychiatric disease, participation in other intervention trials

11.1. Exposure: Folate Supplementation with other vitamins

Method	Description	Analysis
supplementation	capsule of antioxidant vitamins (221 mg of α-tocopherol and 167 mg of vitamin C) and B-group vitamins (1.67 mg folic acid, 1.67 mg vitamin B-2, 20 mg vitamin B-6, 0.134 mg vitamin B-12) or an identical placebo daily for 90 days *plasma folate also measured at baseline and at 3 months in both groups (placebo vs intervention) and were significantly different at 3 months (p=0.001) ["Fasting blood samples were drawn into 2 vacutainer tubes, containing potassium EDTA as anticoagulant. The samples were thoroughly mixed at room temperature and immediately transferred to the laboratory. Both tubes were centrifuged immediately for 10 min at 4000 rotations/min. Plasma and serum were collected and stored at −80C for future determinations of vitamins."]	intervention, fasting 10 mL of blood taken to determine [serum and plasma] folate status at baseline and after 3 months

Outcomes

	Outcome	Diagnostic Description
A	Number of Infections at 12 months	Infection incidence data were obtained from symptoms and

	Outcome	Diagnostic Description
	(self-reported)	treatment checklist diaries recorded during fact-to-face interviews at 3 months and through telephone interviews at 12-month follow-up. Using the infection incidence diary record, the research officer then assigned a specific diagnosis and duration of illness. Standard criteria were used to diagnose common adult infectious illnesses (upper respiratory tract, lower respiratory tract infection, influenza-like illnesses, sore throat, sinusitis, skin infections, eye and ear infections, gastrointestinal infections and urinary tract infections.
B	Number of Infections at 3 months (self-reported)	Infection incidence data were obtained from symptoms and treatment checklist diaries recorded during fact-to-face interviews at 3 months and through telephone interviews at 12-month follow-up. Using the infection incidence diary record, the research officer then assigned a specific diagnosis and duration of illness. Standard criteria were used to diagnose common adult infectious illnesses (upper respiratory tract, lower respiratory tract infection, influenza-like illnesses, sore throat, sinusitis, skin infections, eye and ear infections, gastrointestinal infections and urinary tract infections.

Results

11.1.A Number of Infections at 12 months

Population: Type 2 Diabetes Intervention Trial in the United Arab Emirates (UAE)
Exposure: Folate Supplementation with other vitamins
Outcome: Number of Infections at 12 months
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	-	-	
Intervention	-	-	0.488

11.1.B Number of Infections at 3 months

Population: Type 2 Diabetes Intervention Trial in the United Arab Emirates (UAE)
Exposure: Folate Supplementation with other vitamins
Outcome: Number of Infections at 3 months
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	-	-	
Intervention	-	-	0.623

Statistical Method(s)

Endpoints: Number of Infections at 3 months
Adjustment factors: age, body mass index (BMI), duration of diabetes, treatment of diabetes
Statistical metric: other
Statistical metric description: % occurrences of infection

Endpoints: Number of Infections at 12 months
Adjustment factors: body mass index (BMI), duration of diabetes, sex, treatment of diabetes

Statistical metric: other
Statistical metric description: % occurrences of infections

12. GRANELL, 2008

Full citation: Granell R, Heron J, Lewis S, Davey Smith G, Sterne JA, Henderson J. 2008. The association between mother and child MTHFR C677T polymorphisms, dietary folate intake and childhood atopy in a population-based, longitudinal birth cohort. Clin Exp Allergy 38(2): 320-328.

Funding: The UK Medical Research Council, the Wellcome Trust and the University of Bristol provide core support for ALSPAC. The SPTs were funded by a grant from the British Lung Foundation.

CHILDREN IN THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN (ALSPAC), 1991-2000

Age: All outcomes assessed at 7 years of age	**Study design:** Prospective (**n =** 5364)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United Kingdom **Region:** Avon County **State:**
Inclusion criteria: complete data on atopy and MTHFR C677T genotype	**Exclusion critieria:**

12.1. Exposure: Dietary folate intake of children at age 3

Method	Description	Analysis
questionnaire	ug/day folate intake estimated from the FFQ	no mention

Outcomes

	Outcome	Diagnostic Description
A	Childhood Atopy, all subjects (medical professional or test)	positive response to question at 91 months... Atopic asthma was defined similarly PLUS any positive SPT response and non-atopic asthma was characterized by the absence of a positive skin test response at age 7 years
B	Childhood Atopy, subset with genotypes (medical professional or test)	per 100 ug/day; skin prick test

Results

12.1.A Childhood Atopy, all subjects

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Dietary folate intake of children at age 3
Outcome: Childhood Atopy, all subjects
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	-	
Atopy cases	1075	-	0.36

12.1.B Childhood Atopy, subset with genotypes

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Dietary folate intake of children at age 3
Outcome: Childhood Atopy, subset with genotypes
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	1.0 (1.0, 1.0)	
Atopy cases	1075	0.86 (0.71, 1.05)	

Statistical Method(s)

Endpoints: Childhood Atopy, all subjects
Adjustment factors:
Statistical metric: t-test
Statistical metric description:

Endpoints: Childhood Atopy, subset with genotypes
Adjustment factors: maternal education, maternal social class, postnatal parental smoking, smoking prenatal
Statistical metric: adjusted odds ratio
Statistical metric description: We first analysed relationships between allergy and atopy, respectively, in the mothers and children with dietary determinants of folate status and possible confounders, including maternal age, mothers' smoking during and after pregnancy, mothers' education and social class, and the gender of the child.

12.2. Exposure: Dietary folate intake of children at age 7

Method	Description	Analysis
questionnaire	individual 3-day food frequency questionnaires	no mention

Outcomes

	Outcome	Diagnostic Description
A	Childhood Atopy, all subjects (self-reported)	positive response to question at 91 months... Atopic asthma was defined similarly PLUS any positive SPT response and non-atopic asthma was characterized by the absence of a positive skin test response at age 7 years
B	Childhood Atopy, subset with genotypes (medical professional or test)	per 100 ug/day; skin prick test

Results

12.2.A Childhood Atopy, all subjects

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Dietary folate intake of children at age 7

Outcome: Childhood Atopy, all subjects
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	-	
Atopy cases	1075	-	0.29

12.2.B Childhood Atopy, subset with genotypes

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Dietary folate intake of children at age 7
Outcome: Childhood Atopy, subset with genotypes
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	1.0 (1.0, 1.0)	
Atopy cases	1075	0.91 (0.78, 1.07)	

Statistical Method(s)

Endpoints: Childhood Atopy, all subjects
Adjustment factors:
Statistical metric: t-test
Statistical metric description:

Endpoints: Childhood Atopy, subset with genotypes
Adjustment factors: maternal education, maternal social class, postnatal parental smoking, smoking prenatal
Statistical metric: adjusted odds ratio
Statistical metric description: We first analysed relationships between allergy and atopy, respectively, in the mothers and children with dietary determinants of folate status and possible confounders, including maternal age, mothers' smoking during and after pregnancy, mothers' education and social class, and the gender of the child.

12.3. Exposure: Dietary folate intake of pregnant mothers (32 weeks)

Method	Description	Analysis
questionnaire	Dietary folate intake (mg/day) of mothers at 32 weeks of pregnancy (excluding supplements)...were estimated from individual 3-day food frequency questionnaires in ug/day	n/a

Outcomes

	Outcome	Diagnostic Description
A	Childhood Atopy, all subjects (medical professional or test)	positive response to question at 91 months... Atopic asthma was defined similarly PLUS any positive SPT response and non-atopic asthma was characterized by the absence of a positive skin test

	Outcome	Diagnostic Description
		response at age 7 years
B	Childhood Atopy, subset with genotypes (medical professional or test)	per 100 ug/day; skin prick test

Results

12.3.A Childhood Atopy, all subjects

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Dietary folate intake of pregnant mothers (32 weeks)
Outcome: Childhood Atopy, all subjects
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	-	
Atopy cases	1075	-	0.91

12.3.B Childhood Atopy, subset with genotypes

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Dietary folate intake of pregnant mothers (32 weeks)
Outcome: Childhood Atopy, subset with genotypes
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	1.0 (1.0, 1.0)	
Atopy cases	1075	0.98 (0.88, 1.1)	

Statistical Method(s)

Endpoints: Childhood Atopy, all subjects
Adjustment factors:
Statistical metric: t-test
Statistical metric description:

Endpoints: Childhood Atopy, subset with genotypes
Adjustment factors: maternal education, maternal social class, mothers' folate supplementation at 32 weeks, postnatal parental smoking, smoking prenatal
Statistical metric: adjusted odds ratio
Statistical metric description: We first analysed relationships between allergy and atopy, respectively, in the mothers and children with dietary determinants of folate status and possible confounders, including maternal age, mothers' smoking during and after pregnancy, mothers' education and social class, and the gender of the child.

12.4. Exposure: Folate supplement use of pregnant mothers (18 weeks)

Method	Description	Analysis
questionnaires	The reported use of folate supplements by the mother was obtained from self-completion questionnaires administered at 18 and 32 weeks of pregnancy.	n/a

Outcomes

	Outcome	Diagnostic Description
A	Childhood Atopy, all subjects (medical professional or test)	positive response to question at 91 months... Atopic asthma was defined similarly PLUS any positive SPT response and non-atopic asthma was characterized by the absence of a positive skin test response at age 7 years
B	Childhood Atopy, subset with genotypes (medical professional or test)	per 100 ug/day; skin prick test

Results

12.4.A Childhood Atopy, all subjects

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Folate supplement use of pregnant mothers (18 weeks)
Outcome: Childhood Atopy, all subjects
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	-	
Atopy cases	1075	-	0.89

12.4.B Childhood Atopy, subset with genotypes

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Folate supplement use of pregnant mothers (18 weeks)
Outcome: Childhood Atopy, subset with genotypes
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	1.0 (1.0, 1.0)	
Atopy cases	1075	0.99 (0.78, 1.25)	

Statistical Method(s)

Endpoints: Childhood Atopy, all subjects
Adjustment factors:
Statistical metric: other
Statistical metric description:

Endpoints: Childhood Atopy, subset with genotypes
Adjustment factors: maternal education, maternal social class, mothers folate intake at 32 weeks,

postnatal parental smoking, smoking prenatal
Statistical metric: adjusted odds ratio
Statistical metric description: We first analysed relationships between allergy and atopy, respectively, in the mothers and children with dietary determinants of folate status and possible confounders, including maternal age, mothers' smoking during and after pregnancy, mothers' education and social class, and the gender of the child.

12.5. Exposure: Folate supplement use of pregnant mothers (32 weeks)

Method	Description	Analysis
questionnaire	Additionally, the reported use of folate supplements by the mother was obtained from self-completion questionnaires administered at 18 and 32 weeks of pregnancy	n/a

Outcomes

	Outcome	Diagnostic Description
A	Childhood Atopy, all subjects (medical professional or test)	positive response to question at 91 months... Atopic asthma was defined similarly PLUS any positive SPT response and non-atopic asthma was characterized by the absence of a positive skin test response at age 7 years
B	Childhood Atopy, subset with genotypes (medical professional or test)	per 100 ug/day; skin prick test

Results

12.5.A Childhood Atopy, all subjects

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Folate supplement use of pregnant mothers (32 weeks)
Outcome: Childhood Atopy, all subjects
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	-	
Atopy cases	1075	-	0.07

12.5.B Childhood Atopy, subset with genotypes

Population: Children in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Folate supplement use of pregnant mothers (32 weeks)
Outcome: Childhood Atopy, subset with genotypes
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Controls (children w/o atopy)	4289	1.0 (1.0, 1.0)	
Atopy cases	1075	1.15 (0.98, 1.35)	

Statistical Method(s)

Endpoints: Childhood Atopy, all subjects
Adjustment factors:
Statistical metric: other
Statistical metric description:

Endpoints: Childhood Atopy, subset with genotypes
Adjustment factors: maternal education, maternal social class, mothers folate intake at 32 weeks, postnatal parental smoking, smoking prenatal
Statistical metric: adjusted odds ratio
Statistical metric description: We first analysed relationships between allergy and atopy, respectively, in the mothers and children with dietary determinants of folate status and possible confounders, including maternal age, mothers' smoking during and after pregnancy, mothers' education and social class, and the gender of the child.

MOTHERS IN THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN (ALSPAC), 1991-2000

Age: 28.4 (mean)	**Study design:** Cross-sectional (**n =** 7356)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** United Kingdom **Region:** Avon County **State:**
Inclusion criteria: complete data on atopy and MTHFR C677T genotype	**Exclusion critieria:**

12.6. Exposure: Dietary folate intake of pregnant mothers (32 weeks)

Method	Description	Analysis
questionnaire	Dietary folate intake (mg/day) of mothers at 32 weeks of pregnancy (excluding supplements)...were estimated from individual 3-day food frequency questionnaires in ug/day.	n/a

Outcomes

	Outcome	Diagnostic Description
A	Asthma and/or allergy, all subjects (self-reported)	History of asthma and/or allergy in the mother was obtained from a self-completion questionnaire administered during pregnancy.
B	Asthma and/or allergy, subset with genotypes (self-reported)	per 100 ug/day; History of asthma and/or allergy in the mother was obtained from a self-completion questionnaire administered during pregnancy.

Results

12.6.A Asthma and/or allergy, all subjects

Population: Mothers in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Dietary folate intake of pregnant mothers (32 weeks)
Outcome: Asthma and/or allergy, all subjects
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Controls (mothers w/o atopy)	4048	-	
Asthma and/or allergy	3308	-	0.02

12.6.B Asthma and/or allergy, subset with genotypes

Population: Mothers in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Dietary folate intake of pregnant mothers (32 weeks)
Outcome: Asthma and/or allergy, subset with genotypes
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Controls (mothers w/o atopy)	4048	1.0 (1.0, 1.0)	
Asthma and/or allergy	3308	1.03 (0.95, 1.12)	

Statistical Method(s)

Endpoints: Asthma and/or allergy, all subjects
Adjustment factors:
Statistical metric: t-test
Statistical metric description:

Endpoints: Asthma and/or allergy, subset with genotypes
Adjustment factors: maternal education, maternal social class, mothers' folate supplementation at 32 weeks, postnatal parental smoking, smoking prenatal
Statistical metric: adjusted odds ratio
Statistical metric description: We first analysed relationships between allergy and atopy, respectively, in the mothers and children with dietary determinants of folate status and possible confounders, including maternal age, mothers' smoking during and after pregnancy, mothers' education and social class, and the gender of the child.

12.7. Exposure: Folate supplement use of pregnant mothers (18 weeks)

Method	Description	Analysis
questionnaires	The reported use of folate supplements by the mother was obtained from self-completion questionnaires administered at 18 and 32 weeks of pregnancy.	n/a

Outcomes

	Outcome	Diagnostic Description
A	Asthma and/or allergy, all subjects (self-reported)	History of asthma and/or allergy in the mother was obtained from a self-completion questionnaire administered during pregnancy.
B	Asthma and/or allergy, subset with genotypes (self-reported)	History of asthma and/or allergy in the mother was obtained from a self-completion questionnaire administered during pregnancy.

Results

12.7.A Asthma and/or allergy, all subjects

Population: Mothers in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Folate supplement use of pregnant mothers (18 weeks)
Outcome: Asthma and/or allergy, all subjects
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Controls (mothers w/o atopy)	4048	-	
Asthma and/or allergy	3308	-	0.003

12.7.B Asthma and/or allergy, subset with genotypes

Population: Mothers in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Folate supplement use of pregnant mothers (18 weeks)
Outcome: Asthma and/or allergy, subset with genotypes
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Controls (mothers w/o atopy)	4048	1.0 (1.0, 1.0)	
Asthma and/or allergy	3308	1.16 (0.97, 1.37)	

Statistical Method(s)

Endpoints: Asthma and/or allergy, subset with genotypes
Adjustment factors: maternal education, maternal social class, mothers folate intake at 32 weeks, postnatal parental smoking, smoking prenatal
Statistical metric: adjusted odds ratio
Statistical metric description: We first analysed relationships between allergy and atopy, respectively, in the mothers and children with dietary determinants of folate status and possible confounders, including maternal age, mothers' smoking during and after pregnancy, mothers' education and social class, and the gender of the child.

Endpoints: Asthma and/or allergy, all subjects
Adjustment factors:
Statistical metric: other
Statistical metric description:

12.8. Exposure: Folate supplement use of pregnant mothers (32 weeks)

Method	Description	Analysis
questionnaire	Additionally, the reported use of folate supplements by the mother was obtained from self-completion questionnaires administered at 18 and 32 weeks of pregnancy.	n/a

Outcomes

	Outcome	Diagnostic Description
A	Asthma and/or allergy, all subjects (self-reported)	History of asthma and/or allergy in the mother was obtained from a self-completion questionnaire administered during pregnancy.
B	Asthma and/or allergy, subset with genotypes (self-reported)	History of asthma and/or allergy in the mother was obtained from a self-completion questionnaire administered during pregnancy.

Results

12.8.A Asthma and/or allergy, all subjects

Population: Mothers in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Folate supplement use of pregnant mothers (32 weeks)
Outcome: Asthma and/or allergy, all subjects
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Controls (mothers w/o atopy)	4048	-	
Asthma and/or allergy	3308	-	0.02

12.8.B Asthma and/or allergy, subset with genotypes

Population: Mothers in the Avon Longitudinal Study of Parents and Children (ALSPAC), 1991-2000
Exposure: Folate supplement use of pregnant mothers (32 weeks)
Outcome: Asthma and/or allergy, subset with genotypes
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Controls (mothers w/o atopy)	4048	1.0 (1.0, 1.0)	
Asthma and/or allergy	3308	1.09 (0.96, 1.22)	

Statistical Method(s)

Endpoints: Asthma and/or allergy, all subjects
Adjustment factors:

Statistical metric: other
Statistical metric description:

Endpoints: Asthma and/or allergy, subset with genotypes
Adjustment factors: maternal education, maternal social class, mothers folate intake at 32 weeks, postnatal parental smoking, smoking prenatal
Statistical metric: adjusted odds ratio
Statistical metric description: We first analysed relationships between allergy and atopy, respectively, in the mothers and children with dietary determinants of folate status and possible confounders, including maternal age, mothers' smoking during and after pregnancy, mothers' education and social class, and the gender of the child.

13. HAMER, 2009

Full citation: Hamer DH, Sempertegui F, Estrella B, Tucker KL, Rodriguez A, Egas J, Dallal GE, Selhub J, Griffiths JK, Meydani SN. 2009. Micronutrient deficiencies are associated with impaired immune response and higher burden of respiratory infections in elderly Ecuadorians. J Nutr 139(1): 113-119.

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ECUADORIAN ELDERLY MICRONUTRIENT STATUS

Age: 65.0-97.0 years	**Study design:** Cross-sectional (**n =** 349)
Gender: Male and Female **Ethnicities:**	**Country:** Ecuador **Region:** Northwestern Quito **State:**
Inclusion criteria: able to give written consent, mental competence, older than 65	**Exclusion critieria:**

13.1. Exposure: Serum folate

Method	Description	Analysis
serum	A 10-mL venous blood sample was drawn from each participant, after an overnight fast, into an EDTA-treated tube without anticoagulant. Samples were immediately transported to the laboratory and centrifuged.	Serum or plasma was collected in plastic tubes, frozen at -20C, and shipped to Boston, MA for analysis of B vitamins (including folate)

Outcomes

	Outcome	Diagnostic Description
A	Interferon-gamma (INF-g) (medical professional or test)	We measured PHA-stimulated interferon-g (IFNg) production in culture supernatant (25,26) using commercially available ELISA kits (R&D Systems).
B	Interleukin-2 (IL-2) (medical professional or test)	We measured PHA-stimulated interleukin-2 (IL-2) production in culture supernatant (25,26) using commercially available ELISA kits (R&D Systems).

Results

13.1.A Interferon-gamma (INF-g)

Population: Ecuadorian elderly micronutrient status
Exposure: Serum folate
Outcome: Interferon-gamma (INF-g)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Serum folate	-	112.5	0.41

13.1.B Interleukin-2 (IL-2)

Population: Ecuadorian elderly micronutrient status
Exposure: Serum folate
Outcome: Interleukin-2 (IL-2)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Serum folate	-	-1.1	0.99

Statistical Method(s)

Endpoints: Interleukin-2 (IL-2); Interferon-gamma (INF-g)
Adjustment factors: age, body mass index (BMI), sex
Statistical metric: adjusted beta
Statistical metric description: Multiple linear or logistic regression models were developed to assess the relationship between micronutrient concentrations likely to have an effect on immune function.. Response variables were log transformed to improve model fit, as needed.

14. HUSEMOEN, 2006

Full citation: Husemoen LL, Toft U, Fenger M, Jorgensen T, Johansen N, Linneberg A. 2006. The association between atopy and factors influencing folate metabolism: is low folate status causally related to the development of atopy? Int J Epidemiol 35(4): 954-961.

Funding: The Inter99 study was supported by The Danish Medical Research Council, The Danish Centre for Evaluation and Health Technology Assessment, Novo Nordisk, Copenhagen County, The Danish Heart Foundation, The Danish Pharmaceutical Association, Augustinus foundation, Ib Henriksens foundation, and Beckett foundation.

INTER99 STUDY, DENMARK

Age: aged 30–60 years	**Study design:** Cross-sectional (**n =** 1671)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Denmark **Region:** Southwestern Copenhagen County **State:** Copenhagen County
Inclusion criteria:	**Exclusion critieria:** alcoholism or drug abuse, linguistic problems

14.1. Exposure: Dietary folate intake

Method	Description	Analysis
questionnaire	extensive food frequency questionnaire (FFQ) of previous month used	The food consumption quantity was obtained by multiplying the frequency of consumption of each unit of food by standard portion sizes

Outcomes

	Outcome	Diagnostic Description
A	Atopy (medical professional or test)	Measurement of atopy was performed by using the ADVIA Centaur Allergy Screen (AS) assay
B	Atopy (per 100 ug/day of folate intake) (medical professional or test)	Measurement of atopy was performed by using the ADVIA Centaur Allergy Screen (AS) assay (per 100 ug/day of folate intake)

Results

14.1.A <u>Atopy</u>

Population: Inter99 Study, Denmark
Exposure: Dietary folate intake
Outcome: Atopy
Statistical metric: Wilcoxon Test

Group	N	Wilcoxon Test 95% CI (low, high)	*p*-value
Folate intake (no Atopy)	-	-	
Folate intake (yes Atopy)	-	-	

14.1.B Atopy (per 100 ug/day of folate intake)

Population: Inter99 Folate and Atopy; Denmark
Exposure: Dietary folate intake
Outcome: Atopy (per 100 ug/day of folate intake)
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Folate intake (no Atopy)	-	1.0	
Folate intake (yes Atopy)	-	0.91 (0.82, 1.01)	0.07

Statistical Method(s)

Endpoints: Atopy
Adjustment factors: age, sex, smoking, total energy intake
Statistical metric: Wilcoxon Test
Statistical metric description: Comparisons between atopic and non-atopic individuals... were done by the Wilcoxon two-sample test, the Kruskall–Wallis test for continuous outcome variables, and the chi-squared test for frequency outcomes. All models were adjusted for sex, age, and smoking status. Models including dietary variables were adjusted for total energy intake. Additionally, potential confounders (alcohol consumption, physical activity, social class) were included if statistically significant and/or influencing effect estimates.

Endpoints: Atopy (per 100 ug/day of folate intake)
Adjustment factors: age, sex, smoking, total energy intake
Statistical metric: adjusted odds ratio
Statistical metric description: Comparisons between atopic and non-atopic individuals... were done by the Wilcoxon two-sample test, the Kruskall–Wallis test for continuous outcome variables, and the chi-squared test for frequency outcomes. All models were adjusted for sex, age, and smoking status. Models including dietary variables were adjusted for total energy intake. Additionally, potential confounders (alcohol consumption, physical activity, social class) were included if statistically significant and/or influencing effect estimates.

15. HÅBERG, 2009

Full citation: Håberg SE SE, London SJ, Stigum H, Nafstad P, Nystad W. 2009. Folic acid supplements in pregnancy and early childhood respiratory health. Arch Dis Child 94(3): 180-184.

Funding: The study was supported by the Norwegian Association of Heart and Lung patients with EXTRA funds from the Norwegian Foundation for Health and Rehabilitation. The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health, NIH/NIEHS (grant no. N01-ES-85433), NIH/NINDS (grant no. 1 UO1 NS 047537-01) and the Norwegian Research Council/FUGE (grant no. 151918/S10). The funding sources had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

NORWEGIAN MOTHER AND CHILD STUDY (MOBA), 2000-2005

Age: 0.0-1.5 years	**Study design:** Prospective (**n =** 32077)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Norway **Region:** national **State:**
Inclusion criteria: Born between 2000 and June 2005, questionnaires had been processed, reached 18 months of age	**Exclusion critieria:**

15.1. Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after 1st trimester (collapsed)

Method	Description	Analysis
questionnaire	Maternal intake of folic acid supplements in pregnancy was assessed from week 0 to 30 in pregnancy. The pregnant women recorded in which 4-week period they used different supplements, according to the label on their supplement container.	Exposure to folic acid in any 4-week period during weeks 0–12 in pregnancy was defined as exposure in the first trimester, and any use after week 12 as exposure after the first trimester.

Outcomes

	Outcome	Diagnostic Description
A	Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-18 months (self-reported)	Children with reports of hospitalisations for any of these conditions were classified as “hospitalised for Lower Respiratory Tract Infections (LRTIs)”. LRTIs, with or without hospitalisation, were compared to no episode of LRTI.
B	Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-6 months (self-reported)	Children with reports of hospitalisations for any of these conditions were classified as “hospitalised for Lower Respiratory Tract Infections (LRTIs)”. LRTIs, with or without hospitalisation, were compared to no episode of LRTI.
C	Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 6-18 months	Children with reports of hospitalisations for any of these conditions were classified as “hospitalised for Lower Respiratory Tract Infections (LRTIs)”. LRTIs, with or without hospitalisation, were compared to no

	Outcome	Diagnostic Description
	(self-reported)	episode of LRTI.
D	Lower respiratory tract infections (LRTIs), 0-18 months (self-reported)	Lower respiratory tract infections (LRTI) included maternal reports of respiratory syncytial virus, bronchiolitis, bronchitis and pneumonia
E	Lower respiratory tract infections (LRTIs), 0-6 months (self-reported)	Lower Respiratory Tract Infections included maternal reports of respiratory syncytial virus, bronchiolitis, bronchitis and pneumonia.
F	Lower respiratory tract infections (LRTIs), 6-18 months (self-reported)	Lower respiratory tract infections (LRTI) included maternal reports of respiratory syncytial virus, bronchiolitis, bronchitis and pneumonia.
G	Wheeze, 6-18 months (self-reported)	Wheeze was defined as chest congestion/tightness or whistling/wheezing in the chest between 6 and 18 months of age. Episodes of wheeze before 6 months of age were not enquired about. Mothers were also asked at which age (in 3-month intervals) wheezing occurred but were not asked about the number of episodes. In addition to assessing reports of any wheeze, we compared children with recurrent wheeze to non-wheezers.

Results

15.1.A Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-18 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after 1st trimester (collapsed)
Outcome: Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-18 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use in first trimester	5799	1.0	
Use in first trimester	6117	1.24 (1.09, 1.41)	0.05
No use after first trimester	5950	1.0	
Use after first trimester	6062	0.86 (0.75, 0.97)	0.05

15.1.B Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-6 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after 1st trimester (collapsed)
Outcome: Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-6 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use in first trimester	5799	1.0	
Use in first trimester	6117	1.28 (1.06, 1.55)	0.05
No use after first trimester	5950	1.0	
Use after first trimester	6062	0.88 (0.73, 1.06)	

15.1.C Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 6-18 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after 1st

trimester (collapsed)
Outcome: Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 6-18 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use in first trimester	5799	1.0	
Use in first trimester	6117	1.19 (1.02, 1.4)	0.05
No use after first trimester	5950	1.0	
Use after first trimester	6062	0.86 (0.74, 1.01)	

15.1.D Lower respiratory tract infections (LRTIs), 0-18 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after 1st trimester (collapsed)
Outcome: Lower respiratory tract infections (LRTIs), 0-18 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use in first trimester	5799	1.0	
Use in first trimester	6117	1.09 (1.02, 1.15)	0.05
No use after first trimester	5950	1.0	
Use after first trimester	6062	0.98 (0.92, 1.04)	

15.1.E Lower respiratory tract infections (LRTIs), 0-6 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after 1st trimester (collapsed)
Outcome: Lower respiratory tract infections (LRTIs), 0-6 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use in first trimester	5799	1.0	
Use in first trimester	6117	1.11 (0.99, 1.24)	
No use after first trimester	5950	1.0	
Use after first trimester	6062	0.98 (0.87, 1.1)	

15.1.F Lower respiratory tract infections (LRTIs), 6-18 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after 1st trimester (collapsed)
Outcome: Lower respiratory tract infections (LRTIs), 6-18 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use in first trimester	5799	1.0	
Use in first trimester	6117	1.08 (1.01, 1.16)	0.05
No use after first trimester	5950	1.0	
Use after first trimester	6062	1.0 (0.93, 1.07)	

15.1.G Wheeze, 6-18 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after 1st trimester (collapsed)
Outcome: Wheeze, 6-18 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use in first trimester	5799	1.0	
Use in first trimester	6117	1.06 (1.03, 1.1)	0.05
No use after first trimester	5950	1.0	
Use after first trimester	6062	1.03 (0.97, 1.03)	

Statistical Method(s)

Endpoints: Lower respiratory tract infections (LRTIs), 0-6 months; Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-6 months
Adjustment factors: birth weight, breast feeding, exposure to folic acid in first vs after first trimester, maternal age, maternal atopy, maternal education, maternal smoking during pregnancy, maternal use of cod liver oil in pregancy, maternal use of other vitamin supplements during pregnancy, parity, postnatal parental smoking, season born, sex
Statistical metric: adjusted relative risk
Statistical metric description: Data were analysed using Stata 9.2 (Stata Corporation, College Station, Texas). For regression analyses, we used the binreg command with the relative risk option. This is a generalised linear model with a log-link for binary data which gives relative risks as association measures. First, models included an exposure variable with four mutually excluding categories: no exposure, exposure in first trimester, exposure after first trimester or exposure in both time periods. We also used models which included variables for folate exposure in first trimester and after first trimester simultaneously, obtaining adjusted effects for each time period.

Endpoints: Wheeze, 6-18 months; Lower respiratory tract infections (LRTIs), 6-18 months; Lower respiratory tract infections (LRTIs), 0-18 months; Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-18 months; Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 6-18 months
Adjustment factors: birth weight, breast feeding, exposure to cod liver oil at 6 months of age, exposure to folic acid in first vs after first trimester, exposure to vitamin supplements at 6 months of age, maternal age, maternal atopy, maternal education, maternal smoking during pregnancy, maternal use of cod liver oil in pregancy, maternal use of other vitamin supplements during pregnancy, parity, postnatal parental smoking, season born, sex, type of day care
Statistical metric: adjusted relative risk
Statistical metric description: Data were analysed using Stata 9.2 (Stata Corporation, College Station, Texas). For regression analyses, we used the binreg command with the relative risk option. This is a generalised linear model with a log-link for binary data which gives relative risks as association measures. First, models included an exposure variable with four mutually excluding categories: no exposure, exposure in first trimester, exposure after first trimester or exposure in both time periods. We also used models which included variables for folate exposure in first trimester and after first trimester simultaneously, obtaining adjusted effects for each time period.

15.2. Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after week 12 (separate)

Method	Description	Analysis
questionnaire	Maternal intake of folic acid supplements in pregnancy was assessed from week 0 to 30 in pregnancy. The pregnant women recorded in which 4-week period they used different supplements, according to the label on their supplement container.	Exposure to folic acid in any 4-week period during weeks 0–12 in pregnancy was defined as exposure in the first trimester, and any use after week 12 as exposure after the first trimester.

Outcomes

	Outcome	Diagnostic Description
A	Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-18 months (self-reported)	Children with reports of hospitalisations for any of these conditions were classified as 'hospitalised for LRTI". LRTIs, with or without hospitalisation, were compared to no episode of LRTI.
B	Lower respiratory tract infections (LRTIs), 0-18 months (self-reported)	Lower respiratory tract infections (LRTI) included maternal reports of respiratory syncytial virus, bronchiolitis, bronchitis and pneumonia.
C	Wheeze, 6-18 months (self-reported)	"Wheeze was defined as chest congestion/tightness or whistling/wheezing in the chest between 6 and 18 months of age. Episodes of wheeze before 6 months of age were not enquired about. Mothers were also asked at which age (in 3-month intervals) wheezing occurred but were not asked about the number of episodes. In addition to assessing reports of any wheeze, we compared children with recurrent wheeze to non-wheezers"

Results

15.2.A Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-18 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after week 12 (separate)
Outcome: Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-18 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use (before or after 12 weeks)	6835	1.0	
Use only after 12 weeks	4431	0.92 (0.73, 1.15)	
Use only before 12 weeks	7145	1.28 (1.07, 1.53)	
Use before and after 12 weeks	13666	1.08 (0.9, 1.29)	

15.2.B Lower respiratory tract infections (LRTIs), 0-18 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after week 12 (separate)

Outcome: Lower respiratory tract infections (LRTIs), 0-18 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use (before or after 12 weeks)	6835	1.0	
Use only after 12 weeks	4431	0.97 (0.88, 1.08)	
Use only before 12 weeks	7145	1.1 (1.01, 1.2)	0.05
Use before and after 12 weeks	13666	1.07 (0.98, 1.16)	

15.2.C Wheeze, 6-18 months

Population: Norwegian Mother and Child Study (MoBa) 2000-2005, children ages 0-18 months
Exposure: Maternal Supplementation with Folic Acid supplements during Pregnancy, before/after week 12 (separate)
Outcome: Wheeze, 6-18 months
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
No use (before or after 12 weeks)	6835	1.0	
Use only after 12 weeks	4431	1.01 (0.96, 1.07)	
Use only before 12 weeks	7145	1.07 (1.03, 1.12)	0.05
Use before and after 12 weeks	13666	1.07 (1.02, 1.12)	0.05

Statistical Method(s)

Endpoints: Wheeze, 6-18 months; Lower respiratory tract infections (LRTIs), 0-18 months; Hospitalizations for Lower Respiratory Tract Infections (LRTIs), 0-18 months
Adjustment factors: birth weight, breast feeding, exposure to cod liver oil at 6 months of age, exposure to vitamin supplements at 6 months of age, maternal age, maternal atopy, maternal education, maternal smoking during pregnancy, maternal use of cod liver oil in pregancy, maternal use of other vitamin supplements during pregnancy, parity, postnatal parental smoking, season born, sex, type of day care
Statistical metric: adjusted relative risk
Statistical metric description: Data were analysed using Stata 9.2 (Stata Corporation, College Station, Texas). For regression analyses, we used the binreg command with the relative risk option. This is a generalised linear model with a log-link for binary data which gives relative risks as association measures. First, models included an exposure variable with four mutually excluding categories: no exposure, exposure in first trimester, exposure after first trimester or exposure in both time periods. We also used models which included variables for folate exposure in first trimester and after first trimester simultaneously, obtaining adjusted effects for each time period.

16. HÅBERG, 2011

Full citation: Håberg SE, London SJ, Nafstad P, Nilsen RM, Ueland PM, Vollset SE, Nystad W. 2011. Maternal folate levels in pregnancy and asthma in children at age 3 years. Journal of Allergy and Clinical Immunology 127(1): 262-264.

Funding: The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health, NIH/NIEHS (grant no N01-ES-85433), NIH/NINDS (grant no.1 UO1 NS 047537-01), and the Norwegian Research Council/FUGE (grant no. 185643 and 151918/S10), and by the Division of Intramural Research, National Institute of Environmental Health Sciences, National Institute of Health, United States (contract ES044008 and project ZO1 ES 49019).

NORWEGIAN MOTHER AND CHILD STUDY (MOBA), 2002-2004

Age: Outcome assessed at 3 years of age	**Study design:** Prospective (**n =** 1962)
Gender: Not reported **Ethnicities:** Unknown/Unspecified	**Country:** Norway **Region:** national **State:**
Inclusion criteria: AND selected all asthma cases born between July 2002 and June 2004 (427 additional cases identified), enrolled in MoBa during pregnancy, had questionnaire follow-up through age 3 years, live singleton baby, mothers donated a blood sample during 2nd trimester, registered in the Medical Birth Registry of Norway, returned the baseline questionnaire from pregnancy, selected in random sample of MoBa cohort born between July 2002 and December 2003 (80 cases, 1455 controls)	**Exclusion critieria:**

16.1. Exposure: Maternal plasma folate during pregnancy

Method	Description	Analysis
plasma	Median gestational week for blood sample collection was 18 weeks. Nonfasting blood samples were collected at the hospitals in EDTA tubes. The samples were centrifuged within 30 minutes after collection and placed in the hospital's refrigerator at 4 C until shipped overnight to the Biobank of MoBa at the Norwegian Institute of Public Health in Oslo. On the day of receipt (usually within 1-2 days), plasma were aliquoted onto polypropylene microtiter plates and stored at –80 C. Plasma folate concentration was measured by using the Lactobacillus casei microbiological assay.	Plasma folate levels were divided into quintiles on the basis of levels in the sample of 1535 women initially drawn from the cohort. The follow-up rate through age 3 years was around 55% in this substudy, and loss to follow-up could have biased results if folate levels and asthma prevalence were different in our study population of children with follow-up at age 3 years and children whose mothers did not return the 3-year questionnaire. Fortunately we have data to evaluate this possibility from random samples of 2939 singleton mothers with folate levels measured in pregnancy. Folate levels were similar between the 1535 mothers who were followed to their children's age 3 years and the 1404 mothers who were not. For the 1404 children who were lost to follow-up, the maternal plasma folate quintiles were 5.2, 7.2, 10.0, and 16.0 nmol/L. For the 1535 children followed to age 3 years, the maternal plasma quintiles were 5.5, 7.7, 10.6, and 17.8 nmol/L.

Outcomes

	Outcome	Diagnostic Description
A	Asthma at 3 years of age (self-reported)	Mothers reported current asthma at age 3 years and had listed a name of an inhalation medication for asthma when asked to list medications used by their child during the last 12 months

Results

16.1.A Asthma at 3 years of age

Population: Norwegian Mother and Child Study (MoBa), 2002-2004
Exposure: Maternal plasma folate during pregnancy
Outcome: Asthma at 3 years of age
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
<5.54	376	1.0	
5.54-7.68	392	1.16 (0.8, 1.66)	0.44
7.68-10.60	388	1.48 (1.03, 2.11)	0.03

Group	N	adjOR 95% CI (low, high)	*p*-value
10.60-17.84	388	1.28 (0.89, 1.85)	0.18
>17.84	418	1.66 (1.16, 2.37)	0.01

Statistical Method(s)

Endpoints: Asthma at 3 years of age
Adjustment factors: maternal age, maternal atopy, maternal body mass index (BMI), maternal education, maternal smoking at age 3 years, maternal smoking during pregnancy, parity, supplement use at age 3 years
Statistical metric: adjusted odds ratio
Statistical metric description: We estimated odds ratios with 95% CIs for asthma at age 3 years across quintiles of maternal plasma folate. We used univariate and multivariate logistic regression analyses, with the lowest quintile as the reference category. P values for trend were obtained by treating the quintile variable as linear term in the logistic regression analyses. Missing data on co-variates were not included in analyses. The inclusion period for case children was 6 months longer (July 2002 to July 2004) than for the control children (July 2002 to Dec 31, 2003) to increase the number of case children and the power. However, we also conducted the analyses without the case children from this added 6-month period (children born in 2004), and the results are similar.

17. KEET, 2014

Full citation: Keet CA et al. Associations between serum folate and vitamin D levels and incident mouse sensitization in adults. J. Allergy Clin. Immunol. 2014; 133 (2):399-404.

Funding: Supported in part by National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH) grant no. 1K23AI103187 (to C.A.K.) and NIAID/NIH grant no. R01AI081845 (to E.C.M.).

JACKSON LABORATORY WORKERS, 2004-2010

Age: Median (IQR) cases = 29 (22-35), controls = 32 (24-40)	**Study design:** Prospective (**n =** 82)
Gender: Male and Female **Ethnicities:** White, Other	**Country:** United States **Region:** **State:** Maine
Inclusion criteria: age 18 and over, employed at Jackson Laboratory, full-time, non-temporary, started work between July 2004 and December 2007	**Exclusion critieria:** mouse sensitivity, positive skin prick test at baseline

17.1. Exposure: Serum folate, baseline

Method	Description	Analysis
assay	blood samples taken at baseline, stored at -80 C, paramagnetic particle chemiluminescent immunoassay (Access Immunoassay Systems, Beckman Coulter, Brea, Calif)	categorized into tertiles (2.5-10.5, 10.5-16.2, and 16.2-78.4 ng/mL, respectively)

Outcomes

	Outcome	Diagnostic Description
A	Mouse sensitization, incident (medical professional or test)	Skin prick testing was performed at baseline and every 6 months by using the Multi-Test II device (Lincoln Diagnostics, Decatur, Ill). A positive result was defined as an orthogonal wheal size of at least 3 mm greater than that elicited by the negative control. Subjects were followed for up to 36 months.

Results

17.1.A Mouse sensitization, incident

Population: Jackson Laboratory workers, 2004-2010
Exposure: Serum folate, baseline
Outcome: Mouse sensitization, incident
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Tertile 1 (2.5-10.5 ng/mL)	-	1.0	
Tertile 2 (10.5-16.2 ng/mL)	-	10.5 (1.8, 61.5)	0.009
Tertile 3 (16.2-78.4 ng/mL)	-	5.6 (1.8, 31.3)	0.049
Serum Folate (natural log)	82	2.0 (0.7, 5.3)	0.17

Statistical Method(s)

Endpoints: Mouse sensitization, incident
Adjustment factors: age, education, mouse allergen level, season, sex, smoking, vitamin D level
Statistical metric: adjusted odds ratio
Statistical metric description: Analysis of predictors of case and control status was done by using conditional logistic regression, except for the demographic characteristics... which were analyzed by using Chi2 statistics for dichotomous variables and Wilcoxon rank sum statistics for continuous variables and categorized subjects by whether they ever became cases or remained control subjects.

18. KEMP, 2002

Full citation: Kemp FW, DeCandia J, Li WJ, Bruening K, Baker H, Rigassio D, Bendich A, Bogden JD. 2002. Relationships between immunity and dietary and serum antioxidants, trace metals, B vitamins, and homocysteine in elderly men and women. Nutrition Research 22(1-2): 45-53.

Funding: This project was supported in part by Roche Vitamins Inc.

ELDERLY MEN AND WOMEN, US

Age: 69.8 (mean), from 53.0-86.0 years	**Study design:** Cross-sectional (**n =** 65)
Gender: Male and Female **Ethnicities:**	**Country:** United States **Region:** **State:** New Jersey
Inclusion criteria: older than 50 years of age	**Exclusion critieria:** diagnosed with cancers in the past 5 years other than basal or squamous cell skin cancers, history of substance abuse (including ethanol), infectious disease in the past 3 months, use of medications known to influence the immune system (steroids, estrogens, cyclosporin, and antineoplastic agents), vitamin supplement use in the past 3 months

18.1. Exposure: Plasma folate

Method	Description	Analysis
plasma	Blood samples of approximately 45 ml were obtained from each participant by venipuncture and delivered to the laboratory within 4 hours of collection. Blood for plasma analysis for folate was collected into evacuated tubes (Becton Dickinson) containing EDTA as an anticoagulant. Daily intake also assessed.	Folate determined by microbiological procedures.

Outcomes

	Outcome	Diagnostic Description
A	Serum interleukin-2 receptor concentrations (sIL-2R) (medical professional or test)	Serum IL-2R concentrations were determined by an enzyme-linked immunosorbent assay using.reagents from Biosource International (Camarillo, CA)

Results

18.1.A Serum interleukin-2 receptor concentrations (sIL-2R)

Population: Elderly men and women, US
Exposure: Plasma folate

Outcome: Serum interleukin-2 receptor concentrations (sIL-2R)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Plasma folate	-	-0.168	

Statistical Method(s)

Endpoints: Serum interleukin-2 receptor concentrations (sIL-2R)
Adjustment factors:
Statistical metric: correlation
Statistical metric description:

19. KIEFTE-DE JONG, 2012

Full citation: Kiefte-de Jong JC, Timmermans S, Jaddoe VW, Hofman A, Tiemeier H, Steegers EA, de Jongste JC, Moll HA. 2012. High circulating folate and vitamin B-12 concentrations in women during pregnancy are associated with increased prevalence of atopic dermatitis in their offspring. J Nutr 142(4): 731-738.

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GENERATION R COHORT, NETHERLANDS

Age: ages 12, 24, 36, and 48 months	**Study design:** Prospective (**n =** 8742)
Gender: Male and Female **Ethnicities:** White, Other	**Country:** Netherlands **Region:** Rotterdam **State:**
Inclusion criteria: Delivery date from April 2002 to January 2006, resident in the study area in Rotterdam at delivery date	**Exclusion critieria:** multiple pregnancies

19.1. Exposure: Maternal folic acid supplementation during pregnancy

Method	Description	Analysis
questionnaire	At enrollment, we assessed folic acid exposure during pregnancy by asking the following question by questionnaire: "Have you taken folic acid, either as a single supplement or as part of multivitamin supplement during the first trimester?" Self-reported maternal folic acid intake was classified as follows as previously described (15): 1) no exposure, defined as no folic acid use at all; 2) periconceptional exposure, defined as the start of a folic acid supplement prior to conception; and 3) start of folic acid supplement within first 10 wk of conception (i.e., from the moment that pregnancy was recognized but in any case before 10 wk of pregnancy). Approximately 15% of the mothers used folic acid as part of a multivitamin supplement. The doses of folic acid in these multivitamins were comparable with single supplements of folic acid (between 0.4 and 0.5 mg/d), which is the recommended dose of folic acid for women in the preconceptional phase in The Netherlands. No valid information on dietary intake of B vitamins from food was available.	Intake was classified as: 1) no exposure, defined as no folic acid use at all; 2) start of folic acid supplement within first 10 wk of conception (i.e., from the moment that pregnancy was recognized but in any case before 10 wk of pregnancy); and 3) periconceptional exposure, defined as the start of a folic acid supplement prior to conception.

Outcomes

	Outcome	Diagnostic Description
A	Atopic dermatitis (self-reported)	Core questions from the validated International Study of Asthma and Allergies in Childhood: "Has your child had an itchy rash that came and went during the past year?"
B	Shortness of breath (self-reported)	Core questions from the validated International Study of Asthma and Allergies in Childhood: "Has your child had problems with a wheezing chest during the last year?," "Has your child had problems with tightness of the chest or shortness of breath during the past year?"
C	Wheeze (self-reported)	Core questions from the validated International Study of Asthma and Allergies in Childhood: "Has your child had problems with a wheezing chest during the last year?," "Has your child had problems with tightness of the chest or shortness of breath during the past year?"

Results

19.1.A Atopic dermatitis

Population: Generation R, 2002-2006
Exposure: Maternal folic acid supplementation during pregnancy
Outcome: Atopic dermatitis
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No folic acid use	2738	1.0	
Folic acid started within 10 wk of conception	2710	1.15 (0.9, 1.47)	
Periconceptional start	3322	1.17 (0.97, 1.4)	

19.1.B Shortness of breath

Population: Generation R, 2002-2006
Exposure: Maternal folic acid supplementation during pregnancy
Outcome: Shortness of breath
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No folic acid use	2738	1.0	
Folic acid started within 10 wk of conception	2710	1.16 (0.85, 1.57)	
Periconceptional start	3322	1.04 (0.84, 1.29)	

19.1.C Wheeze

Population: Generation R, 2002-2006
Exposure: Maternal folic acid supplementation during pregnancy
Outcome: Wheeze
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No folic acid use	2738	1.0	
Folic acid started within 10 wk of conception	2710	1.02 (0.9, 1.16)	
Periconceptional start	3322	0.99 (0.89, 1.09)	

Statistical Method(s)

Endpoints: Shortness of breath; Wheeze
Adjustment factors: age, birth weight SD score derived from generalized estimation equations, breast feeding duration, day care, maternal BMI, maternal age at birth, maternal alcohol consumption during pregnancy, maternal education, maternal ethnicity, maternal smoking during pregnancy, parental history of atopic dermatitis, asthma, hay fever, or allergy to house dust, parity, sex
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic GEE analyses were performed. Briefly, GEE analysis assesses the association by correction for the within-subject dependence as a result of the repeated observations on shortness of breath. Because the within-subject correlation coefficient for the outcome variables at the

four time points were comparable (r = 0.2–0.4 for wheezing and shortness of breath), an exchangeable working correlation structure was used for the GEE models. The primary independent variables in the GEE model were use of folic acid during pregnancy (0 = no, 1 = start within 10 wk of conception, and 2 = periconceptional start). All crude models were adjusted for time (12, 24, 36, and 48 mo). Subsequently, we created multivariate models including adjustment for potential confounders as maternal age, maternal BMI, ethnicity, family history of atopic constitution, parity, maternal educational level, maternal smoking, maternal alcohol consumption, gender, parity, daycare attendance, breastfeeding duration, and birth weight SD score. Additionally, to assess whether the associations among folate and shortness of breath were different by age of the child or by the MTHFR C677T polymorphism, folic acid supplementation, maternal smoking, or parental atopic constitution, the statistical interaction was evaluated by adding the product term of the covariate (e.g., folate concentrations) and stratum (folate X stratum) as an independent variable to the models. Nonresponse analysis showed that mothers who had no postnatal data on the child's health had lower mean folate (14.7 +/- 8.3 nmol/L) concentrations during pregnancy relative to mothers who filled out the questionnaires concerning the child's health (19 +/- 9 nmol/L; P < 0.01) and used folic acid supplements less frequently during pregnancy (54 vs. 81%; P < 0.01). To reduce potential bias associated with attrition, a multiple imputation procedure for all variables used in this study was performed (n = 5 imputations) (Supplemental Fig. 1; Supplemental Tables 1 and 2). The multiple imputation was based on the correlation between each variable with missing values with other participant characteristics as previously described (22). GEE analyses were then separately performed in each of the five datasets to obtain the desired effect sizes and SEE. OR were pooled by taking the mean of the effect sizes of the five imputed datasets. The pooled SEE was then calculated by using Rubin's rules. The pooled regression results of the five imputed datasets were reported in this paper as OR and 95% CI or as mean +/- SD values. P < 0.05 was considered significant.

Endpoints: Atopic dermatitis
Adjustment factors: age, birth weight SD score derived from generalized estimation equations, breast feeding duration, day care, maternal BMI, maternal age at birth, maternal alcohol consumption during pregnancy, maternal education, maternal ethnicity, maternal smoking during pregnancy, parental history of atopic dermatitis, asthma, hay fever, or allergy to house dust, parity, sex
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic GEE analyses were performed. Briefly, GEE analysis assesses the association by correction for the within-subject dependence as a result of the repeated observations on atopic dermatitis. Because the within-subject correlation coefficient for the outcome variables at the four time points were comparable (r = 0.3–0.5 for atopic dermatitis), an exchangeable working correlation structure was used for the GEE models. The primary independent variable in the GEE model was use of folic acid during pregnancy (0 = no, 1 = start within 10 wk of conception, and 2 = periconceptional start). All crude models were adjusted for time (12, 24, 36, and 48 mo). Subsequently, we created multivariate models including adjustment for potential confounders as maternal age, maternal BMI, ethnicity, family history of atopic constitution, parity, maternal educational level, maternal smoking, maternal alcohol consumption, gender, parity, daycare attendance, breastfeeding duration, and birth weight SD score. Additionally, to assess whether the associations among folate and atopic dermatitis were different by age of the child or by the MTHFR C677T polymorphism, folic acid supplementation, maternal smoking, or parental atopic constitution, the statistical interaction was evaluated by adding the product term of the covariate (e.g., folate concentrations) and stratum (folate X stratum) as an independent variable to the models. Nonresponse analysis showed that mothers who had no postnatal data on the child's health had lower mean folate (14.7 +/- 8.3 nmol/L) concentrations during pregnancy relative to mothers who filled out the questionnaires concerning the child's health (19 +/- 9 nmol/L; P < 0.01) and used folic acid supplements less frequently during pregnancy (54 vs. 81%; P <

0.01). To reduce potential bias associated with attrition, a multiple imputation procedure for all variables used in this study was performed (n = 5 imputations) (Supplemental Fig. 1; Supplemental Tables 1 and 2). The multiple imputation was based on the correlation between each variable with missing values with other participant characteristics as previously described (22). GEE analyses were then separately performed in each of the five datasets to obtain the desired effect sizes and SEE. OR were pooled by taking the mean of the effect sizes of the five imputed datasets. The pooled SEE was then calculated by using Rubin's rules. The pooled regression results of the five imputed datasets were reported in this paper as OR and 95% CI or as mean +/- SD values. P < 0.05 was considered significant.

19.2. Exposure: Maternal plasma folate concentration during pregnancy

Method	Description	Analysis
plasma	Nonfasting blood plasma (EDTA) and serum samples were collected during the first trimester of pregnancy (13.5 6 2.0 wk of gestation).	Plasma folate concentrations were analyzed using microparticle-enhanced immunoassay on the AxSYM and Architect system (Abbott Diagnostics). The between-run CV for plasma folate were 8.9%at 5.6 nmol/L, 2.5% at 16.6 nmol/L, and 1.5%at 33.6 nmol/L, with an analytic range of 1.8–45.3 nmol/L.

Outcomes

	Outcome	Diagnostic Description
A	Atopic dermatitis (self-reported)	Core questions from the validated International Study of Asthma and Allergies in Childhood: "Has your child had an itchy rash that came and went during the past year?"
B	Shortness of breath (self-reported)	Core questions from the validated International Study of Asthma and Allergies in Childhood: "Has your child had problems with a wheezing chest during the last year?," "Has your child had problems with tightness of the chest or shortness of breath during the past year?"
C	Wheeze (self-reported)	Core questions from the validated International Study of Asthma and Allergies in Childhood: "Has your child had problems with a wheezing chest during the last year?," "Has your child had problems with tightness of the chest or shortness of breath during the past year?"

Results

19.2.A Atopic dermatitis

Population: Generation R, 2002-2006
Exposure: Maternal plasma folate concentration during pregnancy
Outcome: Atopic dermatitis
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1: <10.30	-	1.0	
Q2: 10.31 - 16.20	-	1.1 (0.98, 1.25)	
Q3: 16.21 - 23.20	-	1.16 (1.03, 1.32)	0.05

Group	N	adjOR 95% CI (low, high)	*p*-value
Q4: >= 23.21	-	1.18 (1.05, 1.33)	0.05

19.2.B Shortness of breath

Population: Generation R, 2002-2006
Exposure: Maternal plasma folate concentration during pregnancy
Outcome: Shortness of breath
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1: <10.30	-	1.0	
Q2: 10.31 - 16.20	-	1.03 (0.87, 1.22)	
Q3: 16.21 - 23.20	-	0.98 (0.78, 1.23)	
Q4: >= 23.21	-	0.98 (0.79, 1.22)	

19.2.C Wheeze

Population: Generation R, 2002-2006
Exposure: Maternal plasma folate concentration during pregnancy
Outcome: Wheeze
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1: <10.30	-	1.0	
Q2: 10.31 - 16.20	-	1.0 (0.9, 1.11)	
Q3: 16.21 - 23.20	-	0.98 (0.85, 1.12)	
Q4: >= 23.21	-	1.02 (0.89, 1.18)	

Statistical Method(s)

Endpoints: Atopic dermatitis
Adjustment factors: age, birth weight SD score derived from generalized estimation equations, breast feeding duration, day care, maternal BMI, maternal age at birth, maternal alcohol consumption during pregnancy, maternal education, maternal ethnicity, maternal smoking during pregnancy, parental history of atopic dermatitis, asthma, hay fever, or allergy to house dust, parity, sex
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic GEE analyses were performed. Briefly, GEE analysis assesses the association by correction for the within-subject dependence as a result of the repeated observations on atopic dermatitis. Because the within-subject correlation coefficient for the outcome variables at the four time points were comparable (r = 0.3–0.5 for atopic dermatitis), an exchangeable working correlation structure was used for the GEE models. The primary independent variables in the GEE model were plasma folate concentration (after stratification into quartiles with the first quartile as reference). All crude models were adjusted for time (12, 24, 36, and 48 mo). Subsequently, we created multivariate models including adjustment for potential confounders as maternal age, maternal BMI, ethnicity, family history of atopic constitution, parity, maternal educational level, maternal smoking, maternal alcohol consumption, gender, parity, daycare attendance, breastfeeding duration, and birth weight SD score. Additionally, to assess whether the associations among folate and atopic dermatitis were different by age of the child or by the MTHFR C677T polymorphism, folic acid supplementation, maternal smoking, or parental atopic constitution, the statistical interaction was evaluated by adding the product term of

the covariate (e.g., folate concentrations) and stratum (folate X stratum) as an independent variable to the models. Nonresponse analysis showed that mothers who had no postnatal data on the child's health had lower mean folate (14.7 +/- 8.3 nmol/L) concentrations during pregnancy relative to mothers who filled out the questionnaires concerning the child's health (19 +/- 9 nmol/L; P < 0.01) and used folic acid supplements less frequently during pregnancy (54 vs. 81%; P < 0.01). To reduce potential bias associated with attrition, a multiple imputation procedure for all variables used in this study was performed (n = 5 imputations) (Supplemental Fig. 1; Supplemental Tables 1 and 2). The multiple imputation was based on the correlation between each variable with missing values with other participant characteristics as previously described (22). GEE analyses were then separately performed in each of the five datasets to obtain the desired effect sizes and SEE. OR were pooled by taking the mean of the effect sizes of the five imputed datasets. The pooled SEE was then calculated by using Rubin's rules. The pooled regression results of the five imputed datasets were reported in this paper as OR and 95% CI or as mean +/- SD values. P < 0.05 was considered significant.

Endpoints: Shortness of breath
Adjustment factors: age, birth weight SD score derived from generalized estimation equations, breast feeding duration, day care, maternal BMI, maternal age at birth, maternal alcohol consumption during pregnancy, maternal education, maternal ethnicity, maternal smoking during pregnancy, parental history of atopic dermatitis, asthma, hay fever, or allergy to house dust, parity, sex
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic GEE analyses were performed. Briefly, GEE analysis assesses the association by correction for the within-subject dependence as a result of the repeated observations on shortness of breath. Because the within-subject correlation coefficient for the outcome variables at the four time points were comparable (r = 0.2–0.4 for wheezing and shortness of breath), an exchangeable working correlation structure was used for the GEE models. The primary independent variables in the GEE model were plasma folate concentration (after stratification into quartiles with the first quartile as reference). All crude models were adjusted for time (12, 24, 36, and 48 mo). Subsequently, we created multivariate models including adjustment for potential confounders as maternal age, maternal BMI, ethnicity, family history of atopic constitution, parity, maternal educational level, maternal smoking, maternal alcohol consumption, gender, parity, daycare attendance, breastfeeding duration, and birth weight SD score. Additionally, to assess whether the associations among folate and shortness of breath were different by age of the child or by the MTHFR C677T polymorphism, folic acid supplementation, maternal smoking, or parental atopic constitution, the statistical interaction was evaluated by adding the product term of the covariate (e.g., folate concentrations) and stratum (folate X stratum) as an independent variable to the models. Nonresponse analysis showed that mothers who had no postnatal data on the child's health had lower mean folate (14.7 +/- 8.3 nmol/L) concentrations during pregnancy relative to mothers who filled out the questionnaires concerning the child's health (19 +/- 9 nmol/L; P < 0.01) and used folic acid supplements less frequently during pregnancy (54 vs. 81%; P < 0.01). To reduce potential bias associated with attrition, a multiple imputation procedure for all variables used in this study was performed (n = 5 imputations) (Supplemental Fig. 1; Supplemental Tables 1 and 2). The multiple imputation was based on the correlation between each variable with missing values with other participant characteristics as previously described (22). GEE analyses were then separately performed in each of the five datasets to obtain the desired effect sizes and SEE. OR were pooled by taking the mean of the effect sizes of the five imputed datasets. The pooled SEE was then calculated by using Rubin's rules. The pooled regression results of the five imputed datasets were reported in this paper as OR and 95% CI or as mean +/- SD values. P < 0.05 was considered significant.

Endpoints: Wheeze
Adjustment factors: age, birth weight SD score derived from generalized estimation equations, breast feeding duration, day care, maternal BMI, maternal age at birth, maternal alcohol consumption during pregnancy, maternal education, maternal ethnicity, maternal smoking during pregnancy, parental history of atopic dermatitis, asthma, hay fever, or allergy to house dust, parity, sex
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic GEE analyses were performed. Briefly, GEE analysis assesses the association by correction for the within-subject dependence as a result of the repeated observations on wheezing. Because the within-subject correlation coefficient for the outcome variables at the four time points were comparable (r = 0.2–0.4 for wheezing and shortness of breath), an exchangeable working correlation structure was used for the GEE models. The primary independent variables in the GEE model were plasma folate concentration (after stratification into quartiles with the first quartile as reference). All crude models were adjusted for time (12, 24, 36, and 48 mo). Subsequently, we created multivariate models including adjustment for potential confounders as maternal age, maternal BMI, ethnicity, family history of atopic constitution, parity, maternal educational level, maternal smoking, maternal alcohol consumption, gender, parity, daycare attendance, breastfeeding duration, and birth weight SD score. Additionally, to assess whether the associations among folate and wheezing were different by age of the child or by the MTHFR C677T polymorphism, folic acid supplementation, maternal smoking, or parental atopic constitution, the statistical interaction was evaluated by adding the product term of the covariate (e.g., folate concentrations) and stratum (folate X stratum) as an independent variable to the models. Nonresponse analysis showed that mothers who had no postnatal data on the child's health had lower mean folate (14.7 +/- 8.3 nmol/L) concentrations during pregnancy relative to mothers who filled out the questionnaires concerning the child's health (19 +/- 9 nmol/L; $P < 0.01$) and used folic acid supplements less frequently during pregnancy (54 vs. 81%; $P < 0.01$). To reduce potential bias associated with attrition, a multiple imputation procedure for all variables used in this study was performed (n = 5 imputations) (Supplemental Fig. 1; Supplemental Tables 1 and 2). The multiple imputation was based on the correlation between each variable with missing values with other participant characteristics as previously described (22). GEE analyses were then separately performed in each of the five datasets to obtain the desired effect sizes and SEE. OR were pooled by taking the mean of the effect sizes of the five imputed datasets. The pooled SEE was then calculated by using Rubin's rules. The pooled regression results of the five imputed datasets were reported in this paper as OR and 95% CI or as mean +/- SD values. $P < 0.05$ was considered significant.

20. LEVANDER-LINDGREN, 1957

Full citation: Levander-Lindgren M. 1957. Hypersensitivity to folic acid in a case of erythroblastomatosis. Acta medica Scandinavica 157(3): 233-234.

Funding: none reported

CASE REPORT, WOMAN IN SWEDEN

Age: 73.0 (None)	**Study design:** Case-report (**n** = 1)
Gender: Female **Ethnicities:**	**Country:** Sweden **Region:** Stockholm **State:**
Inclusion criteria:	**Exclusion critieria:**

20.1. Exposure: desensitizing dosing, folic acid

Method	Description	Analysis
15	Desensitizing dosing with folic acid: small doses were gradually increased to 1 tablet folacin (5mg each) three times a day for 2 months	intervention

Outcomes

	Outcome	Diagnostic Description
A	allergic reaction (medical records)	monitoring for any sign of allergic reaction

Results

20.1.A allergic reaction

Population: case report, woman in Sweden
Exposure: desensitizing dosing, folic acid
Outcome: allergic reaction
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
desensitizing dosing, folic acid	1	-	

Statistical Method(s)

Endpoints: allergic reaction
Adjustment factors:
Statistical metric: other
Statistical metric description:

20.2. Exposure: Folacin tablet

Method	Description	Analysis
10	2 tablets of folacin, each containing 5mg, were given "on the same evening" (unclear timing, but mild reaction noted after first dose)	intervention

Outcomes

	Outcome	Diagnostic Description
A	allergic reaction (medical records)	nausea, increased temperature (39 degrees C), bright red papular rash (1.5 cm in diameter), painful swelling and stiffness of the joints

Results

20.2.A allergic reaction

Population: case report, woman in Sweden
Exposure: Folacin tablet
Outcome: allergic reaction
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Folacin tablet	1	-	

Statistical Method(s)

Endpoints: allergic reaction
Adjustment factors:
Statistical metric: other
Statistical metric description:

20.3. Exposure: intracutaneous test, folic acid

Method	Description	Analysis
not reported	intracutaneous tests with folic acid were carried out a four weeks after the initial allergic reaction to oral folic acid	intervention

Outcomes

	Outcome	Diagnostic Description
A	skin reaction (medical professional or test)	skin reaction to intracutaneous tests

Results

20.3.A skin reaction

Population: case report, woman in Sweden
Exposure: intracutaneous test, folic acid
Outcome: skin reaction
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
intracutaneous test, folic acid	1	-	

Statistical Method(s)

Endpoints: skin reaction
Adjustment factors:
Statistical metric: other
Statistical metric description:

21. LIN, 2013

Full citation: Lin JH et al. Relationships between folate and inflammatory features of asthma. J. Allergy Clin. Immunol. 2013; 131 (3):918-20.

Funding:

URBAN, PREDOMINANTLY BLACK, CHILDREN AND ADOLESCENTS WITH ASTHMA

Age: 11.0 (mean), from 5.0-17.0 years	**Study design:** Prospective (**n =** 144)
Gender: Male and Female **Ethnicities:** Black or African American, White, Other	**Country:** United States **Region:** **State:**
Inclusion criteria: had an asthma exacerbation in the 12 months prior to enrollment, met criteria for persistant asthma	**Exclusion critieria:** insufficient serum for folate analysis

21.1. Exposure: Serum folate, baseline

Method	Description	Analysis
assay	Folate level was measured in baseline neopuncture samples by immunoassay by the Clinical Laboratory at The Johns Hopkins Hospital.	The limit of detection for the folate assay was 0.4 ng/mL. Serum folate levels were categorized by quartile: Q1 (below detection, 29.2 ng/mL), Q2 (9.3-16.7 ng/mL), Q3 (16.8-21.5 ng/mL), and Q4 (21.6->50.0 ng/mL)

Outcomes

	Outcome	Diagnostic Description
A	Fractional exhaled nitric oxide (FENO) (medical professional or test)	FENO was measured by using standard procedures on the NIOX Mino (Aerocrine AB, Solna, Sweden) at repeated clinic visits during a 1-year follow-up period.
B	IL-13 cytokines, baseline (medical professional or test)	Venipuncture was performed at the baseline visit. The Bioplex 200 platform was used to determine the concentration (pg/ml) of IL-4, IL-5, and IL-13 in previously banked samples. This multiplexed bead-based immunoassay was performed following the manufacturer's protocols, and the concentration was determined by using the supplied cytokine standards and software (Biorad, Hercules, Calif). For IL-13 the outcomes were continuous.
C	IL-4 cytokines, baseline (medical professional or test)	Venipuncture was performed at the baseline visit. The Bioplex 200 platform was used to determine the concentration (pg/ml) of IL-4, IL-5, and IL-13 in previously banked samples. This multiplexed bead-based immunoassay was performed following the manufacturer's protocols, and the concentration was determined by using the supplied cytokine standards and software (Biorad, Hercules, Calif). Outcome was dichotomous variable (a detectable serum level of IL-4)
D	IL-5 cytokines, baseline	Venipuncture was performed at the baseline visit. The Bioplex 200

	Outcome	Diagnostic Description
	(medical professional or test)	platform was used to determine the concentration (pg/ml) of IL-4, IL-5, and IL-13 in previously banked samples. This multiplexed bead-based immunoassay was performed following the manufacturer's protocols, and the concentration was determined by using the supplied cytokine standards and software (Biorad, Hercules, Calif). For IL-5 the outcomes were continuous.
E	Number of Positive Skin Test Reactions, baseline (medical professional or test)	At baseline, participants underwent skin prick testing to a panel of 14 common aeroallergens (Lincoln Diagnostics, Decatur, Ill): cat, dog, rat, mouse, Dermatophagoides farinae, Dermatophagoides pteronyssinus, Aspergillus fumigatus, German cockroach, American cockroach, Cladosporium herbarum, Alternaria tenius, grass, oak, and ragweed. Skin prick test sensitivity was defined as a net wheal size of 3 mm or more
F	Total IgE, baseline (medical professional or test)	Venipuncture was performed at the baseline visit for the measurement of total IgE (ImmunoCAPsystem, Phadia, Uppsala, Sweden).

Results

21.1.A Fractional exhaled nitric oxide (FENO)

Population: Urban, predominantly black, children and adolescents with asthma
Exposure: Serum folate, baseline
Outcome: Fractional exhaled nitric oxide (FENO)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Q1 (<0.4-29.2 ng/mL)	36	-	
Q2 (9.3-16.7 ng/mL)	36	-	0.05
Q3 (16.8-21.5 ng/mL)	36	-	
Q4 (21.6->50.0 ng/mL)	36	-	

21.1.B IL-13 cytokines, baseline

Population: Urban, predominantly black, children and adolescents with asthma
Exposure: Serum folate, baseline
Outcome: IL-13 cytokines, baseline
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Q1 (<0.4-29.2 ng/mL)	36	-	
Q2 (9.3-16.7 ng/mL)	36	0.25 (0.02, 0.52)	0.07
Q3 (16.8-21.5 ng/mL)	36	0.12 (-0.14, 0.39)	
Q4 (21.6->50.0 ng/mL)	36	0.43 (0.15, 0.7)	

21.1.C IL-4 cytokines, baseline

Population: Urban, predominantly black, children and adolescents with asthma
Exposure: Serum folate, baseline
Outcome: IL-4 cytokines, baseline
Statistical metric: crude odds ratio

Group	N	OR 95% CI (low, high)	*p*-value
Q1 (<0.4-29.2 ng/mL)	36	1.0	
Q2 (9.3-16.7 ng/mL)	36	4.4 (1.1, 17.9)	0.04
Q3 (16.8-21.5 ng/mL)	36	0.6 (0.1, 4.0)	
Q4 (21.6->50.0 ng/mL)	36	2.6 (0.6, 11.3)	

21.1.D IL-5 cytokines, baseline

Population: Urban, predominantly black, children and adolescents with asthma
Exposure: Serum folate, baseline
Outcome: IL-5 cytokines, baseline
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Q1 (<0.4-29.2 ng/mL)	36	-	
Q2 (9.3-16.7 ng/mL)	36	0.15 (0.02, 0.32)	0.09
Q3 (16.8-21.5 ng/mL)	36	0.03 (-0.14, 0.39)	
Q4 (21.6->50.0 ng/mL)	36	0.05 (-0.13, 0.23)	

21.1.E Number of Positive Skin Test Reactions, baseline

Population: Urban, predominantly black, children and adolescents with asthma
Exposure: Serum folate, baseline
Outcome: Number of Positive Skin Test Reactions, baseline
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Q1 (<0.4-29.2 ng/mL)	36	-	
Q2 (9.3-16.7 ng/mL)	36	-	0.05
Q3 (16.8-21.5 ng/mL)	36	-	
Q4 (21.6->50.0 ng/mL)	36	-	

21.1.F Total IgE, baseline

Population: Urban, predominantly black, children and adolescents with asthma
Exposure: Serum folate, baseline
Outcome: Total IgE, baseline
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Q1 (<0.4-29.2 ng/mL)	36	-	
Q2 (9.3-16.7 ng/mL)	36	-	0.01
Q3 (16.8-21.5 ng/mL)	36	-	
Q4 (21.6->50.0 ng/mL)	36	-	

Statistical Method(s)

Endpoints: IL-13 cytokines, baseline; IL-5 cytokines, baseline
Adjustment factors:
Statistical metric: adjusted beta
Statistical metric description: The folate data were inspected by using summary graphs and statistics to explore relationships with covariates and outcome variables. Folate was analyzed as the main predictor

variable both continuously and categorically as quartiles from low to high levels. The models were adjusted for baseline age, sex, and parent/guardian educational attainment. Regression analyses were performed with StataSE 11.0 (College Station, Tex). Cubic spline models were constructed to examine nonlinear relationships between folate and outcomes of interest. Predicted probabilities and 95% CIs were generated from the final multivariate models. Generalized estimating equations were used to account for the repeated measurements.

Endpoints: IL-4 cytokines, baseline
Adjustment factors:
Statistical metric: crude odds ratio
Statistical metric description: The folate data were inspected by using summary graphs and statistics to explore relationships with covariates and outcome variables. Folate was analyzed as the main predictor variable both continuously and categorically as quartiles from low to high levels. The models were adjusted for baseline age, sex, and parent/guardian educational attainment. Regression analyses were performed with StataSE 11.0 (College Station, Tex). Cubic spline models were constructed to examine nonlinear relationships between folate and outcomes of interest. Predicted probabilities and 95% CIs were generated from the final multivariate models. Generalized estimating equations were used to account for the repeated measurements.

Endpoints: Total IgE, baseline
Adjustment factors: age, education, sex
Statistical metric: other
Statistical metric description: The folate data were inspected by using summary graphs and statistics to explore relationships with covariates and outcome variables. Folate was analyzed as the main predictor variable both continuously and categorically as quartiles from low to high levels. The models were adjusted for baseline age, sex, and parent/guardian educational attainment. Regression analyses were performed with StataSE 11.0 (College Station, Tex). Cubic spline models were constructed to examine nonlinear relationships between folate and outcomes of interest. Predicted probabilities and 95% CIs were generated from the final multivariate models.

Endpoints: Fractional exhaled nitric oxide (FENO); Number of Positive Skin Test Reactions, baseline
Adjustment factors: age, education, sex
Statistical metric: other
Statistical metric description: The folate data were inspected by using summary graphs and statistics to explore relationships with covariates and outcome variables. Folate was analyzed as the main predictor variable both continuously and categorically as quartiles from low to high levels. The models were adjusted for baseline age, sex, and parent/guardian educational attainment. Regression analyses were performed with StataSE 11.0 (College Station, Tex). Cubic spline models were constructed to examine nonlinear relationships between folate and outcomes of interest. Predicted probabilities and 95% CIs were generated from the final multivariate models. Generalized estimating equations were used to account for the repeated measurements.

22. MAGDELIJNS, 2011

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KOALA BIRTH COHORT STUDY

Age: birth cohort, outcomes at age 2 and 6-7 years in this study	**Study design:** Prospective (**n =** 2640)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Netherlands **Region:** **State:**
Inclusion criteria: 14-18 weeks of gestation, enrolled in pregnancy-related pelvic girdle pain (PPGP study) or recruited through "alternative" recruitment channels	**Exclusion critieria:** congenital abnormalities related to immunity (Down syndrome), missing data on health outcomes, missing exposure information, multiple pregnancies, no response to any of the questionnaires in the first year of life, preterm birth

22.1. Exposure: Folic acid from supplements in pregnancy

Method	Description	Analysis
questionnaire	Questionnaire was completed by the mother in weeks 14 and 34 of pregnancy. Women were asked "Did you take folic acid, either as a stand-alone supplement or as part of a multivitamin supplement, before or during your pregnancy?" and when they had started taking supplements: before or after conception and in which trimester (first, second, and/or third).	We categorized subjects into 2 categories: any use of folic acid versus no use. Additionally, we divided the folic acid users into early users (use during the advice period [4 weeks before until 8 weeks after conception] and/or use solely during the first trimester), use during whole pregnancy, and a "rest" category (users that did not fit in any of these categories [eg, use solely during the second and third trimesters]). To eliminate the possibility that other vitamins in the multivitamin supplements could be the cause of a possible association, we also analyzed folic acid use as a stand-alone supplement.

Outcomes

	Outcome	Diagnostic Description
A	%FEV1 lung function at 6-7yr (medical professional or test)	During the home visit at the child's age of 6 to 7 years, spirometry was performed by a trained research assistant using the handheld Medikro SpiroStar USB spirometer (Medikro Oy, Kuopio, Finland). Forced expiratory volume in 1 second (FEV1) was assessed as percentage of the predicted FEV1 (%FEV1), with gender, age, ethnicity, weight and height, ambient temperature, humidity, and barometric pressure taken into account. The testing protocol followed the guidelines of the American Thoracic Society and the European Respiratory Society. Testing was performed when the child was sitting and continued until at least 3 acceptable curves were achieved, with a maximum of 8 attempts.
B	%FVC lung function at 6-7 yr (medical professional or test)	During the home visit at the child's age of 6 to 7 years, spirometry was performed by a trained research assistant using the handheld Medikro SpiroStar USB spirometer (Medikro Oy, Kuopio, Finland). Forced vital capacity (FVC) was assessed as percentage of the predicted FVC (%FVC), with gender, age, ethnicity, weight and height, ambient temperature, humidity, and barometric pressure taken into account. The testing protocol followed the guidelines of the American Thoracic Society and the European Respiratory Society. Testing was performed when the child was sitting and continued until at least 3 acceptable curves were achieved, with a maximum of 8 attempts.
C	Asthma at 6-7 yr (self-reported)	Asthma was defined as ever physician diagnosed asthma with clinical symptoms and/or the use of asthma medication in the last 12 months. Clinical symptoms were defined as having had at least 1 attack of wheeze or dyspnea in the last 12 months. The use of asthma medication was defined as regular use (everyday use during

	Outcome	Diagnostic Description
		at least 2 months or use associated with physical activity) of short-acting inhalation bronchodilators or the use of inhaled corticosteroids and medication use according to the Dutch guidelines of treatment of bronchial asthma in children. Assessment of asthma symptoms was based on the following ISAAC questions at age 6 to 7 years: "Did your child suffer from wheezing in the last 12 months?" and "Did your child suffer from shortness of breath in the last 12 months?" We assessed physician's diagnosis and asthma medication use with the questions: "Did a physician ever diagnose asthma in your child?" and "Did your child use medication for asthma or wheezing in the last 12 months, and if so, what medication?"
D	Atopic dermatitis at 2 yr (medical professional or test)	A trained nurse examined the child for manifestations of AD during the home visit at the child's age of 2 years using the UK Working Party criteria... The probability of AD was derived from the presence of 4 clinical symptoms: (1) itchy rash; (2) history of flexural dermatitis; (3) visible flexural dermatitis; and (4) onset before the age of 2 years. Children with a UK Working Party probability of >0.9 were considered children with AD.
E	Eczema until 6-7 yr (self-reported)	Eczema was assessed at age 7, 12, and 24 months and 6 to 7 years with the following International Study of Asthma and Allergies in Childhood (ISAAC) 21 question: "Did your child suffer from an itchy rash that was coming and going in the past months?" If this question was answered affirmatively, infants were classified as having developed eczema. Children were classified as having no eczema if the parents did not report eczema in any of the 4 questionnaires, or if only diaper rash, rash around the eyes, and/or scalp scaling was reported.
F	Increased specific IgE at 2 yr (medical professional or test)	Specific IgE levels were determined in 815 venous blood samples that were taken at age 2 years. A radioallergosorbent test with a detection limit of <0.13 IU/mL was used to determine the serum level of specific IgE against hen's egg, cow's milk, peanut, birch pollen, grass pollen, cat dander, dog dander, and house dust mite. Allergic sensitization (increased specific IgE) was defined as a specific IgE level >0.3 IU/mL for >/=1 of the tested allergens.
G	Increased total IgE at 2 yr (medical professional or test)	Total IgE levels were determined in 815 venous blood samples that were taken at age 2 years. Total serum IgE levels were measured by using radioimmunoassay, with a detection limit of 0.50 IU/mL. Increased total IgE level was defined as 25.0 IU/mL, based on the 67th percentile of the distribution in the total cohort.
H	Wheeze until 6-7 yr (self-reported)	Wheeze was assessed by the following ISAAC question in the questionnaires at age 2 years, 4 to 5 years, and 6 to 7 years: "Did your child suffer from wheezing in the last 12 months?" Using the same ISAAC question, at child's age 3, 7, and 12 months, parents were asked if their child suffered from wheezing since the last follow-up.

Results

22.1.A %FEV1 lung function at 6-7yr

Population: KOALA Birth Cohort Study
Exposure: Folic acid from supplements in pregnancy

Outcome: %FEV1 lung function at 6-7yr
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
No folic acid use	356	-	
Any folic acid use	2284	0.55 (-4.5, 5.61)	
Folic acid use during early pregnancy (4 wks pre-8wks pos conception)	851	1.96 (-3.37, 7.28)	
Folic acid use during whole pregnancy	820	-0.45 (-6.14, 5.23)	
Folic acid use during another period	613	-0.62 (-6.65, 5.4)	

22.1.B %FVC lung function at 6-7 yr

Population: KOALA Birth Cohort Study
Exposure: Folic acid from supplements in pregnancy
Outcome: %FVC lung function at 6-7 yr
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
No folic acid use	356	-	
Any folic acid use	2284	0.34 (-4.21, 4.9)	
Folic acid use during early pregnancy (4 wks pre-8wks pos conception)	851	1.08 (-3.78, 5.95)	
Folic acid use during whole pregnancy	820	1.02 (-4.17, 6.21)	
Folic acid use during another period	613	-1.95 (-7.45, 3.56)	

22.1.C Asthma at 6-7 yr

Population: KOALA Birth Cohort Study
Exposure: Folic acid from supplements in pregnancy
Outcome: Asthma at 6-7 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No folic acid use	255	1.0	
Any folic acid use	1647	1.19 (0.65, 2.2)	
Folic acid use during early pregnancy (4 wks pre-8wks pos conception)	624	1.27 (0.67, 2.41)	
Folic acid use during whole pregnancy	607	1.06 (0.51, 2.17)	
Folic acid use during another period	416	1.15 (0.57, 2.32)	

22.1.D Atopic dermatitis at 2 yr

Population: KOALA Birth Cohort Study
Exposure: Folic acid from supplements in pregnancy
Outcome: Atopic dermatitis at 2 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No folic acid use	136	1.0	
Any folic acid use	706	1.15 (0.63, 2.1)	
Folic acid use during early pregnancy (4 wks pre-8wks pos conception)	305	1.15 (0.6, 2.2)	

Group	N	adjOR 95% CI (low, high)	*p*-value
Folic acid use during whole pregnancy	234	1.26 (0.6, 2.63)	
Folic acid use during another period	167	1.06 (0.5, 2.21)	

22.1.E Eczema until 6-7 yr

Population: KOALA Birth Cohort Study
Exposure: Folic acid from supplements in pregnancy
Outcome: Eczema until 6-7 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No folic acid use	356	1.0	
Any folic acid use	2284	1.16 (0.9, 1.48)	
Folic acid use during early pregnancy (4 wks pre-8wks pos conception)	851	1.12 (0.86, 1.46)	
Folic acid use during whole pregnancy	820	1.27 (0.96, 1.66)	
Folic acid use during another period	613	1.08 (0.81, 1.43)	

22.1.F Increased specific IgE at 2 yr

Population: KOALA Birth Cohort Study
Exposure: Folic acid from supplements in pregnancy
Outcome: Increased specific IgE at 2 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No folic acid use	131	1.0	
Any folic acid use	668	1.06 (0.67, 1.68)	
Folic acid use during early pregnancy (4 wks pre-8wks pos conception)	292	1.02 (0.62, 1.67)	
Folic acid use during whole pregnancy	220	1.11 (0.63, 1.96)	
Folic acid use during another period	156	1.13 (0.64, 1.98)	

22.1.G Increased total IgE at 2 yr

Population: KOALA Birth Cohort Study
Exposure: Folic acid from supplements in pregnancy
Outcome: Increased total IgE at 2 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No folic acid use	131	1.0	
Any folic acid use	676	0.71 (0.47, 1.07)	
Folic acid use during early pregnancy (4 wks pre-8wks pos conception)	295	0.72 (0.46, 1.12)	
Folic acid use during whole pregnancy	222	0.78 (0.46, 1.32)	
Folic acid use during another period	159	0.62 (0.37, 1.05)	

22.1.H Wheeze until 6-7 yr

Population: KOALA Birth Cohort Study
Exposure: Folic acid from supplements in pregnancy

Outcome: Wheeze until 6-7 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No folic acid use	356	1.0	
Any folic acid use	2284	0.99 (0.8, 1.23)	
Folic acid use during early pregnancy (4 wks pre-8wks pos conception)	851	1.0 (0.79, 1.26)	
Folic acid use during whole pregnancy	820	0.97 (0.76, 1.23)	
Folic acid use during another period	613	1.02 (0.8, 1.3)	

Statistical Method(s)

Endpoints: Asthma at 6-7 yr
Adjustment factors: birth weight, breastfeeding during the first 2 years of life, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Univariable and multivariable logistic regression was used for the association between folic acid use during pregnancy and asthma.

Endpoints: Eczema until 6-7 yr
Adjustment factors: birth weight, breastfeeding during the first 2 years of life, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Generalized estimating equation (GEE) models with an exchangeable correlation structure were used for repeated outcomes: eczema.

Endpoints: Wheeze until 6-7 yr
Adjustment factors: birth weight, breastfeeding during the first 2 years of life, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Generalized estimating equation (GEE) models with an exchangeable correlation structure were used for repeated outcomes: wheeze. In the GEE analysis, we adjusted for exposure to environmental tobacco smoke at each moment of measurement separately (3, 7, 12, and 24 months, 4 –5 years, and 6 –7 years).

Endpoints: Increased specific IgE at 2 yr
Adjustment factors: birth weight, breastfeeding during the first 2 years of life, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Univariable and multivariable logistic regression was used for the association between folic acid use during pregnancy and IgE.

Endpoints: Increased total IgE at 2 yr
Adjustment factors: birth weight, breastfeeding during the first 2 years of life, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Univariable and multivariable logistic regression was used for the association between folic acid use during pregnancy and total IgE.

Endpoints: %FVC lung function at 6-7 yr; %FEV1 lung function at 6-7yr
Adjustment factors: birth weight, breastfeeding during the first 2 years of life, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted beta
Statistical metric description: Linear regression was used for lung function outcomes.

Endpoints: Atopic dermatitis at 2 yr
Adjustment factors: birth weight, breastfeeding during the first 2 years of life, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Univariable and multivariable logistic regression was used for the association between folic acid use during pregnancy and AD.

22.2. Exposure: Intracellular folic acid (ICF) levels during pregnancy

Method	Description	Analysis
erythrocytes	In the blood samples, taken in week 35 of pregnancy, fluorimmunoassay was used to measure lysed folic acid in erythrocytes	The concentration of folic acid in erythrocytes was calculated by using the following formula: lysed folic acid (nmol/L) 23 (dilution factor) (100/hematocrit %).

Outcomes

	Outcome	Diagnostic Description
A	%FEV1 lung function at 6-7 yr (medical professional or test)	During the home visit at the child's age of 6 to 7 years, spirometry was performed by a trained research assistant using the handheld Medikro SpiroStar USB spirometer (Medikro Oy, Kuopio, Finland). Forced expiratory volume in 1 second (FEV1) was assessed as percentage of the predicted FEV1 (%FEV1), with gender, age, ethnicity, weight and height, ambient temperature, humidity, and barometric pressure taken into account. The testing protocol followed the guidelines of the American Thoracic Society and the European Respiratory Society. Testing was performed when the child was sitting and continued until at least 3 acceptable curves were achieved, with a maximum of 8 attempts.
B	%FVC lung function at 6-7 yr (medical professional or test)	During the home visit at the child's age of 6 to 7 years, spirometry was performed by a trained research assistant using the handheld Medikro SpiroStar USB spirometer (Medikro Oy, Kuopio, Finland). Forced vital capacity (FVC) was assessed as percentage of the predicted FVC (%FVC), with gender, age, ethnicity, weight and height, ambient temperature, humidity, and barometric pressure taken into account. The testing protocol followed the guidelines of the American Thoracic Society and the European Respiratory Society. Testing was performed when the child was sitting and continued until at least 3 acceptable curves were achieved, with a maximum of 8 attempts.
C	Asthma at 6-7 yr (self-reported)	Asthma was defined as ever physician diagnosed asthma with clinical symptoms and/or the use of asthma medication in the last 12 months. Clinical symptoms were defined as having had at least 1 attack of wheeze or dyspnea in the last 12 months. The use of asthma medication was defined as regular use (everyday use during at least 2 months or use associated with physical activity) of short-acting inhalation bronchodilators or the use of inhaled corticosteroids and medication use according to the Dutch guidelines of treatment of bronchial asthma in children. Assessment of asthma symptoms was based on the following ISAAC questions at age 6 to 7 years: "Did your child suffer from wheezing in the last 12 months?" and "Did your child suffer from shortness of breath in the last 12 months?" We assessed physician's diagnosis and asthma medication use with the questions: "Did a physician ever diagnose asthma in your child?" and "Did your child use medication for asthma or wheezing in the last 12 months, and if so, what medication?"
D	Atopic dermatitis at 2 yr (medical professional or test)	A trained nurse examined the child for manifestations of AD during the home visit at the child's age of 2 years using the UK Working

	Outcome	Diagnostic Description
		Party criteria... The probability of AD was derived from the presence of 4 clinical symptoms: (1) itchy rash; (2) history of flexural dermatitis; (3) visible flexural dermatitis; and (4) onset before the age of 2 years. Children with a UK Working Party probability of 0.9 were considered children with AD.
E	Eczema until 6-7 yr (self-reported)	Eczema was assessed at age 7, 12, and 24 months and 6 to 7 years with the following International Study of Asthma and Allergies in Childhood (ISAAC) 21 question: "Did your child suffer from an itchy rash that was coming and going in the past months?" If this question was answered affirmatively, infants were classified as having developed eczema. Children were classified as having no eczema if the parents did not report eczema in any of the 4 questionnaires, or if only diaper rash, rash around the eyes, and/or scalp scaling was reported.
F	Increased specific IgE at 2 yr (medical professional or test)	Specific IgE levels were determined in 815 venous blood samples that were taken at age 2 years. A radioallergosorbent test with a detection limit of 0.13 IU/mL was used to determine the serum level of specific IgE against hen's egg, cow's milk, peanut, birch pollen, grass pollen, cat dander, dog dander, and house dust mite. Allergic sensitization (increased specific IgE) was defined as a specific IgE level 0.3 IU/mL for 1 of the tested allergens. [NOTE this outcome is labeled "Allergic sensitization at 2y" in Table 3, used the same outcome label from Table 2 "Increased specific IgE at 2y" for consistency.]
G	Increased total IgE at 2 yr (medical professional or test)	Total IgE levels were determined in 815 venous blood samples that were taken at age 2 years. Total serum IgE levels were measured by using radioimmunoassay, with a detection limit of 0.50 IU/mL. Increased total IgE level was defined as 25.0 IU/mL, based on the 67th percentile of the distribution in the total cohort.
H	Wheeze until 6-7 yr (self-reported)	Wheeze was assessed by the following ISAAC question in the questionnaires at age 2 years, 4 to 5 years, and 6 to 7 years: "Did your child suffer from wheezing in the last 12 months?" Using the same ISAAC question, at child's age 3, 7, and 12 months, parents were asked if their child suffered from wheezing since the last follow-up.

Results

22.2.A %FEV1 lung function at 6-7 yr

Population: KOALA Birth Cohort Study
Exposure: Intracellular folic acid (ICF) levels during pregnancy
Outcome: %FEV1 lung function at 6-7 yr
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
1st Quintile (≤480 nmol/l)	158	-	
2nd Quintile (481-643 nmol/l)	158	0.25 (-6.55, 7.06)	
3rd Quintile (644-862 nmol/l)	158	-2.58 (-8.74, 3.58)	
4th Quintile (863-1139 nmol/l)	158	-2.97 (-9.27, 3.33)	
5th Quintile (≥1140 nmol/l)	158	-0.92 (-6.82, 6.64)	

22.2.B %FVC lung function at 6-7 yr

Population: KOALA Birth Cohort Study
Exposure: Intracellular folic acid (ICF) levels during pregnancy
Outcome: %FVC lung function at 6-7 yr
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
1st Quintile (≤480 nmol/l)	158	-	
2nd Quintile (481-643 nmol/l)	158	1.13 (-4.97, 7.24)	
3rd Quintile (644-862 nmol/l)	158	-1.36 (-6.88, 4.17)	
4th Quintile (863-1139 nmol/l)	158	-1.19 (-6.84, 4.46)	
5th Quintile (≥1140 nmol/l)	158	-0.65 (-6.68, 5.39)	

22.2.C Asthma at 6-7 yr

Population: KOALA Birth Cohort Study
Exposure: Intracellular folic acid (ICF) levels during pregnancy
Outcome: Asthma at 6-7 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
1st Quintile (≤480 nmol/l)	158	1.0	
2nd Quintile (481-643 nmol/l)	158	0.73 (0.27, 1.94)	
3rd Quintile (644-862 nmol/l)	158	0.46 (0.15, 1.41)	
4th Quintile (863-1139 nmol/l)	158	0.41 (0.12, 1.34)	
5th Quintile (≥1140 nmol/l)	158	0.31 (0.09, 1.1)	

22.2.D Atopic dermatitis at 2 yr

Population: KOALA Birth Cohort Study
Exposure: Intracellular folic acid (ICF) levels during pregnancy
Outcome: Atopic dermatitis at 2 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
1st Quintile (≤480 nmol/l)	158	1.0	
2nd Quintile (481-643 nmol/l)	158	1.32 (0.53, 3.29)	
3rd Quintile (644-862 nmol/l)	158	1.44 (0.56, 3.71)	
4th Quintile (863-1139 nmol/l)	158	2.25 (0.89, 5.67)	
5th Quintile (≥1140 nmol/l)	158	0.94 (0.33, 2.67)	

22.2.E Eczema until 6-7 yr

Population: KOALA Birth Cohort Study
Exposure: Intracellular folic acid (ICF) levels during pregnancy
Outcome: Eczema until 6-7 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
1st Quintile (≤480 nmol/l)	158	1.0	
2nd Quintile (481-643 nmol/l)	158	1.29 (0.83, 2.01)	
3rd Quintile (644-862 nmol/l)	158	1.04 (0.65, 1.67)	

Group	N	adjOR 95% CI (low, high)	*p*-value
4th Quintile (863-1139 nmol/l)	158	1.13 (0.74, 1.74)	
5th Quintile (≥1140 nmol/l)	158	1.35 (0.87, 2.09)	

22.2.F Increased specific IgE at 2 yr

Population: KOALA Birth Cohort Study
Exposure: Intracellular folic acid (ICF) levels during pregnancy
Outcome: Increased specific IgE at 2 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
1st Quintile (≤480 nmol/l)	158	1.0	
2nd Quintile (481-643 nmol/l)	158	0.47 (0.23, 0.99)	0.05
3rd Quintile (644-862 nmol/l)	158	0.86 (0.43, 1.71)	
4th Quintile (863-1139 nmol/l)	158	0.86 (0.42, 1.78)	
5th Quintile (≥1140 nmol/l)	158	0.7 (0.32, 1.51)	

22.2.G Increased total IgE at 2 yr

Population: KOALA Birth Cohort Study
Exposure: Intracellular folic acid (ICF) levels during pregnancy
Outcome: Increased total IgE at 2 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
1st Quintile (≤480 nmol/l)	158	1.0	
2nd Quintile (481-643 nmol/l)	158	0.75 (0.38, 1.46)	
3rd Quintile (644-862 nmol/l)	158	0.87 (0.44, 1.74)	
4th Quintile (863-1139 nmol/l)	158	1.79 (0.89, 3.61)	
5th Quintile (≥1140 nmol/l)	158	1.33 (0.64, 2.8)	

22.2.H Wheeze until 6-7 yr

Population: KOALA Birth Cohort Study
Exposure: Intracellular folic acid (ICF) levels during pregnancy
Outcome: Wheeze until 6-7 yr
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
1st Quintile (≤480 nmol/l)	158	1.0	
2nd Quintile (481-643 nmol/l)	158	0.88 (0.6, 1.29)	
3rd Quintile (644-862 nmol/l)	158	0.73 (0.51, 1.06)	
4th Quintile (863-1139 nmol/l)	158	0.8 (0.54, 1.19)	
5th Quintile (≥1140 nmol/l)	158	1.01 (0.69, 1.49)	

Statistical Method(s)

Endpoints: Increased total IgE at 2 yr
Adjustment factors: birth weight, breast feeding duration, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal alcohol consumption

during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, multivitamin or other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Univariable and multivariable logistic regression was used for the association between ICF levels during pregnancy and total IgE.

Endpoints: %FEV1 lung function at 6-7 yr
Adjustment factors: birth weight, breast feeding duration, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, multivitamin or other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted beta
Statistical metric description: Linear regression was used for lung function outcomes.

Endpoints: %FVC lung function at 6-7 yr
Adjustment factors: birth weight, breast feeding duration, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, multivitamin or other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted beta
Statistical metric description: Linear regression was used for lung function outcomes.

Endpoints: Asthma at 6-7 yr
Adjustment factors: birth weight, breast feeding duration, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, multivitamin or other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Univariable and multivariable logistic regression was used for the association between ICF level during pregnancy and asthma.

Endpoints: Atopic dermatitis at 2 yr
Adjustment factors: birth weight, breast feeding duration, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, multivitamin or other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Univariable and multivariable logistic regression was used for the association between folic acid use during pregnancy and AD.

Endpoints: Wheeze until 6-7 yr
Adjustment factors: birth weight, breast feeding duration, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, multivitamin or other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Generalized estimating equation (GEE) models with an exchangeable correlation structure were used for repeated outcomes: wheeze. In the GEE analysis, we adjusted for exposure to environmental tobacco smoke at each moment of measurement separately (3, 7, 12, and 24 months, 4 –5 years, and 6 –7 years).

Endpoints: Increased specific IgE at 2 yr
Adjustment factors: birth weight, breast feeding duration, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, multivitamin or other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Univariable and multivariable logistic regression was used for the association between ICF level during pregnancy and IgE.

Endpoints: Eczema until 6-7 yr
Adjustment factors: birth weight, breast feeding duration, day care, exposure to domestic animals during first 2 years of life, exposure to domestic animals during pregnancy, exposure to environmental tobacco smoke in the first 6 to 7 years of life, family history of atopy, maternal alcohol consumption during pregnancy, maternal antibiotic use during pregnancy, maternal education, maternal smoking during pregnancy, mode of delivery, multivitamin or other supplement use during pregnancy, place of delivery, recruitment group, sex, siblings, treatment with antibiotics during the first 6 months of life
Statistical metric: adjusted odds ratio
Statistical metric description: Generalized estimating equation (GEE) models with an exchangeable correlation structure were used for repeated outcomes: eczema.

23. MARTINUSSEN, 2012

Full citation: Martinussen MP, Risnes KR, Jacobsen GW, Bracken MB. 2012. Folic acid supplementation in early pregnancy and asthma in children aged 6 years. Am J Obstet Gynecol 206(1): 72 e71-77.

Funding: This work was supported in part by Grants AI41040 and DA05484 from the National Institutes of Health.

PERINATAL RISK OF ASTHMA IN INFANTS OF ASTHMATIC MOTHERS (PRAM), 2003-2007

Age: 6.0 (mean)	**Study design:** Prospective (**n =** 1499)
Gender: Male and Female **Ethnicities:** Asian, Black or African American, Hispanic/Latino, White	**Country:** United States **Region:** **State:** Massachusetts and Connecticut
Inclusion criteria: Participated in the Asthma in Pregnancy (AIP) study	**Exclusion critieria:** infant death, missing information on marital status, family income and maternal asthma, non-English speaker, refusal, inability to locate, and missed interviews

23.1. Exposure: Maternal supplementation with Folic Acid during Pregnancy

Method	Description	Analysis
questionnaire	The pregnant women were interviewed, usually at home, before 24 weeks of gestational age. Information on folic acid, iron, and vitamin use was obtained before 24 weeks of gestation from the following questions in the prenatal exposure questionnaire: “Have you used any of the following vitamin or mineral supplements: prenatal supplement vitamins, multivitamin, vitamin A, vitamin C, vitamin E, iron/ferrous sulphate, folic acid/folate, calcium, or other; specify.” If a respondent answered yes, she was specifically asked how often each item had been used (not at all, once a month, 2-3 times a month, twice a week, 3-4 times a week, 5-6 times a week, once a day, or 2 or more times a day). This information was collected for the month before conception through the third month of pregnancy.	We collected information on folic acid content (micrograms) in each of the selfreported vitamin supplements. Using the detailed frequency information from the pregnancy questionnaire, we could calculate mean daily folic acid intake. Prenatal vitamins were estimated to contain 800 ug folic acid per tablet, whereas vitamin supplements were estimated to contain 400 ug folic acid per tablet. Adichotomous variable was created to characterize users from nonusers. Mean daily intake was calculated for each month from the month before pregnancy through the third month, and mean folic acid intake in the first trimester was defined as the average daily intake over these 4 months. For each month and for the total first trimester, daily folic acid intake was also divided into 4 categories (0, <400 ug, 400-800ug, >800 ug). The majority of women (n = 1457) were enrolled in the study after starting their third month of pregnancy and reported all 3 months of folic acid intake directly. Because 85% of the women with complete information reported the same intake in months 2 and 3, women who were enrolled in the study and interviewed in their second month of pregnancy (n = 42) were assumed to have the same folic acid intake in the third month as in the second.

Outcomes

	Outcome	Diagnostic Description
A	Asthma at 6 years (self-reported)	Mother was asked "has the child ever been diagnosed by a doctor or health professional as having asthma?" and "Has your child had wheezing or whistling in the chest in the last 12 months?" A positive answer to both these questions was considered a positive definition of current asthma.

Results

23.1.A Asthma at 6 years

Population: Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM), 2003-2007
Exposure: Maternal supplementation with Folic Acid during Pregnancy
Outcome: Asthma at 6 years
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Month before Conception	768	0.95 (0.68, 1.32)	
First Month	913	0.89 (0.69, 1.23)	
Second Month	1218	1.31 (0.89, 1.93)	
Third Month	1288	0.94 (0.62, 1.43)	
First trimester	1381	1.23 (0.73, 2.07)	

Statistical Method(s)

Endpoints: Asthma at 6 years
Adjustment factors: family income, maternal asthma, maternal marital status
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic regression was used to assess the association between folic acid supplementation in pregnancy and asthma in the children and expressed the effect estimates as odds ratios with 95% confidence intervals (CIs).

23.2. Exposure: Maternal supplementation with Folic Acid during Pregnancy (amount per month)

Method	Description	Analysis
questionnaire	The pregnant women were interviewed, usually at home, before 24 weeks of gestational age. Information on folic acid, iron, and vitamin use was obtained before 24 weeks of gestation from the following questions in the prenatal exposure questionnaire: “Have you used any of the following vitamin or mineral supplements: prenatal supplement vitamins, multivitamin, vitamin A, vitamin C, vitamin E, iron/ferrous sulphate, folic acid/folate, calcium, or other; specify.” If a respondent answered yes, she was specifically asked how often each item had been used (not at all, once a month, 2-3 times a month, twice a week, 3-4 times a week, 5-6 times a week, once a day, or 2 or more times a day). This information was collected for the month before conception through the third month of pregnancy.	We collected information on folic acid content (micrograms) in each of the selfreported vitamin supplements. Using the detailed frequency information from the pregnancy questionnaire, we could calculate mean daily folic acid intake. Prenatal vitamins were estimated to contain 800 ug folic acid per tablet, whereas vitamin supplements were estimated to contain 400 ug folic acid per tablet. Adichotomous variable was created to characterize users from nonusers. Mean daily intake was calculated for each month from the month before pregnancy through the third month, and mean folic acid intake in the first trimester was defined as the average daily intake over these 4 months. For each month and for the total first trimester, daily folic acid intake was also divided into 4 categories (0, <400 ug, 400-800ug, >800 ug). The majority of women (n = 1457) were enrolled in the study after starting their third month of pregnancy and reported all 3 months of folic acid intake directly. Because 85% of the women with complete information reported the same intake in months 2 and 3, women who were enrolled in the study and interviewed in their second month of pregnancy (n = 42) were assumed to have the same folic acid intake in the third month as in the second.

Outcomes

	Outcome	Diagnostic Description
A	Asthma at 6 years (self-reported)	Mother was asked "has the child ever been diagnosed by a doctor or health professional as having asthma?" and "Has your child had wheezing or whistling in the chest in the last 12 months?" A positive answer to both these questions was considered a positive definition of current asthma.

Results

23.2.A Asthma at 6 years

Population: Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM), 2003-2007
Exposure: Maternal supplementation with Folic Acid during Pregnancy (amount per month)
Outcome: Asthma at 6 years
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No use, month before conception	731	1.0	
<400 ug, month before conception	89	1.29 (0.7, 2.4)	
400-800 ug, month before conception	625	0.89 (0.62, 1.27)	
>800 ug, month before conception	54	1.02 (0.44, 2.4)	
No use, month 1 of pregnancy	586	1.0	
<400 ug, month 1 of pregnancy	87	1.31 (0.71, 2.41)	
400-800 ug, month 1 of pregnancy	746	0.82 (0.58, 1.17)	
>800 ug, month 1 of pregnancy	80	0.94 (0.46, 1.97)	
No use, month 2 of pregnancy	281	1.0	
<400 ug, month 2 of pregnancy	92	1.03 (0.49, 2.14)	
400-800 ug, month 2 of pregnancy	1009	1.45 (0.97, 2.16)	
>800 ug, month 2 of pregnancy	117	0.88 (0.42, 1.82)	
No use, month 3 of pregnancy	191	1.0	
<400 ug, month 3 of pregnancy	69	0.8 (0.37, 1.72)	
400-800 ug, month 3 of pregnancy	1144	0.96 (0.63, 1.47)	
>800 ug, month 3 of pregnancy	95	0.79 (0.37, 1.68)	
No use, first trimester overall	118	1.0	
<400 ug, first trimester overall	342	1.34 (0.76, 2.35)	
400-800 ug, first trimester overall	953	1.18 (0.76, 2.35)	
>800 ug, first trimester overall	86	0.73 (0.28, 1.87)	

Statistical Method(s)

Endpoints: Asthma at 6 years
Adjustment factors: family income, maternal asthma, maternal marital status
Statistical metric: adjusted odds ratio
Statistical metric description: Logistic regression was used to assess the association between folic acid supplementation in pregnancy and asthma in the children and expressed the effect estimates as odds ratios with 95% confidence intervals (CIs).

23.3. Exposure: Maternal supplementation with Folic Acid during Pregnancy (per 100 ug increase in daily intake)

Method	Description	Analysis
questionnaire	The pregnant women were interviewed, usually at home, before 24 weeks of gestational age. Information on folic acid, iron, and vitamin use was obtained before 24 weeks of gestation from the following questions in the prenatal exposure questionnaire: “Have you used any of the following vitamin or mineral supplements: prenatal supplement vitamins, multivitamin, vitamin A, vitamin C, vitamin E, iron/ferrous sulphate, folic acid/folate, calcium, or other; specify.” If a respondent answered yes, she was specifically asked how often each item had been used (not at all, once a month, 2-3 times a month, twice a week, 3-4 times a week, 5-6 times a week, once a day, or 2 or more times a day). This information was collected for the month before conception through the third month of pregnancy.	We collected information on folic acid content (micrograms) in each of the selfreported vitamin supplements. Using the detailed frequency information from the pregnancy questionnaire, we could calculate mean daily folic acid intake. Prenatal vitamins were estimated to contain 800 ug folic acid per tablet, whereas vitamin supplements were estimated to contain 400 ug folic acid per tablet. Adichotomous variable was created to characterize users from nonusers. Mean daily intake was calculated for each month from the month before pregnancy through the third month, and mean folic acid intake in the first trimester was defined as the average daily intake over these 4 months. For each month and for the total first trimester, daily folic acid intake was also divided into 4 categories (0, <400 ug, 400-800ug, >800 ug). The majority of women (n = 1457) were enrolled in the study after starting their third month of pregnancy and reported all 3 months of folic acid intake directly. Because 85% of the women with complete information reported the same intake in months 2 and 3, women who were enrolled in the study and interviewed in their second month of pregnancy (n = 42) were assumed to have the same folic acid intake in the third month as in the second.

Outcomes

	Outcome	Diagnostic Description
A	Asthma at 6 years (self-reported)	Mother was asked "has the child ever been diagnosed by a doctor or health professional as having asthma?" and "Has your child had wheezing or whistling in the chest in the last 12 months?" A positive answer to both these questions was considered a positive definition of current asthma

Results

23.3.A Asthma at 6 years

Population: Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM), 2003-2007
Exposure: Maternal supplementation with Folic Acid during Pregnancy (per 100 ug increase in daily intake)
Outcome: Asthma at 6 years
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Month before Conception	768	0.98 (0.94, 1.03)	
First Month	913	0.98 (0.94, 1.02)	
Second Month	1218	0.99 (0.95, 1.03)	
Third Month	1288	0.99 (0.95, 1.03)	
First trimester	1381	0.98 (0.93, 1.04)	

Statistical Method(s)

Endpoints: Asthma at 6 years
Adjustment factors: family income, maternal asthma, maternal marital status
Statistical metric: adjusted odds ratio
Statistical metric description:

24. MATSUI, 2009

Full citation: Matsui EC and Matsui W. Higher serum folate levels are associated with a lower risk of atopy and wheeze. J. Allergy Clin. Immunol. 2009; 123 (6):1253-9.e2.

Funding: Supported by grants from the National Institute of Allergy and Infectious Diseases (R01AI070630) and the National Institutes of Environmental Health Sciences (DISCOVER Award 5P50ES015903).

NHANES (2005-2006)

Age: 38.3 (mean), from 2.0-85.0 years	**Study design:** Cross-sectional (**n =** 8083)
Gender: Male and Female **Ethnicities:** Black or African American, Hispanic/Latino, White, Other	**Country:** United States **Region:** national **State:**
Inclusion criteria: serum folate and total IgE measured	**Exclusion critieria:**

24.1. Exposure: Serum folate

Method	Description	Analysis
assay	Serum folate levels were measured by means of radioassay with the Quantaphase II Folate kit (Bio-Rad Laboratories, Hercules, Calif).	Serum folate levels ranged from 0.7 to 171.0 ng/mL and were stratified by quintile. The quintile cutoff points were as follows: quintile 1, 0.7 to 8.1 ng/mL; quintile 2, 8.2 to 10.9 ng/mL; quintile 3, 11.0 to 13.8 ng/mL; quintile 4, 13.9 to 17.9 ng/mL; and quintile 5, 18.0 to 171.0 ng/mL.

Outcomes

	Outcome	Diagnostic Description
A	Asthma, doctor diagnosed (medical professional or test)	A participant was considered to have doctor-diagnosed asthma if he or she responded affirmatively to the following question: ‘‘Has a doctor or other health professional ever told you that you have asthma?"
B	Atopy (medical professional or test)	Serum total IgE levels were measured with the ImmunoCAP system (Phadia, Uppsala, Sweden). Cat-, dog (e5)–, Dermatophagoides farinae-, Dermatophagoides pteronyssinus-, Alternaria species-, and cockroach-specific IgE levels were also measured with the ImmunoCAP system. A level of 0.35 kU/L or greater was considered positive, and atopy was defined as at least 1 positive allergen-specific IgE measurement.
C	High total IgE (>100kU/l) (medical professional or test)	Serum total IgE levels were measured with the ImmunoCAP system (Phadia, Uppsala, Sweden). Cat-, dog (e5)–, Dermatophagoides farinae-, Dermatophagoides pteronyssinus-, Alternaria species-, and cockroach-specific IgE levels were also measured with the

	Outcome	Diagnostic Description
		ImmunoCAP system. A level of 0.35 kU/L or greater was considered positive, and atopy was defined as at least 1 positive allergen-specific IgE measurement.
D	Serum total IgE (medical professional or test)	Serum total IgE levels were measured with the ImmunoCAP system (Phadia, Uppsala, Sweden). Cat-, dog (e5)–, Dermatophagoides farinae-, Dermatophagoides pteronyssinus-, Alternaria species-, and cockroach-specific IgE levels were also measured with the ImmunoCAP system. A level of 0.35 kU/L or greater was considered positive, and atopy was defined as at least 1 positive allergen-specific IgE measurement.
E	Wheeze, past 12 months (medical professional or test)	A participant was considered to have had wheeze in the preceding 12 months if he or she responded affirmatively to the following question: ''In the past 12 months, have you had wheezing or whistling in your chest?''

Results

24.1.A Asthma, doctor diagnosed

Population: NHANES (2005-2006)
Exposure: Serum folate
Outcome: Asthma, doctor diagnosed
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1 (0.7-8.1 ng/mL)	-	1.0	
Q2 (8.2-10.9 ng/mL)	-	1.01 (0.76, 1.33)	
Q3 (11.0-13.8 ng/mL)	-	0.82 (0.63, 1.07)	
Q4 (13.9-17.9 ng/mL)	-	0.83 (0.64, 1.07)	
Q5 (18.0-171.0 ng/mL)	-	0.84 (0.7, 1.02)	

24.1.B Atopy

Population: NHANES (2005-2006)
Exposure: Serum folate
Outcome: Atopy
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1 (0.7-8.1 ng/mL)	-	1.0	
Q2 (8.2-10.9 ng/mL)	-	0.89 (0.71, 1.12)	
Q3 (11.0-13.8 ng/mL)	-	0.76 (0.65, 0.88)	0.05
Q4 (13.9-17.9 ng/mL)	-	0.77 (0.59, 0.99)	0.05
Q5 (18.0-171.0 ng/mL)	-	0.69 (0.57, 0.85)	0.05

24.1.C High total IgE (>100kU/l)

Population: NHANES (2005-2006)
Exposure: Serum folate
Outcome: High total IgE (>100kU/l)
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1 (0.7-8.1 ng/mL)	-	1.0	
Q2 (8.2-10.9 ng/mL)	-	0.94 (0.73, 1.21)	
Q3 (11.0-13.8 ng/mL)	-	0.89 (0.77, 1.03)	
Q4 (13.9-17.9 ng/mL)	-	0.73 (0.58, 0.93)	0.05
Q5 (18.0-171.0 ng/mL)	-	0.7 (0.53, 0.92)	0.05

24.1.D Serum total IgE

Population: NHANES (2005-2006)
Exposure: Serum folate
Outcome: Serum total IgE
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Q1 (0.7-8.1 ng/mL)	-	-	
Q2 (8.2-10.9 ng/mL)	-	-	
Q3 (11.0-13.8 ng/mL)	-	-	
Q4 (13.9-17.9 ng/mL)	-	-	
Q5 (18.0-171.0 ng/mL)	-	-	0.001

24.1.E Wheeze, past 12 months

Population: NHANES (2005-2006)
Exposure: Serum folate
Outcome: Wheeze, past 12 months
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1 (0.7-8.1 ng/mL)	-	1.0	
Q2 (8.2-10.9 ng/mL)	-	0.81 (0.57, 1.15)	
Q3 (11.0-13.8 ng/mL)	-	0.82 (0.64, 1.04)	
Q4 (13.9-17.9 ng/mL)	-	0.64 (0.46, 0.89)	0.05
Q5 (18.0-171.0 ng/mL)	-	0.6 (0.44, 0.82)	0.05

Statistical Method(s)

Endpoints: Serum total IgE
Adjustment factors:
Statistical metric: other
Statistical metric description: Statistical analyses were performed with StataSE 8.0 software (StataCorp, College Station, Tex). The primary sampling units and strata were taken into account using the variables provided in the NHANES dataset to account for the complex survey design. Sampling weights provided by the NHANES were used to generate estimates that are representative of the US noninstitutionalized civilian population. Relationships between variables of interest were examined by using logistic or linear regression methods that accounted for the sampling design and the weighting of the observations in the NHANES dataset. Bivariate analyses of folate and the outcome variables of interest were used to examine trends in outcomes across a continuous measure of serum folate, as well as quintiles of folate. A test for trend was performed by using either the continuous folate variable or the variable for quintiles of folate, without inclusion of dummy variables. Multivariate models were adjusted for age,

sex, race/ethnicity, and poverty income ratio, which is the ratio of family income to the poverty threshold.

Endpoints: High total IgE (>100kU/l); Atopy; Asthma, doctor diagnosed; Wheeze, past 12 months
Adjustment factors: age, poverty index ratio, race/ethnicity, sex
Statistical metric: adjusted odds ratio
Statistical metric description: Statistical analyses were performed with StataSE 8.0 software (StataCorp, College Station, Tex). The primary sampling units and strata were taken into account using the variables provided in the NHANES dataset to account for the complex survey design. Sampling weights provided by the NHANES were used to generate estimates that are representative of the US noninstitutionalized civilian population. Relationships between variables of interest were examined by using logistic or linear regression methods that accounted for the sampling design and the weighting of the observations in the NHANES dataset. Bivariate analyses of folate and the outcome variables of interest were used to examine trends in outcomes across a continuous measure of serum folate, as well as quintiles of folate. A test for trend was performed by using either the continuous folate variable or the variable for quintiles of folate, without inclusion of dummy variables. Multivariate models were adjusted for age, sex, race/ethnicity, and poverty income ratio, which is the ratio of family income to the poverty threshold.

25. MDA, 2010

Full citation: Mda S, van Raaij JM, de Villiers FP, MacIntyre UE, Kok FJ. 2010. Short-term micronutrient supplementation reduces the duration of pneumonia and diarrheal episodes in HIV-infected children. J Nutr 140(5): 969-974.

Funding: Supported by the Ellison Medical Foundation.

HIV-INFECTED CHILDREN

Age: age 4-24 months	**Study design:** Controlled trial (**n =** 118)
Gender: Male and Female **Ethnicities:**	**Country:** South Africa **Region:** **State:**
Inclusion criteria: children admitted with diarrhea or pneumonia	**Exclusion critieria:** children admitted because of pneumonia complicated by respiratory failure, children who received vitamin or micronutrient supplementation in the previous 2 mo, children whose diarrheal episode was already longer than 72 h on admission, children who were on antiretroviral therapy (ART), chronic illness unrelated to HIV

25.1. Exposure: Multiple micronutrient supplementation

Method	Description	Analysis
supplementation	crushable tablet form: 70 ug folic acid + 0.6 mg riboflavin, 8 mg niacin, 0.6 mg pyridoxine, 1 ug cobalamin, 300 ug retinol, 0.6 mg thiamin, 25 mg ascorbic acid, 5 mg 1,25-dihydrocholecalciferol, etc. per day (until discharge from hospital) (serum measures via blood samples NOT taken for folate)	intervention administered by the nurse in the ward

Outcomes

	Outcome	Diagnostic Description
A	Duration of hospitalization with pneumonia (medical professional or test)	Pneumonia was defined as an illness during which a child is reported to have a cough, has a temperature of 388C or more, and has an elevated respiratory rate above the age-specific value on a minute estimation (50 breaths/min)

Results

25.1.A Duration of hospitalization with pneumonia

Population: HIV-infected children in South Africa
Exposure: Multiple micronutrient supplementation

Outcome: Duration of hospitalization with pneumonia
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Placebo	28	-	
Multi supplement with 70 ug folic acid/day	32	-	

Statistical Method(s)

Endpoints: Duration of hospitalization with pneumonia
Adjustment factors:
Statistical metric: mean
Statistical metric description:

26. MIYAKE, 2011

Full citation: Miyake Y, Sasaki S, Tanaka K, Hirota Y. 2011. Maternal B vitamin intake during pregnancy and wheeze and eczema in Japanese infants aged 16-24 months: the Osaka Maternal and Child Health Study. Pediatr Allergy Immunol 22(1 Pt 1): 69-74.

Funding: This study was supported by a Grant-in-Aid (13770206, 16790351) for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology and Health and Labour Sciences Research Grants, Research on Allergic Disease and Immunology from the Ministry of Health, Labour, and Welfare, Japan.

OSAKA MATERNAL AND CHILD HEALTH STUDY

Age: 16-24 months	**Study design:** Prospective (**n =** 763)
Gender: Male and Female **Ethnicities:** Asian	**Country:** Japan **Region:** Osaka Prefecture **State:**
Inclusion criteria: mother-child pairs who participated in the baseline, second, and third surveys, women who became pregnant in Neyagawa City and other municipalities in Osaka Prefecture	**Exclusion critieria:**

26.1. Exposure: Maternal intake of folate during pregnancy

Method	Description	Analysis
questionnaire	A self-administered, semi-quantitative, comprehensive, diet history questionnaire (DHQ) administered at baseline that assesses dietary habits during the preceding month. This structured questionnaire that asks about the consumption frequency and portion size of selected foods commonly consumed in Japan as well as general dietary behavior and usual cooking methods.	Estimates of daily intake of foods (150 items in total), energy, and selected nutrients were calculated using an ad hoc computer algorithm for the DHQ, based on the Standard Tables of Food Composition in Japan. Because only a small number of participants used vitamin B complex (4.1%) and multivitamin (4.2%) supplements at least once a week at baseline, information on these dietary supplements was not considered in the present analysis. According to a validation study of 92 women of 31–69 yr of age, Pearson's correlation coefficients between the DHQ and 16-day weighed dietary records were 0.60 for folate.

Outcomes

	Outcome	Diagnostic Description

	Outcome	Diagnostic Description
A	Eczema (self-reported)	Symptoms of eczema based on the International Study of Asthma and Allergies in Childhood (ISAAC) phase-I questionnaire. Affirmative answers to the following three questions were required: 'Has your child ever had an itchy rash which was coming and going for at least 6 months?', 'Has your child had this itchy rash at any time in the last 12 months?' and 'Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?'
B	Wheeze (self-reported)	Wheeze based on the International Study of Asthma and Allergies in Childhood (ISAAC) phase-I questionnaire, defined as present if the mother answered 'yes' to the question 'Has your child had wheezing or whistling in the chest in the last 12 months?'

Results

26.1.A Eczema

Population: OMCHS cohort, infants aged 16-24 months
Exposure: Maternal intake of folate during pregnancy
Outcome: Eczema
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1 (median = 206.8)	-	1.0	
Q2 (median = 255.1)	-	0.57 (0.31, 1.01)	
Q3 (median = 291.2)	-	1.0 (0.57, 1.79)	
Q4 (median = 370.6)	-	1.01 (0.51, 2.0)	

26.1.B Wheeze

Population: OMCHS cohort, infants aged 16-24 months
Exposure: Maternal intake of folate during pregnancy
Outcome: Wheeze
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1 (median = 206.8)	-	1.0	
Q2 (median = 255.1)	-	1.12 (0.65, 1.95)	
Q3 (median = 291.2)	-	1.56 (0.89, 2.75)	
Q4 (median = 370.6)	-	1.28 (0.65, 2.5)	

Statistical Method(s)

Endpoints: Eczema; Wheeze
Adjustment factors: age, age at which solid foods were introduced, birth weight, breast feeding duration, changes in maternal diet in previous 1 month, family income, gestational age, household smoking in same room as infant, maternal age at birth, maternal education, maternal history of allergic rhinitis, maternal history of asthma, maternal history of atopic eczema, maternal intake of beta carotene, maternal intake of calcium, maternal intake of docosahexaenoic acid, maternal intake of n-6 polyunsaturated fatty acids, maternal intake of vitamin D, maternal intake of vitamin E, maternal smoking during pregnancy, number older siblings, paternal education, paternal history of allergic

rhinitis, paternal history of asthma, paternal history of atopic eczema, residential municipality at baseline, season when baseline data were collected, sex
Statistical metric: adjusted odds ratio
Statistical metric description: Intake of dietary factors under study was categorized at quartile points based on the distribution in 763 subjects. Maternal age, gestation at baseline, residential municipality at baseline, family income, paternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, changes in maternal diet in the previous 1 month, season when data at baseline were collected, maternal smoking during pregnancy, baby's older siblings, baby's sex, baby's birth weight, household smoking in the same room as the infant, breastfeeding duration, age at which solid foods were introduced, age of the infant at the third survey, and maternal intake of docosahexaenoic acid, n-6 polyunsaturated fatty acids, vitamin D, calcium, vitamin E, and b-carotene during pregnancy were a priori selected as potential confounding factors. Logistic regression analysis was performed to estimate crude odds ratios (ORs) and their 95% confidence intervals (CIs) of wheeze and eczema according to the quartile of dietary factors under investigation, with the lowest quartile as the reference. Multiple logistic regression analysis was employed to adjust for potential confounding factors. Trend of association was assessed by a logistic regression model assigning consecutive integers (1 to 4) to the quartiles of the exposure variables.

27. NWARU, 2011

Full citation: Nwaru BI, Erkkola M, Ahonen S, Kaila M, Kronberg-Kippila C, Ilonen J, Simell O, Knip M, Veijola R, Virtanen SM. 2011. Intake of antioxidants during pregnancy and the risk of allergies and asthma in the offspring. European Journal of Clinical Nutrition 65(8): 937-943.

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FINNISH TYPE 1 DIABETES PREDICTION AND PREVENTION NUTRITION STUDY

Age: 5.0 (mean)	**Study design:** Prospective (**n =** 2441)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Finland **Region:** Northern & Southern Finland **State:** Oulu and Tampere
Inclusion criteria: born between 20 October 1997 and 29 February 2004, participation in dietary follow-up of Finnish Type 1 Diabetes Prediction and Prevention Study	**Exclusion critieria:**

27.1. Exposure: Maternal intake of folate during pregnancy- dietary

Method	Description	Analysis
questionnaire	Maternal food consumption during the eighth month of pregnancy was assessed by means of a validated 181-item food frequency questionnaire (FFQ) (Erkkola et al., 2001) designed specially to reflect the diet of Finnish women of child-bearing age." "Information was also requested concerning the use of supplements during the whole pregnancy period, including the type, brand, and manufacturer of all the supplements used, the amount of each supplement used per day or week, and the weeks of pregnancy during which each supplement was used.	Average daily intakes of supplements were calculated as separate variables by in-house software of the National Institute of Health and Welfare.

Outcomes

	Outcome	Diagnostic Description
A	Allergic Rhinitis	Rhinitis was defined as sneezing, nasal congestion or rhinitis other

	Outcome	Diagnostic Description
	(self-reported)	than with respiratory infections, accompanied by itching of the eye and tearing during the previous 12 months. Age of onset of rhinitis was indicated by the parents at the time of doctor diagnosis.
B	Asthma (self-reported)	"At the age of 5 years, families of the participating children completed a questionnaire modified from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire on the child's history of allergic symptoms and asthma (Asher et al., 1995; Remes et al., 1998). Asthma was defined as doctor-diagnosed asthma plus either any wheezing symptom during the preceding 12 months or use of asthma medication during the preceding 12 months. Age of the child at asthma diagnosis was determined by the question: 'at what age was asthma diagnosed by a doctor?'"
C	Atopic Eczema (self-reported)	Eczema was defined with a positive answer to the question, 'Has your child ever had atopic eczema?'

Results

27.1.A Allergic Rhinitis

Population: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study, dietary follow-up
Exposure: Maternal intake of folate during pregnancy- dietary
Outcome: Allergic Rhinitis
Statistical metric: adjusted hazard ratio

Group	N	adjHR 95% CI (low, high)	*p*-value
Dietary Folic Acid Intake	2441	0.95 (0.79, 1.15)	

27.1.B Asthma

Population: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study, dietary follow-up
Exposure: Maternal intake of folate during pregnancy- dietary
Outcome: Asthma
Statistical metric: adjusted hazard ratio

Group	N	adjHR 95% CI (low, high)	*p*-value
Dietary Folic Acid Intake	2441	1.04 (0.71, 1.52)	

27.1.C Atopic Eczema

Population: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study, dietary follow-up
Exposure: Maternal intake of folate during pregnancy- dietary
Outcome: Atopic Eczema
Statistical metric: adjusted hazard ratio

Group	N	adjHR 95% CI (low, high)	*p*-value
Dietary Folic Acid Intake	2441	0.91 (0.75, 1.09)	

Statistical Method(s)

Endpoints: Atopic Eczema
Adjustment factors: atopic eczema by 6 months of age, gestational age, maternal age at birth, maternal basic education (less than high school, high school graduate), maternal intake of polyunsaturated fatty

acids, maternal intake of vitamin D, maternal smoking during pregnancy, mode of delivery, parental allergic rhinitis, parental asthma, pets at home at 1 year of age, place of birth (Southern or Northern Finland), season born, sex, siblings, total energy intake
Statistical metric: adjusted hazard ratio
Statistical metric description: logistic regression was used for the eczema endpoint

Endpoints: Asthma
Adjustment factors: atopic eczema by 6 months of age, gestational age, maternal age at birth, maternal basic education (less than high school, high school graduate), maternal intake of polyunsaturated fatty acids, maternal intake of vitamin D, maternal smoking during pregnancy, mode of delivery, parental allergic rhinitis, parental asthma, pets at home at 1 year of age, place of birth (Southern or Northern Finland), season born, sex, siblings, total energy intake
Statistical metric: adjusted hazard ratio
Statistical metric description: Cox proportional hazards regression was used to analyze the association between the antioxidants and asthma

Endpoints: Allergic Rhinitis
Adjustment factors: atopic eczema by 6 months of age, gestational age, maternal age at birth, maternal basic education (less than high school, high school graduate), maternal intake of polyunsaturated fatty acids, maternal intake of vitamin D, maternal smoking during pregnancy, mode of delivery, parental allergic rhinitis, parental asthma, pets at home at 1 year of age, place of birth (Southern or Northern Finland), season born, sex, siblings, total energy intake
Statistical metric: adjusted hazard ratio
Statistical metric description: Cox proportional hazards regression was used to analyze the association between the antioxidants and rhinitis endpoints

27.2. Exposure: Maternal intake of folate during pregnancy- total

Method	Description	Analysis
questionnaire	Maternal food consumption during the eighth month of pregnancy was assessed by means of a validated 181-item food frequency questionnaire (FFQ) (Erkkola et al., 2001) designed specially to reflect the diet of Finnish women of child-bearing age." "Information was also requested concerning the use of supplements during the whole pregnancy period, including the type, brand, and manufacturer of all the supplements used, the amount of each supplement used per day or week, and the weeks of pregnancy during which each supplement was used.	Average daily intakes of supplements were calculated as separate variables by in-house software of the National Institute of Health and Welfare.

Outcomes

	Outcome	Diagnostic Description
A	Allergic Rhinitis (self-reported)	Rhinitis was defined as sneezing, nasal congestion or rhinitis other than with respiratory infections, accompanied by itching of the eye and tearing during the previous 12 months. Age of onset of rhinitis was indicated by the parents at the time of doctor diagnosis.
B	Asthma (self-reported)	"At the age of 5 years, families of the participating children completed a questionnaire modified from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire on the child's history of allergic symptoms and asthma (Asher et al., 1995; Remes et al., 1998). Asthma was defined as doctor-diagnosed asthma plus either any wheezing symptom during the preceding 12 months or use of asthma medication during the preceding 12 months. Age of the child at asthma diagnosis was determined by the question: 'at what age was asthma diagnosed by a doctor?'"
C	Atopic Eczema (self-reported)	Eczema was defined with a positive answer to the question, 'Has your child ever had atopic eczema?'

Results

27.2.A Allergic Rhinitis

Population: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study, dietary follow-up
Exposure: Maternal intake of folate during pregnancy- total
Outcome: Allergic Rhinitis
Statistical metric: adjusted hazard ratio

Group	N	adjHR 95% CI (low, high)	*p*-value
Total Folic Acid Intake	2441	-	

27.2.B Asthma

Population: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study, dietary follow-up
Exposure: Maternal intake of folate during pregnancy- total
Outcome: Asthma
Statistical metric: adjusted hazard ratio

Group	N	adjHR 95% CI (low, high)	*p*-value
Total Folic Acid Intake	2441	-	

27.2.C Atopic Eczema

Population: Finnish Type 1 Diabetes Prediction and Prevention Nutrition Study, dietary follow-up
Exposure: Maternal intake of folate during pregnancy- total
Outcome: Atopic Eczema
Statistical metric: adjusted hazard ratio

Group	N	adjHR 95% CI (low, high)	*p*-value
Total Folic Acid Intake	2441	-	

Statistical Method(s)

Endpoints: Atopic Eczema
Adjustment factors: atopic eczema by 6 months of age, gestational age, maternal age at birth, maternal basic education (less than high school, high school graduate), maternal intake of polyunsaturated fatty acids, maternal intake of vitamin D, maternal smoking during pregnancy, mode of delivery, parental allergic rhinitis, parental asthma, pets at home at 1 year of age, place of birth (Southern or Northern Finland), season born, sex, siblings, total energy intake
Statistical metric: adjusted hazard ratio
Statistical metric description: logistic regression was used for the eczema endpoint

Endpoints: Asthma
Adjustment factors: atopic eczema by 6 months of age, gestational age, maternal age at birth, maternal basic education (less than high school, high school graduate), maternal intake of polyunsaturated fatty acids, maternal intake of vitamin D, maternal smoking during pregnancy, mode of delivery, parental allergic rhinitis, parental asthma, pets at home at 1 year of age, place of birth (Southern or Northern Finland), season born, sex, siblings, total energy intake
Statistical metric: adjusted hazard ratio
Statistical metric description: Cox proportional hazards regression was used to analyze the association between the antioxidants and asthma

Endpoints: Allergic Rhinitis
Adjustment factors: atopic eczema by 6 months of age, gestational age, maternal age at birth, maternal basic education (less than high school, high school graduate), maternal intake of polyunsaturated fatty acids, maternal intake of vitamin D, maternal smoking during pregnancy, mode of delivery, parental allergic rhinitis, parental asthma, pets at home at 1 year of age, place of birth (Southern or Northern Finland), season born, sex, siblings, total energy intake
Statistical metric: adjusted hazard ratio
Statistical metric description: Cox proportional hazards regression was used to analyze the association between the antioxidants and rhinitis endpoints

28. OH, 2010

Full citation: Oh SY, Chung J, Kim MK, Kwon SO, Cho BH. 2010. Antioxidant nutrient intakes and corresponding biomarkers associated with the risk of atopic dermatitis in young children. Eur J Clin Nutr 64(3): 245-252.

Funding: This study was supported by grant no. R01-2006-000-10887-0 from the Basic Research Program of the Korea Science and Engineering Foundation.

INTERNATIONAL STUDY OF ASTHMA AND ALLERGIES IN CHILDHOOD (ISAAC), KOREAN VERSION

Age: 5.2 (mean)	**Study design:** Case-control (**n =** 422)
Gender: Male and Female **Ethnicities:** Asian	**Country:** Korea, Democratic People's Republic Of **Region:** Seoul and Incheon **State:**
Inclusion criteria: children not taking medication, children with diet unaffected by atopic dermatitis or other diseases, parental consent	**Exclusion critieria:** Energy intake <500 or >4500 kcal, missing data (measures ie fasting blood and urine samples)

28.1. Exposure: Folic Acid intake through Diet

Method	Description	Analysis
questionnaire	Usual dietary intake was assessed by a modified version of the semi-quantitative food frequency questionnaire (FFQ) with 86 food items with 9 non-overlapping frequency response categories. The caretaker was asked to indicate his/her child's average frequency of consumption and portion size of foods during the previous year. Respective correlation coefficients for reproducibility and validity of this instrument ranged 0.54–0.76 and 0.29–0.57 depending on the nutrient. We also assessed intakes of antioxidant-related nutrients, such as vitamin A, C and E, folic acid, and iron, from supplements. We used nutrition supplement information regarding type, specific brand names, and usual daily dose. Information including four different types of nutrition supplements for multiple supplement users was gathered.	Using Computer Aided Nutritional Analysis Program II (CAN PRO II) developed by the Korean Nutrition Society, the amount of each food item included in the FFQ was converted into grams, from which the daily intakes of nutrients were calculated. Doses of supplement were calculated using nutrient content information on product labels.

Outcomes

	Outcome	Diagnostic Description
A	Atopic dermatitis (self-reported)	Cases were those if their parents reported their children as experiencing appearances and disappearances of rashes for at least 6 months or having experienced itchy rashes during the last 12 months, or if their children had been diagnosed with AD by a physician.

Results

28.1.A Atopic dermatitis

Population: International Study of Asthma and Allergies in Childhood (ISAAC), Korean version
Exposure: Folic Acid intake through Diet
Outcome: Atopic dermatitis
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1 Diet	-	1.0	
Q2 Diet	-	0.9 (0.45, 1.79)	
Q3 Diet	-	0.58 (0.3, 1.15)	
Q4 Diet	-	0.51 (0.25, 1.02)	
Q5 Diet	-	0.37 (0.18, 0.73)	0.05

Statistical Method(s)

Endpoints: Atopic dermatitis
Adjustment factors: body mass index (BMI), child's age, monthly household income, parental histories of allergic diseases, sex, supplement intake (yes/no), total energy intake
Statistical metric: adjusted odds ratio
Statistical metric description: The children were divided into five groups on the basis of the levels of total energy and nutrient residuals and compared higher intakes (Q2–Q5) with a low intake (Q1). Nutrient residuals were obtained by adjusting for total energy using a linear regression model in which total energy intake was the independent variable and each nutrient was the dependent variable (Willett and Stampfer, 1986).

28.2. Exposure: Folic Acid intake through Supplements

Method	Description	Analysis
questionnaire	Usual dietary intake was assessed by a modified version of the semi-quantitative food frequency questionnaire (FFQ) with 86 food items with 9 non-overlapping frequency response categories. The caretaker was asked to indicate his/her child's average frequency of consumption and portion size of foods during the previous year. Respective correlation coefficients for reproducibility and validity of this instrument ranged 0.54–0.76 and 0.29–0.57 depending on the nutrient. We also assessed intakes of antioxidant-related nutrients, such as vitamin A, C and E, folic acid, and iron, from supplements. We used nutrition supplement information regarding type, specific brand names, and usual daily dose. Information including four different types of nutrition supplements for multiple supplement users was gathered.	Using Computer Aided Nutritional Analysis Program II (CAN PRO II) developed by the Korean Nutrition Society, the amount of each food item included in the FFQ was converted into grams, from which the daily intakes of nutrients were calculated. Doses of supplement were calculated using nutrient content information on product labels.

Outcomes

	Outcome	Diagnostic Description
A	Atopic dermatitis (self-reported)	Cases were those if their parents reported their children as experiencing appearances and disappearances of rashes for at least 6 months or having experienced itchy rashes during the last 12 months, or if their children had been diagnosed with AD by a physician.

Results

28.2.A Atopic dermatitis

Population: International Study of Asthma and Allergies in Childhood (ISAAC), Korean version
Exposure: Folic Acid intake through Supplements
Outcome: Atopic dermatitis
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Nonusers	-	1.0	
Q4 (5-120ug) supplement	-	1.88 (0.65, 5.42)	
Q5 (130-780ug) supplement	-	0.88 (0.47, 1.64)	

Statistical Method(s)

Endpoints: Atopic dermatitis
Adjustment factors: body mass index (BMI), child's age, monthly household income, parental histories of allergic diseases, sex, supplement intake (yes/no), total energy intake
Statistical metric: adjusted odds ratio
Statistical metric description: The children were divided into five groups on the basis of the levels of total energy and nutrient residuals and compared higher intakes (Q2–Q5) with a low intake (Q1). Nutrient residuals were obtained by adjusting for total energy using a linear regression model in which total energy intake was the independent variable and each nutrient was the dependent variable (Willett and Stampfer, 1986).

28.3. Exposure: Total Folic acid intake through Food and Dietary Supplements

Method	Description	Analysis
questionnaire	Usual dietary intake was assessed by a modified version of the semi-quantitative food frequency questionnaire (FFQ) with 86 food items with 9 non-overlapping frequency response categories. The caretaker was asked to indicate his/her child's average frequency of consumption and portion size of foods during the previous year. Respective correlation coefficients for reproducibility and validity of this instrument ranged 0.54–0.76 and 0.29–0.57 depending on the nutrient. We also assessed intakes of antioxidant-related nutrients, such as vitamin A, C and E, folic acid, and iron, from supplements. We used nutrition supplement information regarding type, specific brand names, and usual daily dose. Information including four different types of nutrition supplements for multiple supplement users was gathered.	Using Computer Aided Nutritional Analysis Program II (CAN PRO II) developed by the Korean Nutrition Society, the amount of each food item included in the FFQ was converted into grams, from which the daily intakes of nutrients were calculated. Doses of supplement were calculated using nutrient content information on product labels.

Outcomes

	Outcome	Diagnostic Description
A	Atopic dermatitis (self-reported)	Cases were those if their parents reported their children as experiencing appearances and disappearances of rashes for at least 6 months or having experienced itchy rashes during the last 12 months, or if their children had been diagnosed with AD by a physician.

Results

28.3.A Atopic dermatitis

Population: International Study of Asthma and Allergies in Childhood (ISAAC), Korean version
Exposure: Total Folic acid intake through Food and Dietary Supplements
Outcome: Atopic dermatitis
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Q1	-	-	
Q2	-	0.49 (0.24, 0.98)	0.05
Q3	-	0.58 (0.29, 1.16)	
Q4	-	0.37 (0.18, 0.75)	0.05
Q5	-	0.33 (0.16, 0.7)	0.05

Statistical Method(s)

Endpoints: Atopic dermatitis
Adjustment factors: body mass index (BMI), child's age, monthly household income, parental histories of allergic diseases, sex, supplement intake (yes/no), total energy intake
Statistical metric: adjusted odds ratio
Statistical metric description: The children were divided into five groups on the basis of the levels of total energy and nutrient residuals and compared higher intakes (Q2–Q5) with a low intake (Q1). Nutrient residuals were obtained by adjusting for total energy using a linear regression model in which total energy intake was the independent variable and each nutrient was the dependent variable (Willett and Stampfer, 1986).

29. OKUPA, 2013

Full citation: Okupa AY, Lemanske RF, Jr., Jackson DJ, Evans MD, Wood RA, Matsui EC. 2013. Early-life folate levels are associated with incident allergic sensitization. J Allergy Clin Immunol 131(1): 226-228.

Funding: This study was funded by National Institutes of Health grants M01 RR03186, R01 HL61879, 1UL1RR025011, and P01 HL70831 5P50ES015903 P01 ES018176-5R01AI070630.

CHILDHOOD ORIGINS OF ASTHMA (COAST) HIGH-RISK BIRTH COHORT

Age: 2.0-8.0 years	**Study design:** Prospective (**n =** 138)
Gender: Male and Female **Ethnicities:** Other, Black or African American, Hispanic/Latino, White	**Country:** United States **Region:** **State:** Wisconsin
Inclusion criteria: children at risk of developing asthma (at least one parent has asthma, allergy or both)	**Exclusion critieria:** APGAR scores of at least 7 at 5 min., neonatal respiratory difficulties or anomalies, not born at term

29.1. Exposure: Early Childhood Folate Status

Method	Description	Analysis
plasma	Folate levels were measured in our cohort (n 5 138) at ages 2, 4, 6, and 8 years	no description other than "these levels were measured by the Johns Hopkins Hospital Clinical Lab"

Outcomes

	Outcome	Diagnostic Description
A	Allergic sensitization (medical professional or test)	Allergic sensitization was determined by fluorenzyme immunoassay at age 6 years. Any single result of 0.35 kU/L or more was considered as positive. For fluorenzyme immunoassay testing, we collected blood, isolated plasma, utilized the UniCap system to measure IgE levels, and evaluated the following perennial and seasonal allergens—dust mite, cat, dog, birch, timothy grass, alternaria, ragweed, peanut, and egg.
B	Food Sensitization (medical professional or test)	Sensitization was defined as 1 or more positive (>0.34) specific IgE results at the annual blood draw. Foods included milk/egg/peanut for years 1 to 3 and egg/peanut for years 5+. Perennial allergens included dog, cat, Alternaria alternata, Dermatophagoides pteronyssinus and Dermatophagoides farinae. Cockroach was added to the panel of allergens starting at age 5 years. Seasonal allergens were tested starting at age 5 years and included ragweed, timothy grass, and silver birch.
C	Total IgE (medical professional or test)	For fluorenzyme immunoassay testing, we collected blood, isolated plasma, utilized the UniCap system to measure IgE levels.

	Outcome	Diagnostic Description
D	Wheezing Illness (medical professional or test)	A wheezing respiratory illness during the first 3 years of life was defined as meeting 1 or more of the following criteria: (1) physician-diagnosed wheezing at an office visit; (2) an illness for which the child was prescribed short- or long-acting beta-agonists and/or controller medications; or (3) an illness given the following specific diagnoses: bronchiolitis, wheezing illness, reactive airway disease, asthma, or asthma exacerbation.

Results

29.1.A Allergic sensitization

Population: Childhood Origins of Asthma (COAST) high-risk birth cohort
Exposure: Early Childhood Folate Status
Outcome: Allergic sensitization
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Cluster A	104	-	
Cluster B (higher folate status earlier in life)	34	-	0.05

29.1.B Food Sensitization

Population: Childhood Origins of Asthma (COAST) high-risk birth cohort
Exposure: Early Childhood Folate Status
Outcome: Food Sensitization
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Cluster A	104	-	
Cluster B (higher folate status earlier in life)	34	-	0.05

29.1.C Total IgE

Population: Childhood Origins of Asthma (COAST) high-risk birth cohort
Exposure: Early Childhood Folate Status
Outcome: Total IgE
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Cluster A	104	-	
Cluster B (higher folate status earlier in life)	34	-	

29.1.D Wheezing Illness

Population: Childhood Origins of Asthma (COAST) high-risk birth cohort
Exposure: Early Childhood Folate Status
Outcome: Wheezing Illness
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Cluster A	104	-	
Cluster B (higher folate status earlier in life)	34	-	

Statistical Method(s)

Endpoints: Wheezing Illness; Allergic sensitization; Food Sensitization
Adjustment factors: gender, socioeconomic status
Statistical metric: other
Statistical metric description: rates

Endpoints: Total IgE
Adjustment factors:
Statistical metric: other
Statistical metric description: rates

30. PFAB, 2007

Full citation: Pfab F, Willi R, Albert A, Huss-Marp J, Athanasiadis GI, Jakob T, Ollert M, Ring J, Darsow U. 2007. Anaphylactic reaction to folic acid verified by provocational testing. Allergy 62(7): 823-824.

Funding: none reported

CASE REPORT, WOMAN IN GERMANY

Age: 44.0 (None)	**Study design:** Case-report (**n** = 1)
Gender: Female **Ethnicities:** White	**Country:** Germany **Region:** Munchen **State:**
Inclusion criteria:	**Exclusion critieria:**

30.1. Exposure: multivitamin products

Method	Description	Analysis
none	various multivitamin products from different sources, such as multivitamin juices, tablets and sweets in the last 5 years	self-reported

Outcomes

	Outcome	Diagnostic Description
A	anaphylactic reaction (self-reported)	anaphylactic reaction with tachycardia, generalized skin eruption and dyspnea within 20 min after intake

Results

30.1.A <u>anaphylactic reaction</u>

Population: case report, woman in Germany
Exposure: multivitamin products
Outcome: anaphylactic reaction
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
multivitamin products	1	-	

Statistical Method(s)

Endpoints: anaphylactic reaction
Adjustment factors:
Statistical metric: other
Statistical metric description:

30.2. Exposure: oral provocation, Dreisafol

Method	Description	Analysis
500	500 ug folic acid (1/10 tablet)	intervention

Outcomes

	Outcome	Diagnostic Description
A	urticarial eruption, conjunctival injection, dyspnea, tachycardia and blood pressure decrease (medical professional or test)	patient reacted with a generalized urticarial eruption, conjunctival injection, dyspnea, tachycardia and blood pressure decrease (90/50 mmHg) 10 min after ingestion

Results

30.2.A urticarial eruption, conjunctival injection, dyspnea, tachycardia and blood pressure decrease

Population: case report, woman in Germany
Exposure: oral provocation, Dreisafol
Outcome: urticarial eruption, conjunctival injection, dyspnea, tachycardia and blood pressure decrease
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
oral provocation, Dreisafol	1	-	

Statistical Method(s)

Endpoints: urticarial eruption, conjunctival injection, dyspnea, tachycardia and blood pressure decrease
Adjustment factors:
Statistical metric: other
Statistical metric description:

30.3. Exposure: oral provocation, vaso-loges

Method	Description	Analysis
110	oral provocation with 1/4 tablet vaso-loges (one whole tablet contains 440 ug folic acid, 4.4 mg vitamin B6 and 8.8 ug vitamin B12)	intervention

Outcomes

	Outcome	Diagnostic Description
A	urticarial eruption and laryngeal dyspnea (medical professional or test)	generalized urticarial eruption and mild laryngeal dyspnea

Results

30.3.A urticarial eruption and laryngeal dyspnea

Population: case report, woman in Germany
Exposure: oral provocation, vaso-loges
Outcome: urticarial eruption and laryngeal dyspnea
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
oral provocation, vaso-loges	1	-	

Statistical Method(s)

Endpoints: urticarial eruption and laryngeal dyspnea
Adjustment factors:
Statistical metric: other
Statistical metric description:

30.4. Exposure: skin prick test, Dreisafol

Method	Description	Analysis
not reported	Dreisafol (GRY-Pharma GmbH, Kirchzarten, Germany; consisting of folic acid, magnesium stearate, cellulose, lactose and silicium dioxide)	intervention

Outcomes

	Outcome	Diagnostic Description
A	positive reaction, skin prick test (medical professional or test)	Skin prick tests positive reaction

Results

30.4.A positive reaction, skin prick test

Population: case report, woman in Germany
Exposure: skin prick test, Dreisafol
Outcome: positive reaction, skin prick test
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
skin prick test, Dreisafol	1	-	

Statistical Method(s)

Endpoints: positive reaction, skin prick test
Adjustment factors:

Statistical metric: other
Statistical metric description:

30.5. Exposure: skin prick test, vaso-loges

Method	Description	Analysis
not reported	multivitamin tablets vaso-loges (Dr Loges und Co. GmbH, Winsen, Germany; consisting of vitamin B6, B12, folic acid, gelatine, titandioxide, ferrum oxide, magnesium stearate)	intervention

Outcomes

	Outcome	Diagnostic Description
A	positive reaction, skin prick test (medical professional or test)	Skin prick tests positive reaction

Results

30.5.A positive reaction, skin prick test

Population: case report, woman in Germany
Exposure: skin prick test, vaso-loges
Outcome: positive reaction, skin prick test
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
skin prick test, vaso-loges	1	-	

Statistical Method(s)

Endpoints: positive reaction, skin prick test
Adjustment factors:
Statistical metric: other
Statistical metric description:

31. SATO, 2001

Full citation: Sato E, Ohrui T, Matsui T, Arai H, Sasaki H. 2001. Folate deficiency and risk of pneumonia in older people. J Am Geriatr Soc 49(12): 1739-1740.

Funding: none reported

OLDER ADULTS WITH AND WITHOUT BRAIN ATROPHY, JAPAN

Age: 71.4 (mean)	**Study design:** Controlled trial (**n =** 27)
Gender: Male and Female **Ethnicities:** Asian	**Country:** Japan **Region:** **State:**
Inclusion criteria: cases - brain MRI showed atrophy without infarctions; controls - normal MRI, cases had 2+ episodes of aspriational pneumonia within previous 2 years, cases - nursing home or other insitituions; controls - healthy volunteers	**Exclusion critieria:** bedridden, current vitamin supplment use, history of stroke, neurodegenerative disease, or immunocompromised, pneumonia free for 2 months prior to study

31.1. Exposure: folic acid supplementation, 2 years

Method	Description	Analysis
10	folic acid supplementation (5-mg tablet, twice daily) for 2 years	intervention

Outcomes

	Outcome	Diagnostic Description
A	pneumonia (medical professional or test)	Subjects were followed for 2 years for prevalence of pneumonia

Results

31.1.A <u>pneumonia</u>

Population: elderly people, cases have a history of aspirational pneumonia
Exposure: folic acid supplementation, 2 years
Outcome: pneumonia
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
5 mg folic acid tablet, 2x/day, 8 weeks	27	-	

Statistical Method(s)

Endpoints: pneumonia
Adjustment factors:

Statistical metric: other
Statistical metric description:

32. SATOSKAR, 1962

Full citation: Satoskar RS, Kulkarni BS, Mehta BM, Sanzgiri RR, Bamji MS. 1962. Serum vitamin B12 and folic acid (P.G.A.) levels in hypoproteinaemia and marasmus in Indian children. Arch Dis Child 37: 9-16.

Funding: None reported

INDIAN CHILDREN WITH PROTEIN DEFICIENCY AND MARASMUS

Age: 1.0-8.0 years	**Study design:** Case-control (**n =** 67)
Gender: Male and Female **Ethnicities:**	**Country:** India **Region:** **State:**
Inclusion criteria: clinical diagnosis of protein malnutrition or marasmus	**Exclusion critieria:** patients with major illnesses such as tuberculosis or liver disorders

32.1. Exposure: Serum P.G.A. (folic acid) levels

Method	Description	Analysis
Serum	The folic acid levels were assayed with Streptococcus faecalis.The metric units are given as mug/mL.	Assay of serum (Streptococcus faecalis)

Outcomes

	Outcome	Diagnostic Description
A	Respiratory infections (not reported)	Does not describe

Results

32.1.A Respiratory infections

Population: Indian Children with Protein Deficiency and Marasmus
Exposure: Serum P.G.A. (folic acid) levels
Outcome: Respiratory infections
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folic acid	27	-	

Statistical Method(s)

Endpoints: Respiratory infections
Adjustment factors:
Statistical metric: mean
Statistical metric description:

33. SMITH, 2007

Full citation: Smith J, Empson M, Wall C. 2007. Recurrent anaphylaxis to synthetic folic acid. Lancet 370(9588): 652.

Funding: none reported

CASE REPORT, WOMAN IN NEW ZEALAND

Age: not reported	**Study design:** Case-report (**n** = 1)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** New Zealand **Region:** Auckland **State:**
Inclusion criteria:	**Exclusion critieria:**

33.1. Exposure: 160µg folic acid in water

Method	Description	Analysis
200	800 mL lime-flavoured water fortified with 20 µg/100 mL folic acid	self-reported

Outcomes

	Outcome	Diagnostic Description
A	itchy throat, generalised pruritus, and nausea (self-reported)	itchy throat, generalised pruritus, and nausea developed within minutes of ingestion

Results

33.1.A <u>itchy throat, generalised pruritus, and nausea</u>

Population: case report, woman in New Zealand
Exposure: 160µg folic acid in water
Outcome: itchy throat, generalised pruritus, and nausea
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
160µg folic acid in water	1	-	

Statistical Method(s)

Endpoints: itchy throat, generalised pruritus, and nausea
Adjustment factors:
Statistical metric: other
Statistical metric description:

33.2. Exposure: 5 mg folic acid tablet

Method	Description	Analysis
5	5 mg folic acid tablet	self-report

Outcomes

	Outcome	Diagnostic Description
A	itchy throat, nausea, generalised rash, diarrhoea, and lightheadedness (self-reported)	itchy throat, nausea, generalised rash, diarrhoea, and lightheadedness

Results

33.2.A <u>itchy throat, nausea, generalised rash, diarrhoea, and lightheadedness</u>

Population: case report, woman in New Zealand
Exposure: 5 mg folic acid tablet
Outcome: itchy throat, nausea, generalised rash, diarrhoea, and lightheadedness
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
5 mg folic acid tablet	1	-	

Statistical Method(s)

Endpoints: itchy throat, nausea, generalised rash, diarrhoea, and lightheadedness
Adjustment factors:
Statistical metric: other
Statistical metric description:

33.3. Exposure: 80µg folic acid in a beverage

Method	Description	Analysis
80	150 mL of a beverage containing feijoa (a fruit of the Myrtaceae family) and supplements including 53.5 µg/100 mL folic acid	self-report

Outcomes

	Outcome	Diagnostic Description
A	rash, vomiting, and lightheadedness (self-reported)	generalised rash, vomiting, and lightheadedness

Results

33.3.A <u>rash, vomiting, and lightheadedness</u>

Population: case report, woman in New Zealand
Exposure: 80µg folic acid in a beverage

Outcome: rash, vomiting, and lightheadedness
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
80µg folic acid in a beverage	1	-	

Statistical Method(s)

Endpoints: rash, vomiting, and lightheadedness
Adjustment factors:
Statistical metric: other
Statistical metric description:

33.4. Exposure: folic acid solution challenge

Method	Description	Analysis
160	A graded, blinded challenge to the folic acid solution led to wide spread urticaria at a dose of 160 µg.	intervention

Outcomes

	Outcome	Diagnostic Description
A	urticaria (medical professional or test)	wide spread urticaria at a dose of 160 µg

Results

33.4.A <u>urticaria</u>

Population: case report, woman in New Zealand
Exposure: folic acid solution challenge
Outcome: urticaria
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
folic acid solution challenge	1	-	

Statistical Method(s)

Endpoints: urticaria
Adjustment factors:
Statistical metric: other
Statistical metric description:

33.5. Exposure: intradermal testing with folic acid

Method	Description	Analysis
0.0005	Intradermal testing with folic acid 0·05 µg/mL solution containing folic acid, bicarbonate, and water	intervention

Outcomes

	Outcome	Diagnostic Description
A	skin test (medical professional or test)	Positive test (9 mm wheal, 35 mm flare). A control patient was negative. Skin-prick tests to other food and beverage products were negative.

Results

33.5.A skin test

Population: case report, woman in New Zealand
Exposure: intradermal testing with folic acid
Outcome: skin test
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
intradermal testing with folic acid	1	-	

Statistical Method(s)

Endpoints: skin test
Adjustment factors:
Statistical metric: other
Statistical metric description:

34. STRAND, 2007

Full citation: Strand TA, Taneja S, Bhandari N, Refsum H, Ueland PM, Gjessing HK, Bahl R, Schneede J, Bhan MK, Sommerfelt H. 2007. Folate, but not vitamin B-12 status, predicts respiratory morbidity in north Indian children. Am J Clin Nutr 86(1): 139-144.

Funding: Supported by grants from the European Commission (EU-INCO-DC contract number IC18-CT96-0045 and INCO-FP6-003740), the Norwegian Research Council, the Norwegian Advanced Research Programme (NRC project no 164301/V40), and the Norwegian Council of Universities' Committee for Development Research and Education (NUFU project number PRO 52-53/96 and 36/2002). The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

ZINC SUPPLEMENTATION TRIAL, 1999 NESTED

Age: aged 6-30 months; mean 15.3 months +/- 7.5 months	**Study design:** Prospective (**n =**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** India **Region:** Northern **State:**
Inclusion criteria: 6-30 months old	**Exclusion critieria:** consent refused, likely to move out of the study area in the 4 months after enrollment, needed urgent admission to hospital on the enrolment day, received massive dose of vitamin A within the 2 months prior to enrollment

34.1. Exposure: Folate Status

Method	Description	Analysis
plasma folate concentrations	Nested within zinc supplementation trial (Bhandari et al); folate status measured:	plasma folate concentrations were estimated by microbiological assays with the use of a chloramphenicol-resistant strain of Lactobacillus casei and a colistin sulfate–resistant strain ofLactobacillus leichmannii.). Both assays were adapted to a microtiter plate format and carried out by a robotic workstation (analyzed at Bergen University, Norway)

Outcomes

	Outcome	Diagnostic Description
A	Acute lower respiratory infection (ALRI) (medical professional or test)	Acute lower respiratory tract infection was defined by cough and fast breathing or lower chest indrawing. Fast breathing was defined as 2 counts of >/= 50 breaths/min for infants (12 mo of age) and >/= 40 breaths/min for older children

Results

34.1.A Acute lower respiratory infection (ALRI)

Population: North Indian children, ages 6-30 mo
Exposure: Folate Status
Outcome: Acute lower respiratory infection (ALRI)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Referent (Q2-Q4)	-	1.0	
Quartile 1	-	1.44 (1.23, 1.7)	0.001

Statistical Method(s)

Endpoints: Acute lower respiratory infection (ALRI)
Adjustment factors: being enrolled in June to January vs February to May, low length-for-age z score, not being breastfed, young age
Statistical metric: other
Statistical metric description: adjusted incidence rate ratios

35. SUBOTICANEC, 1989

Full citation: Suboticanec K, Stavljenic A, Bilic-Pesic L, Gorajscan M, Gorajscan D, Brubacher G, Buzina R. 1989. Nutritional status, grip strength, and immune function in institutionalized elderly. Int J Vitam Nutr Res 59(1): 20-28.

Funding: none reported

ELDERLY MULTIVITAMIN SUPPLEMENT AND IMMUNE FUNCTION

Age: 65.0-80.0 years	**Study design:** Controlled trial (**n =** 100)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Switzerland **Region:** Zagreb **State:**
Inclusion criteria: Age 65-80, mobile, No symptoms of acute disease	**Exclusion critieria:**

35.1. Exposure: Multivitamin supplement

Method	Description	Analysis
800	vitamin tablets adminjistered daily for 8 weeks (Table IV lists contents, including 0.8mg folic acid) dietary intake and folate status also assessed prior to intervention	intervention

Outcomes

	Outcome	Diagnostic Description
A	Delayed cutaneous hypersensitivity (medical professional or test)	After intradermal application of 0.1 mL of a solution containing 3 I.U. of PPD (purified protein derivative), the diameter of induced induration was read on a milimeter scale after 48 hours.

Results

35.1.A Delayed cutaneous hypersensitivity

Population: Elderly, Switzerland, 65-80 yrs ⚥ (n=100)
Exposure: Multivitamin supplement
Outcome: Delayed cutaneous hypersensitivity
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo before experiment	-	-	
Placebo after experiment	-	-	
Vitamin group before experiment	-	-	
Vitamin group after experiment	-	-	0.01

Statistical Method(s)

Endpoints: Delayed cutaneous hypersensitivity
Adjustment factors:
Statistical metric: mean change
Statistical metric description: p-value of change between before and after experiment

36. TANEJA, 2013

Full citation: Taneja S, Strand TA, Kumar T, Mahesh M, Mohan S, Manger MS, Refsum H, Yajnik CS, Bhandari N. 2013. Folic acid and vitamin B-12 supplementation and common infections in 6-30-mo-old children in India: a randomized placebo-controlled trial. Am J Clin Nutr 98(3): 731-737.

Funding: Supported by the Thrasher Research Fund (grant no 02827) and the Research Council of Norway (project no. 172226).

FOLIC ACID AND VITAMIN B-12 SUPPLEMENTAL TRIAL IN 6-30-MO-OLD CHILDREN IN INDIA

Age: 1.34 (mean)	**Study design:** Controlled trial (**n =** 993)
Gender: Male and Female **Ethnicities:**	**Country:** India **Region:** New Delhi **State:**
Inclusion criteria: Children aged 6-30 months	**Exclusion critieria:** children using folic acid and/ or vitamin B-12 supplements, children with severe anemia (hemoglobin <7 g/dL), children with severe systemic illness requiring hospitalization, with severe acute malnutrition (weight-for-height z score less than -3)

36.1. Exposure: Folic acid and/or vitamin B12 supplementation

Method	Description	Analysis
intervention	We randomly assigned eligible children to 1 of 4 treatment groups: 1) placebo (n = 249), 2) 2 times the Recommended Dietary Allowance (RDA) of folic acid (n = 249), 3) 2 times the RDA of vitamin B-12 (n = 252), and 4) a combination of both vitamin B-12 and folic acid (n = 250) in blocks of 16. Children were supplemented with 1 spoon (5 g) of the relevant supplement if they were 6-11 mo of age and with 2 spoons (10 g) if older than 12 mo. The supplement was administered daily by a fieldworker for 6 mo at home, except on Sundays and public holidays when the mother administered it herself. The supplement was packaged in 330-g jars; this supply was adequate for 1 mo for children aged >12 mo and for 2 mo for children aged 6-11 mo.	n/a

Outcomes

	Outcome	Diagnostic Description
A	>/= 1 episode of Acute Lower Respiratory infection (ALRI) (medical professional or test)	Acute Lower Respiratory infection (ALRI) was defined as cough or difficult breathing with an elevated respiratory rate above the age-specific cutoff values (>/=50 breaths/min in infants and >/=40 breaths/min in older children) according to WHO criteria or cough or difficult breathing and lower chest indrawing
B	>/= 1 episode of clinical pneumonia (medical professional or test)	Clinical pneumonia was defined either by a combination of cough with crepitations or bronchial breathing by auscultations or as an episode of ALRI associated with at least one of the following features: lower chest indrawing, convulsions, inability to drink or feed, extreme lethargy, restlessness or irritability, nasal flaring, or abnormal sleeping and difficulty in waking.
C	Episodes of Acute Lower Respiratory infection (ALRI) (medical professional or test)	Acute Lower Respiratory infection (ALRI) was defined as cough or difficult breathing with an elevated respiratory rate above the age-specific cutoff values (>/=50 breaths/min in infants and >/=40 breaths/min in older children) according to WHO criteria or cough or difficult breathing and lower chest indrawing
D	Episodes of clinical pneumonia (medical professional or test)	Clinical pneumonia was defined either by a combination of cough with crepitations or bronchial breathing by auscultations or as an episode of ALRI associated with at least one of the following features: lower chest indrawing, convulsions, inability to drink or feed, extreme lethargy, restlessness or irritability, nasal flaring, or abnormal sleeping and difficulty in waking.

Results

36.1.A >/= 1 episode of Acute Lower Respiratory infection (ALRI)

Population: 6-30-month-old children in India, supplementation with Folic acid and vitamin B-12
Exposure: Folic acid and/or vitamin B12 supplementation
Outcome: >/= 1 episode of Acute Lower Respiratory infection (ALRI)
Statistical metric: crude odds ratio

Group	N	OR 95% CI (low, high)	*p*-value
Placebo	249	1.0	
Vitamin B-12	252	1.0 (0.8, 1.3)	0.76
Folic Acid	249	1.2 (0.9, 1.4)	0.18
Vitamin B12 + folic acid	250	1.1 (0.9, 1.3)	0.5

36.1.B >/= 1 episode of clinical pneumonia

Population: 6-30-month-old children in India, supplementation with Folic acid and vitamin B-12
Exposure: Folic acid and/or vitamin B12 supplementation
Outcome: >/= 1 episode of clinical pneumonia
Statistical metric: crude odds ratio

Group	N	OR 95% CI (low, high)	*p*-value
Placebo	247	1.0	
Vitamin B-12	250	1.2 (0.9, 1.5)	0.19
Folic Acid	249	1.0 (0.8, 1.3)	0.84
Vitamin B12 + folic acid	247	1.14 (0.9, 1.5)	0.32

36.1.C Episodes of Acute Lower Respiratory infection (ALRI)

Population: 6-30-month-old children in India, supplementation with Folic acid and vitamin B-12
Exposure: Folic acid and/or vitamin B12 supplementation
Outcome: Episodes of Acute Lower Respiratory infection (ALRI)
Statistical metric: crude odds ratio

Group	N	OR 95% CI (low, high)	*p*-value
Placebo	247	1.0	
Vitamin B-12	250	1.0 (0.8, 1.3)	0.97
Folic Acid	249	1.1 (0.9, 1.5)	0.35
Vitamin B12 + folic acid	247	1.0 (0.8, 1.3)	0.97

36.1.D Episodes of clinical pneumonia

Population: 6-30-month-old children in India, supplementation with Folic acid and vitamin B-12
Exposure: Folic acid and/or vitamin B12 supplementation
Outcome: Episodes of clinical pneumonia
Statistical metric: crude odds ratio

Group	N	OR 95% CI (low, high)	*p*-value
Placebo	247	1.0	
Vitamin B-12	250	1.2 (0.9, 1.6)	0.24
Folic Acid	249	1.1 (0.8, 1.4)	0.74
Vitamin B12 + folic acid	247	1.1 (0.8, 1.5)	0.63

Statistical Method(s)

Endpoints: Episodes of Acute Lower Respiratory infection (ALRI)
Adjustment factors:
Statistical metric: crude odds ratio
Statistical metric description: Person time-based analysis: In the generalized estimating equations model, occurrence of a new episode of ... ALRI, or pneumonia in a child period was modeled as a binomial dependent variable and group allocation as the independent variable. The model used a logit link function, binomial variance, and exchangeable correlation to yield ORs. In the main analyses we compared each of the intervention groups (folic acid, vitamin B-12, and folic acid + vitamin B-12) with the group that received only placebo. In this analysis, each treatment arm contained ~250 children

Endpoints: >/= 1 episode of Acute Lower Respiratory infection (ALRI)
Adjustment factors:
Statistical metric: crude odds ratio
Statistical metric description: Child-based analysis: In the generalized estimating equations model, occurrence of a new episode of ... ALRI, or pneumonia in a child period was modeled as a binomial dependent variable and group allocation as the independent variable. The model used a logit link function, binomial variance, and exchangeable correlation to yield ORs. In the main analyses we compared each of the intervention groups (folic acid, vitamin B-12, and folic acid + vitamin B-12) with the group that received only placebo. In this analysis, each treatment arm contained ~250 children.

Endpoints: >/= 1 episode of clinical pneumonia
Adjustment factors:
Statistical metric: crude odds ratio
Statistical metric description: Child-based analysis: In the generalized estimating equations model, occurrence of a new episode of ... ALRI, or pneumonia in a child period was modeled as a binomial dependent variable and group allocation as the independent variable. The model used a logit link function, binomial variance, and exchangeable correlation to yield ORs. In the main analyses we compared each of the intervention groups (folic acid, vitamin B-12, and folic acid + vitamin B-12) with the group that received only placebo. In this analysis, each treatment arm contained ~250 children

Endpoints: Episodes of clinical pneumonia
Adjustment factors:
Statistical metric: crude odds ratio
Statistical metric description: Person time-based analysis: In the generalized estimating equations model, occurrence of a new episode of ... ALRI, or pneumonia in a child period was modeled as a binomial dependent variable and group allocation as the independent variable. The model used a logit link function, binomial variance, and exchangeable correlation to yield ORs. In the main analyses we compared each of the intervention groups (folic acid, vitamin B-12, and folic acid + vitamin B-12) with the group that received only placebo. In this analysis, each treatment arm contained ~250 children.

37. TEBI, 2000

Full citation: Tebi A, Belbraouet S, Chau N, Debry G. 2000. Plasma vitamin, beta-carotene, and alpha-tocopherol status according to age and disease in hospitalized elderly. Nutrition Research 20(10): 1395-1408.

Funding: This investigation has been supported by a grant from the DRASS of Lorraine and by the Fondation de l'Avenir.

ELDERLY PEOPLE, HOSPITALIZED AND HEALTHY

Age: 80.0 (mean)	**Study design:** Case-control (**n =** 772)
Gender: Male and Female **Ethnicities:**	**Country:** France **Region:** Lorraine (northeastern France) **State:**
Inclusion criteria: age 70 or over, good health status (determined by medical exam), no disease at the time study was conducted	**Exclusion critieria:**

37.1. Exposure: Plasma folate

Method	Description	Analysis
plasma	Specimens of venous blood were collected with the subjects in a seated position in the morning following a 12h overnight fast. Then, the samples were dispatched to and analyzed by the Hoffman-La-Roche and Cie (Bale, Switzerland) for concentrations in plasma of folate using microbiologic methods	folate status measured with microbiologic methods

Outcomes

	Outcome	Diagnostic Description
A	Respiratory diseases (medical professional or test)	the main diagnosis and up to five secondary diagnoses were noted and coded using the WHO classification

Results

37.1.A Respiratory diseases

Population: Elderly people, France
Exposure: Plasma folate
Outcome: Respiratory diseases
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Plasma folate	201	-	0.05

Statistical Method(s)

Endpoints: Respiratory diseases
Adjustment factors: age, sex
Statistical metric: other
Statistical metric description: The covariance analysis by taking into account sex and age was made to compare each index between the patients with a category of diseases and the healthy elderly.

38. THUESEN, 2010

Full citation: Thuesen BH, Husemoen LL, Ovesen L, Jorgensen T, Fenger M, Gilderson G, Linneberg A. 2010. Atopy, asthma, and lung function in relation to folate and vitamin B(12) in adults. Allergy 65(11): 1446-1454.

Funding: The Inter99 study was supported by The Danish Medical Research Council, The Danish Centre for Evaluation and Health Technology Assessment, Novo Nordisk, Copenhagen County, The Danish Heart Foundation, The Danish Pharmaceutical Association, Augustinus foundation, Ib Henriksens foundation, and Beckett foundation. This study was further supported by the Danish Agency for Science, Technology and Innovation (grant number 2101-06-0065) and Siemens Healthcare Diagnostics, Denmark, who kindly provided allergen extracts for the specific IgE determinations on the IMMULITE 2000 analyzer.

INTER99 STUDY, BASELINE MEASURES

Age: 46.0 (mean)	**Study design:** Cross-sectional (**n =** 4516)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Denmark **Region:** southwestern part of Copenhagen, Denmark **State:**
Inclusion criteria: age 30-60, residing in southwestern part of Copenhagen	**Exclusion critieria:**

38.1. Exposure: Dietary folate intake from food

Method	Description	Analysis
Questionnaire	Dietary intake of folate and B12 at baseline was estimated by calculations from a 198-item food frequency questionnaire. We had no information on use of vitamin supplements.	The study participants were stratified into quartiles based on their estimated intake of folate and B12 for comparison in statistical analyses

Outcomes

	Outcome	Diagnostic Description
A	Airflow obstruction (medical professional or test)	Spirometry was performed at both baseline and follow-up examinations using the Cardiosoft software ... and a LF501 respiration flow transducer ... Measurements of forced expiratory volume n 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC were recorded, and predicted values of FEV1 were calculated (16). Airflow obstruction was defined as FEV1/FVC < 70%...
B	Asthma (self-reported)	Self-reported doctor-diagnosed asthma; Information on asthma diagnosis and symptoms was obtained from self-administered questionnaires. At baseline, participants were asked the following questions: 'Has a physician ever told you that you have asthma?'

	Outcome	Diagnostic Description
C	Atopy (medical professional or test)	Atopy (>1 positive specific IgE); serum samples collected at both baseline and follow up examinations were analyzed for serum total IgE as well as serum-specific IgE against four inhalant allergens (house dust mite (Dermatophagoides pteronyssinus), cat, grass, and birch); using the IMMULITE 2000 Allergy Immunoassay System(17, 18). The four allergens chosen reflect the most common and clinically important inhalant allergies in Denmark. Atopy was defined as a positive test for specific IgE (‡ 0.35 kU/l) to at least one of the four allergens.
D	High total IgE (>100kU/l) (medical professional or test)	High total IgE (>100 kU/l); serum samples collected at both baseline and follow up examinations were analyzed for serum total IgE as well as serum-specific IgE against four inhalant allergens (house dust mite (Dermatophagoides pteronyssinus), cat, grass, and birch) using the IMMULITE 2000 Allergy Immunoassay System. The four allergens chosen reflect the most common and clinically important inhalant allergies in Denmark.
E	Impaired lung function (medical professional or test)	Spirometry was performed at both baseline and follow-up examinations using the Cardiosoft software ... and a LF501 respiration flow transducer ... Measurements of forced expiratory volume n 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC were recorded, and predicted values of FEV1 were calculated (16)... and impaired lung function as FEV1 < 80% of predicted FEV1.
F	Shortness of breath at rest (self-reported)	Attacks of shortness of breath at rest: Information on asthma diagnosis and symptoms was obtained from self-administered questionnaires. ..Have you ever had an attack of shortness of breath when at rest?' At 5-year follow-up, participants were asked the question: 'Within the last 12 months have you had an attack of shortness of breath when at rest?'

Results

38.1.A Airflow obstruction

Population: Inter99 Study, baseline measures
Exposure: Dietary folate intake from food
Outcome: Airflow obstruction
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<272 ug/day)	-	1.17 (0.86, 1.58)	
Low-Middle (272-<350 ug/day)	-	1.28 (0.99, 1.67)	
Middle-High (350-<449 ug/day)	-	1.08 (0.84, 1.39)	
High (>=449 ug/day)	-	1.0	

38.1.B Asthma

Population: Inter99 Study, baseline measures
Exposure: Dietary folate intake from food
Outcome: Asthma
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<272 ug/day)	-	1.19 (0.86, 1.65)	
Low-Middle (272-<350 ug/day)	-	1.09 (0.81, 1.47)	
Middle-High (350-<449 ug/day)	-	1.1 (0.84, 1.46)	
High (>=449 ug/day)	-	1.0	

38.1.C Atopy

Population: Inter99 Study, baseline measures
Exposure: Dietary folate intake from food
Outcome: Atopy
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<272 ug/day)	-	1.04 (0.85, 1.27)	
Low-Middle (272-<350 ug/day)	-	1.05 (0.88, 1.25)	
Middle-High (350-<449 ug/day)	-	1.1 (0.94, 1.3)	
High (>=449 ug/day)	-	1.0	

38.1.D High total IgE (>100kU/l)

Population: Inter99 Study, baseline measures
Exposure: Dietary folate intake from food
Outcome: High total IgE (>100kU/l)
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<272 ug/day)	-	0.91 (0.72, 1.16)	
Low-Middle (272-<350 ug/day)	-	0.89 (0.72, 1.11)	
Middle-High (350-<449 ug/day)	-	0.95 (0.78, 1.16)	
High (>=449 ug/day)	-	1.0	

38.1.E Impaired lung function

Population: Inter99 Study, baseline measures
Exposure: Dietary folate intake from food
Outcome: Impaired lung function
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<272 ug/day)	-	1.51 (1.11, 2.04)	
Low-Middle (272-<350 ug/day)	-	1.22 (0.92, 1.61)	
Middle-High (350-<449 ug/day)	-	0.94 (0.71, 1.23)	
High (>=449 ug/day)	-	1.0	

38.1.F Shortness of breath at rest

Population: Inter99 Study, baseline measures
Exposure: Dietary folate intake from food
Outcome: Shortness of breath at rest
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<272 ug/day)	-	1.1 (0.84, 1.44)	
Low-Middle (272-<350 ug/day)	-	1.02 (0.79, 1.3)	
Middle-High (350-<449 ug/day)	-	1.05 (0.84, 1.32)	
High (>=449 ug/day)	-	1.0	

Statistical Method(s)

Endpoints: Impaired lung function
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status, total energy intake
Statistical metric: adjusted odds ratio
Statistical metric description: Simple prospective analyses were conducted by chi-squared tests of the categorized variables of changes in status for lung function. In addition, logistic regression models were used to test for associations after adjustment for confounding.

Endpoints: High total IgE (>100kU/l)
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status, total energy intake
Statistical metric: adjusted odds ratio
Statistical metric description: Simple prospective analyses were conducted by chi-squared tests of the categorized variables of changes in status for total IgE. In addition, logistic regression models were used to test for associations after adjustment for confounding.

Endpoints: Airflow obstruction
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status, total energy intake
Statistical metric: adjusted odds ratio
Statistical metric description: Simple prospective analyses were conducted by chi-squared tests of the categorized variables of changes in status for air way symptoms. In addition, logistic regression models were used to test for associations after adjustment for confounding.

Endpoints: Shortness of breath at rest; Asthma
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status, total energy intake
Statistical metric: adjusted odds ratio
Statistical metric description: Multivariable logistic regression models were used to estimate odds ratios for the associations of dietary folate with different dichotomized outcome variables related to asthma. The regression models were adjusted for confounding by age, sex, total energy intake, smoking, alcohol intake, BMI, and socioeconomic status.

Endpoints: Atopy
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status, total energy intake
Statistical metric: adjusted odds ratio
Statistical metric description: Simple prospective analyses were conducted by chi-squared tests of the categorized variables of changes in status for atopy. In addition, logistic regression models were used to test for associations after adjustment for confounding.

38.2. Exposure: Serum folate

Method	Description	Analysis
Serum	Fasting blood samples were collected and stored at)-20degrees C until analysis in 2008. Serum folate and B12 concentrations were measured by competitive chemiluminescent enzyme immunoassays (IMMULITE 2000 System; Siemens HealthcareDiagnostics, Deerfield, IL, USA).	The participants were stratified into quartiles based on their serum folate and B12 levels for comparison in statistical analyses. Serum levels of folate are given in nmol/l (1 nmol/l = 0.441 ug/l)

Outcomes

	Outcome	Diagnostic Description
A	Airflow obstruction (medical professional or test)	Spirometry was performed at both baseline and follow-up examinations using the Cardiosoft software ... and a LF501 respiration flow transducer ... Measurements of forced expiratory volume n 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC were recorded, and predicted values of FEV1 were calculated (16). Airflow obstruction was defined as FEV1/FVC < 70%...
B	Asthma (self-reported)	Self-reported doctor-diagnosed asthma; Information on asthma diagnosis and symptoms was obtained from self-administered questionnaires. At baseline, participants were asked the following questions: 'Has a physician ever told you that you have asthma?'
C	Atopy (medical professional or test)	Atopy (>1 positive specific IgE); serum samples collected at both baseline and follow up examinations were analyzed for serum total IgE as well as serum-specific IgE against four inhalant allergens (house dust mite (Dermatophagoides pteronyssinus), cat, grass, and birch); using the IMMULITE 2000 Allergy Immunoassay System(17, 18). The four allergens chosen reflect the most common and clinically important inhalant allergies in Denmark. Atopy was defined as a positive test for specific IgE (‡ 0.35 kU/l) to at least one of the four allergens.
D	High total IgE (>100kU/l) (medical professional or test)	High total IgE (>100 kU/l); serum samples collected at both baseline and follow up examinations were analyzed for serum total IgE as well as serum-specific IgE against four inhalant allergens (house dust mite (Dermatophagoides pteronyssinus), cat, grass, and birch) using the IMMULITE 2000 Allergy Immunoassay System (17, 18). The four allergens chosen reflect the most common and clinically important inhalant allergies in Denmark.
E	Impaired lung function (medical professional or test)	Spirometry was performed at both baseline and follow-up examinations using the Cardiosoft software ... and a LF501 respiration flow transducer ... Measurements of forced expiratory volume n 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC were recorded, and predicted values of FEV1 were calculated (16)... and impaired lung function as FEV1 < 80% of predicted FEV1.
F	Shortness of breath at rest (self-reported)	Attacks of shortness of breath at rest: Information on asthma diagnosis and symptoms was obtained from self-administered

	Outcome	Diagnostic Description
		questionnaires. ..Have you ever had an attack of shortness of breath when at rest?' At 5-year follow-up, participants were asked the question: 'Within the last 12 months have you had an attack of shortness of breath when at rest?'

Results

38.2.A Airflow obstruction

Population: Inter99 Study, baseline measures
Exposure: Serum folate
Outcome: Airflow obstruction
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<6.2 nmol/L)	-	1.02 (0.8, 1.29)	
Low-Middle (6.2-<8.6 nmol/L)	-	0.88 (0.69, 1.12)	
Middle-High (8.6-<12.3 nmol/L)	-	1.02 (0.81, 1.29)	
High (>=12.3 nmol/L)	-	1.0	

38.2.B Asthma

Population: Inter99 Study, baseline measures
Exposure: Serum folate
Outcome: Asthma
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<6.2 nmol/L)	-	1.37 (1.05, 1.79)	
Low-Middle (6.2-<8.6 nmol/L)	-	1.02 (0.78, 1.35)	
Middle-High (8.6-<12.3 nmol/L)	-	1.13 (0.86, 1.48)	
High (>=12.3 nmol/L)	-	1.0	

38.2.C Atopy

Population: Inter99 Study, baseline measures
Exposure: Serum folate
Outcome: Atopy
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<6.2 nmol/L)	-	0.96 (0.81, 1.12)	
Low-Middle (6.2-<8.6 nmol/L)	-	1.11 (0.95, 1.3)	
Middle-High (8.6-<12.3 nmol/L)	-	1.11 (0.95, 1.29)	
High (>=12.3 nmol/L)	-	1.0	

38.2.D High total IgE (>100kU/l)

Population: Inter99 Study, baseline measures
Exposure: Serum folate
Outcome: High total IgE (>100kU/l)
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<6.2 nmol/L)	-	0.9 (0.74, 1.09)	
Low-Middle (6.2-<8.6 nmol/L)	-	0.92 (0.76, 1.11)	
Middle-High (8.6-<12.3 nmol/L)	-	0.91 (0.75, 1.1)	
High (>=12.3 nmol/L)	-	1.0	

38.2.E Impaired lung function

Population: Inter99 Study, baseline measures
Exposure: Serum folate
Outcome: Impaired lung function
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<6.2 nmol/L)	-	1.18 (0.93, 1.52)	
Low-Middle (6.2-<8.6 nmol/L)	-	0.99 (0.77, 1.28)	
Middle-High (8.6-<12.3 nmol/L)	-	1.03 (0.8, 1.33)	
High (>=12.3 nmol/L)	-	1.0	

38.2.F Shortness of breath at rest

Population: Inter99 Study, baseline measures
Exposure: Serum folate
Outcome: Shortness of breath at rest
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Low (<6.2 nmol/L)	-	1.43 (1.14, 1.79)	
Low-Middle (6.2-<8.6 nmol/L)	-	1.11 (0.88, 1.4)	
Middle-High (8.6-<12.3 nmol/L)	-	1.24 (0.99, 1.56)	
High (>=12.3 nmol/L)	-	1.0	

Statistical Method(s)

Endpoints: Airflow obstruction
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status
Statistical metric: adjusted odds ratio
Statistical metric description: Simple prospective analyses were conducted by chi-squared tests of the categorized variables of changes in status for air way symptoms... In addition, logistic regression models were used to test for associations after adjustment for confounding.

Endpoints: Impaired lung function
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status
Statistical metric: adjusted odds ratio
Statistical metric description: Simple prospective analyses were conducted by chi-squared tests of the categorized variables of changes in status for lung function. In addition, logistic regression models were used to test for associations after adjustment for confounding.

Endpoints: Shortness of breath at rest; Asthma
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status
Statistical metric: adjusted odds ratio

Statistical metric description: Multivariable logistic regression models were used to estimate odds ratios for the associations of dietary folate with different dichotomized outcome variables related to asthma. The regression models were adjusted for confounding by age, sex, total energy intake, smoking, alcohol intake, BMI, and socioeconomic status.

Endpoints: High total IgE (>100kU/l)
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status
Statistical metric: adjusted odds ratio
Statistical metric description: Simple prospective analyses were conducted by chi-squared tests of the categorized variables of changes in status for total IgE. In addition, logistic regression models were used to test for associations after adjustment for confounding.

Endpoints: Atopy
Adjustment factors: age, alcohol intake, body mass index (BMI), sex, smoking, socioeconomic status
Statistical metric: adjusted odds ratio
Statistical metric description: Simple prospective analyses were conducted by chi-squared tests of the categorized variables of changes in status for atopy. In addition, logistic regression models were used to test for associations after adjustment for confounding.

39. TIELSCH, 2006

Full citation: Tielsch JM, Khatry SK, Stoltzfus RJ, Katz J, LeClerq SC, Adhikari R, Mullany LC, Shresta S, Black RE. 2006. Effect of routine prophylactic supplementation with iron and folic acid on preschool child mortality in southern Nepal: community-based, cluster-randomised, placebo-controlled trial. Lancet 367(9505): 144-152.

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PRESCHOOL CHILDREN IN SOUTHERN NEPAL: NEPAL NUTRITION INTERVENTION PROJECT

Age: children aged 1 to 36 months	**Study design:** Controlled trial (**n =** 22841)
Gender: Male and Female **Ethnicities:** Asian	**Country:** Nepal **Region:** Southern Nepal **State:**
Inclusion criteria: All children aged 1-35 months and living in study area during baseline enrollment, Eligible once 1 month old if primary residence in study area	**Exclusion critieria:**

39.1. Exposure: Vitamin Supplementation, <36 months

Method	Description	Analysis
intervention	one tablet daily (or half a tablet if 1 year old), containing: iron (12.5 mg) and folic acid (50 ug), iron and folic acid plus zinc, (or placebo) plus as part of a national program: those aged 12 months or older were given 200 000 IU of vitamin A every 6 months and those aged 6–12 months were given 100 000 IU	"To confirm that the supplements used were active, we selected and tested the iron and zinc status of a sample of children aged 24 months or older after 12 months of follow-up" via blood sample, but NOT done for folate...

Outcomes

	Outcome	Diagnostic Description
A	Acute lower respiratory infection (ALRI) (self-reported)	Children in the morbidity subsamples were visited weekly. Mothers were asked about the onset and length of specific signs and symptoms for every day of the preceding week... We diagnosed acute respiratory infection as one or more consecutive days of fever, cough, and difficulty breathing (all three symptoms had to be present on at least 1 day during the episode) with a minimum of 7 days between episodes

Results

39.1.A Acute lower respiratory infection (ALRI)

Population: Preschool Children in Nepal, 2001-2003
Exposure: Vitamin Supplementation, <36 months
Outcome: Acute lower respiratory infection (ALRI)
Statistical metric: relative risk

Group	N	RR 95% CI (low, high)	*p*-value
Placebo	-	1.0 (1.0, 1.0)	
Iron and Folic acid	-	0.92 (0.77, 1.09)	
Iron and Folic acid and Zinc	-	0.91 (0.76, 1.08)	

Statistical Method(s)

Endpoints: Acute lower respiratory infection (ALRI)
Adjustment factors: cluster randomization
Statistical metric: relative risk
Statistical metric description: Analyses were by intention to treat. Children who migrated out of the study area or who refused further participation were censored at the time they left the study. We used

SAS (version 8) and STATA (version 8.0) for statistical analyses. We compared treatment groups by baseline household, maternal, and child characteristics to assess imbalance after randomisation. We adjusted estimates of standard error to account for the clustered randomisation, using the generalised estimating equations approach. We used two approaches to assess the effect of treatment on mortality: the first estimated the incidence density of mortality with person-time as the denominator of the observed rates; and the second used survival analysis techniques such as Kaplan-Meier survival curves. We used Cox proportional hazard models to adjust for potentially confounding factors imbalanced in the treatment groups and to model potential effect modification. We estimated standard errors of the relative risks from proportional hazards models, using robust variance estimation to account for the clustered randomisation. We calculated incidence density rates of diarrhoea, dysentery, and acute respiratory infections with days during episodes excluded from the denominator of person-years at risk.

40. VAN DER VALK, 2013

Full citation: van der Valk RJ, Kiefte-de Jong JC, Sonnenschein-van der Voort AM, Duijts L, Hafkamp-de Groen E, Moll HA, Tiemeier H, Steegers EA, Hofman A, Jaddoe VW, de Jongste JC. 2013. Neonatal folate, homocysteine, vitamin B12 levels and methylenetetrahydrofolate reductase variants in childhood asthma and eczema. Allergy 68(6): 788-795.

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GENERATION R STUDY

Age: 1.0-6.0 years	**Study design:** Prospective (**n =** 2001)
Gender: Male and Female **Ethnicities:** White	**Country:** Netherlands **Region:** **State:**
Inclusion criteria: cord blood available, part of Generation R cohort	**Exclusion critieria:**

40.1. Exposure: Cord blood folate

Method	Description	Analysis
assay	neonate folate measured from blood cord; cord blood was analysed using an immunoelectrochemoluminesence assay (Abbott Diagnostics	the median (95% CI) values: 21.2 nmol/L (11.9–35.9)

Outcomes

	Outcome	Diagnostic Description
A	Asthma, at 6 years (medical professional or test)	Information on physician-diagnosed asthma ever was obtained at 6 years
B	Eczema, 1st year (self-reported)	physician-diagnosed eczema self-reported yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)
C	Eczema, 2nd year (self-reported)	physician-diagnosed eczema self-reported yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)

	Outcome	Diagnostic Description
D	Eczema, 3rd year (self-reported)	physician-diagnosed eczema self-reported yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)
E	Eczema, 4th year (self-reported)	physician-diagnosed eczema self-reported yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)
F	Eczema, at 6 years (self-reported)	self-reported eczema ever was obtained at 6 years.
G	Eczema, overall (age 1-4) (self-reported)	physician-diagnosed eczema self-reported yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)
H	Fractional exhaled nitric oxide (FeNO), at 6 years (medical professional or test)	Fractional exhaled nitric oxide (FeNO) was measured at 6 years using the NIOX chemiluminescence analyzer
I	Rint, at 6 years (medical professional or test)	Lung function (interrupter resistance, MicroRint, MicroMedical, Rochester, Kent, UK) was measured during tidal breathing, with occlusion of the airway at tidal peak expiratory flow. Median values for at least 5 acceptable Rint measurements were calculated, and these were used to calculate Z-scores (20). Due to technical issues, we had to replace the MicroRint during the study period. This resulted in stepwise variation in the median, which was corrected for.
J	Wheezing, 1st year (self-reported)	Wheezing assessed yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)
K	Wheezing, 2nd year (self-reported)	Wheezing assessed yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)
L	Wheezing, 3rd year (self-reported)	Wheezing assessed yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)
M	Wheezing, 4th year (self-reported)	Wheezing assessed yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)
N	Wheezing, overall (age 1-4) (self-reported)	Wheezing assessed yearly by questionnaires, until 4 years using questions from the International Study of Asthma and Allergies in Childhood (ISAAC)

Results

40.1.A Asthma, at 6 years

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Asthma, at 6 years
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.02 (0.83, 1.25)	

40.1.B Eczema, 1st year

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Eczema, 1st year
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.06 (0.93, 1.2)	

40.1.C Eczema, 2nd year

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Eczema, 2nd year
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.08 (0.93, 1.27)	

40.1.D Eczema, 3rd year

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Eczema, 3rd year
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.0 (0.84, 1.19)	

40.1.E Eczema, 4th year

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Eczema, 4th year
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	0.97 (0.77, 1.22)	

40.1.F Eczema, at 6 years

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Eczema, at 6 years
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.05 (0.95, 1.18)	

40.1.G Eczema, overall (age 1-4)

Population: Generation R, Netherlands
Exposure: Cord blood folate

Outcome: Eczema, overall (age 1-4)
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.05 (0.95, 1.15)	

40.1.H Fractional exhaled nitric oxide (FeNO), at 6 years

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Fractional exhaled nitric oxide (FeNO), at 6 years
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Cord blood folate	1009	1.02 (0.98, 1.06)	

40.1.I Rint, at 6 years

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Rint, at 6 years
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Cord blood folate	-	-0.11 (-0.29, 0.08)	

40.1.J Wheezing, 1st year

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Wheezing, 1st year
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.02 (0.92, 1.14)	

40.1.K Wheezing, 2nd year

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Wheezing, 2nd year
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.0 (0.89, 1.13)	

40.1.L Wheezing, 3rd year

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Wheezing, 3rd year
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.03 (0.89, 1.2)	

40.1.M Wheezing, 4th year

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Wheezing, 4th year
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	0.92 (0.78, 1.09)	

40.1.N Wheezing, overall (age 1-4)

Population: Generation R, Netherlands
Exposure: Cord blood folate
Outcome: Wheezing, overall (age 1-4)
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Cord blood folate	-	1.0 (0.94, 1.08)	

Statistical Method(s)

Endpoints: Wheezing, 1st year; Eczema, 1st year; Wheezing, 2nd year; Wheezing, 3rd year; Wheezing, 4th year; Eczema, 2nd year; Eczema, 3rd year; Eczema, 4th year; Eczema, overall (age 1-4); Wheezing, overall (age 1-4)
Adjustment factors: birth weight, body mass index (BMI), educational level at intake, folic acid use during pregnancy, gender of child, gestational age, history of maternal atopy or asthma, maternal age, maternal smoking during pregnancy, parity
Statistical metric: adjusted odds ratio
Statistical metric description: Odds ratios (95% confidence intervals) were given (allowing for a time trend) for each year of age separately, and for the overall effects using multiple imputation-based generalized estimating equation models. The associations of folate ... at birth with repeated wheezing and eczema in children aged 1 to 4 years were modelled per year (allowing for a time trend), and the overall effects were analysed using multiple imputation-based generalized estimating equation (MI-GEE) models allowing for correction for the within-subject dependence as a result of the repeated measurements, while physician-diagnosed asthma ever and self-reported eczema ever and FeNO and Rint at 6 years were analysed using logistic and linear regression models. FeNO was e log-transformed to obtain a normal distribution.

Endpoints: Eczema, at 6 years
Adjustment factors: birth weight, educational level at intake, folic acid use during pregnancy, gender of child, gestational age, history of maternal atopy or asthma, maternal age, maternal body mass index (BMI), maternal smoking during pregnancy, parity
Statistical metric: adjusted odds ratio
Statistical metric description: Odds ratios (95% confidence intervals) from logistic regression models were given (allowing for a time trend) for each year of age separately, and for the overall effects using multiple imputation-based generalized estimating equation models. The associations of folate ... at

birth with repeated wheezing and eczema in children aged 1 to 4 years were modelled per year (allowing for a time trend), and the overall effects were analysed using multiple imputation-based generalized estimating equation (MI-GEE) models allowing for correction for the within-subject dependence as a result of the repeated measurements, while physician-diagnosed asthma ever and self-reported eczema ever and FeNO and Rint at 6 years were analysed using logistic and linear regression models. FeNO was e log-transformed to obtain a normal distribution.

Endpoints: Asthma, at 6 years
Adjustment factors: birth weight, educational level at intake, folic acid use during pregnancy, gender of child, gestational age, history of maternal atopy or asthma, maternal BMI, maternal age, maternal smoking during pregnancy, parity
Statistical metric: adjusted odds ratio
Statistical metric description: Odds ratios (95% confidence intervals) from logistic regression models were given (allowing for a time trend) for each year of age separately, and for the overall effects using multiple imputation-based generalized estimating equation models. The associations of folate ... at birth with repeated wheezing and eczema in children aged 1 to 4 years were modelled per year (allowing for a time trend), and the overall effects were analysed using multiple imputation-based generalized estimating equation (MI-GEE) models allowing for correction for the within-subject dependence as a result of the repeated measurements, while physician-diagnosed asthma ever and self-reported eczema ever and FeNO and Rint at 6 years were analysed using logistic and linear regression models. FeNO was e log-transformed to obtain a normal distribution

Endpoints: Rint, at 6 years
Adjustment factors: birth weight, body mass index (BMI), educational level at intake, folic acid use during pregnancy, gender of child, gestational age, history of maternal atopy or asthma, maternal age, maternal smoking during pregnancy, parity
Statistical metric: other
Statistical metric description: Z-score change (95% CI) from linear regression models. The associations of folate ... at birth with repeated wheezing and eczema in children aged 1 to 4 years were modelled per year (allowing for a time trend), and the overall effects were analysed using multiple imputation-based generalized estimating equation (MI-GEE) models allowing for correction for the within-subject dependence as a result of the repeated measurements, while physician-diagnosed asthma ever and self-reported eczema ever and FeNO and Rint at 6 years were analysed using logistic and linear regression models. FeNO was e log-transformed to obtain a normal distribution

Endpoints: Fractional exhaled nitric oxide (FeNO), at 6 years
Adjustment factors: birth weight SD score derived from generalized estimation equations, educational level at intake, folic acid use during pregnancy, gender of child, gestational age, history of maternal atopy or asthma, maternal BMI, maternal age, maternal smoking during pregnancy, parity
Statistical metric: other
Statistical metric description: Ratio changes (95% CI) from linear regression models. The associations of folate ... at birth with repeated wheezing and eczema in children aged 1 to 4 years were modelled per year (allowing for a time trend), and the overall effects were analysed using multiple imputation-based generalized estimating equation (MI-GEE) models allowing for correction for the within-subject dependence as a result of the repeated measurements, while physician-diagnosed asthma ever and self-reported eczema ever and FeNO and Rint at 6 years were analysed using logistic and linear regression models. FeNO was e log-transformed to obtain a normal distribution.

41. VEERANKI, 2014

Full citation: Veeranki SP, Gebretsadik T, Dorris SL, Mitchel EF, Hartert TV, Cooper WO, Tylavsky FA, Dupont W, Hartman TJ, Carroll KN. 2014. Association of folic acid supplementation during pregnancy and infant bronchiolitis. Am J Epidemiol 179(8): 938-946.

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TENNCARE RETROSPECTIVE COHORT, 1995-2007

Age:	**Study design:** Retrospective (**n =**)
Gender: Male and Female **Ethnicities:** Black or African American, White, Other	**Country:** United States **Region:** **State:** Tennessee
Inclusion criteria: term, healthy infants, women aged 15–44 years, women enrolled in Tennessee Medicaid program (TennCare), women with singleton infants	**Exclusion critieria:** infants with congenital heart disease, chronic lung disease, or congenital upper airway anomalies

41.1. Exposure: Timing of the filling of folic acid–containing supplements during pregnancy

Method	Description	Analysis
prescriptions	The main predictor was timing of the filling of folic acid– containing supplements during pregnancy. We used prenatal vitamin prescriptions as a surrogate for folic acid supplementation. From pharmacy files, we obtained the national drug code to identify the specific medication, the date the prescription was filled, the dose of folic acid, and the total days' supply. Because of the TennCare policy of administering a 30-day supply for prescription medications and our findings from preparatory work for the research study, we assigned each prenatal vitamin prescription filling to a maximum of 30 days' supply.	We conducted medication database and internet searches to determine the specific folic acid dose in each prenatal vitamin if the information was not available in TennCare files and obtained a specific dose for 97% of prescriptions in the cohort...Overall, 98% of prescriptions contained 1,000 µg of folic acid.

Outcomes

	Outcome	Diagnostic Description
A	Infant Bronchiolitis Diagnosis	The main outcome was bronchiolitis during the first year of life, as

	Outcome	Diagnostic Description
	(medical records)	determined by ICD-9 diagnosis codes. We captured health care visits (clinic, emergency department, 23-hour observation, hospitalization) using ICD-9 codes for bronchiolitis (code 466.1) or respiratory syncytial virus pneumonia (code 480.1) Defined as: At least 1 health care visit for bronchiolitis during the first year of life.
B	Severity of Bronchiolitis (medical records)	To estimate severity, we categorized infants into the following 3 groups on the basis of their most advanced level of health care for bronchiolitis: no visit (no bronchiolitis visits), outpatient (only clinic or emergency department visit), and hospitalization (23-hour observation or hospitalization).

Results

41.1.A Infant Bronchiolitis Diagnosis

Population: TennCare retrospective cohort, 1995-2007
Exposure: Timing of the filling of folic acid–containing supplements during pregnancy
Outcome: Infant Bronchiolitis Diagnosis
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
None filled	30983	1.0	
During first trimester only	16656	1.17 (1.11, 1.22)	
After first trimester	44042	0.98 (0.95, 1.02)	
Both during and after first trimester	75652	1.06 (1.02, 1.09)	

41.1.B Severity of Bronchiolitis

Population: TennCare retrospective cohort, 1995-2007
Exposure: Timing of the filling of folic acid–containing supplements during pregnancy
Outcome: Severity of Bronchiolitis
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
None filled	30983	1.0	
During first trimester only	16656	1.16 (1.11, 1.22)	0.05
After first trimester	44042	0.98 (0.94, 1.02)	
Both during and after first trimester	75652	1.06 (1.02, 1.09)	0.05

Statistical Method(s)

Endpoints: Severity of Bronchiolitis
Adjustment factors: adequacy of prenatal care, estimated gestational age (in weeks), infant birth weight, infant sex, maternal age at delivery, maternal asthma, maternal educational level, maternal marital status, maternal race, maternal smoking during pregnancy, number of living siblings, region of residence, year of pregnancy
Statistical metric: adjusted odds ratio
Statistical metric description: We conducted a proportional odds ordinal logistic regression model to investigate the timing of prescription filling and the ordinal outcome of bronchiolitis severity (categorized as “no visit,” “outpatient” (clinic or emergency department visit), or “hospitalization” (23-hour observation and hospitalization)). We compared differences in maternal and infant characteristics

across the 4 prescription filling groups using χ2 contingency table statistics for categorical variables and the Kruskal-Wallis test for continuous variables. We conducted logistic regression to determine the association between the timing of the filling of prenatal vitamin prescriptions and infant bronchiolitis diagnosis, while adjusting for infant sex, gestational age, birth weight, number of siblings, maternal race, region of residence, pregnancy year, marital status, maternal age, education, smoking, and prenatal care adequacy. We did not detect important correlations among covariates to warrant omission due to multicollinearity issues or redundancy.

Endpoints: Infant Bronchiolitis Diagnosis
Adjustment factors: adequacy of prenatal care, estimated gestational age (in weeks), infant birth weight, infant sex, maternal age at delivery, maternal asthma, maternal educational level, maternal marital status, maternal race, maternal smoking during pregnancy, number of living siblings, region of residence, year of pregnancy
Statistical metric: adjusted odds ratio
Statistical metric description: We compared differences in maternal and infant characteristics across the 4 prescription filling groups using χ2 contingency table statistics for categorical variables and the Kruskal-Wallis test for continuous variables. We conducted logistic regression to determine the association between the timing of the filling of prenatal vitamin prescriptions and infant bronchiolitis diagnosis, while adjusting for infant sex, gestational age, birth weight, number of siblings, maternal race, region of residence, pregnancy year, marital status, maternal age, education, smoking, and prenatal care adequacy. We did not detect important correlations among covariates to warrant omission due to multicollinearity issues or redundancy.

42. WHITROW, 2009

Full citation: Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. 2009. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. Am J Epidemiol 170(12): 1486-1493.

Funding: none reported

GENERATION 1 COHORT STUDY, 1998-2005

Age: assessed at 3.5 and 5.5 years	**Study design:** Prospective (**n =** 557)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Australia **Region:** **State:** Adelaide, South Australia
Inclusion criteria: live singleton baby	**Exclusion critieria:**

42.1. Exposure: Maternal intake of folate during pregnancy

Method	Description	Analysis
questionnaire	A maternal dietary food frequency questionnaire was administered in early and late pregnancy by a trained research nurse. The interviewer proceeded through a list of 197 foods, asking if the woman ate each food, and if so, how often and how much. Food models and photographs were used to assist in estimating serving sizes. Mothers reported retrospective consumption of folic acid supplements before pregnancy (yes/no). Mothers reported detailed (brand, dose, frequency) concurrent use of any supplements at both the early and late pregnancy interviews.	Daily dietary intake of folate was calculated from the food frequency data by using a database of the nutritional content of common foods (NUTTAB91-92). Reported supplement intake (brand, dose, frequency) in early and late pregnancy was converted into daily intake (lg/day) of folic acid for early and late pregnancy by using dosage information provided on the package. When mothers did not report a specific brand of pregnancy supplement, they were assigned the average folic acid from the 3 available brands.

Outcomes

	Outcome	Diagnostic Description
A	Asthma at 3.5 Years (medical professional or test)	Mothers were asked 2 questions on their child's asthma status at 3.5 years ("Has your child been diagnosed with asthma?" and "Who made the diagnosis?") Asthma was affirmed at each age if it had been diagnosed by a physician. In the absence of skin prick or blood test for atopy, asthma was defined as atopic if accompanied by one or more physician-diagnosed allergies (skin including eczema, food, drug, or hay fever) at 3.5 years only (atopy questions not asked at 5.5 years).
B	Asthma at 5.5 years	Mothers were asked 2 questions on their child's asthma status at 5.5

	Outcome	Diagnostic Description
	(medical professional or test)	years ("Have you ever been told by a doctor that the child has asthma?" and "Does the child have asthma now?"). Asthma was affirmed at each age if it had been diagnosed by a physician and, at 5.5 years, the child currently had asthma. Persistent asthma was affirmed if the child had asthma at both 3.5 years and 5.5 years. In the absence of skin prick or blood test for atopy, asthma was defined as atopic if accompanied by one or more physician-diagnosed allergies (skin including eczema, food, drug, or hay fever) at 3.5 years only (atopy questions not asked at 5.5 years).
C	Persistent asthma at 3.5 Years and 5.5 Years (medical professional or test)	Mothers were asked 2 questions on their child's asthma status at 3.5 years ("Has your child been diagnosed with asthma?" and "Who made the diagnosis?") Asthma was affirmed at each age if it had been diagnosed by a physician. In the absence of skin prick or blood test for atopy, asthma was defined as atopic if accompanied by one or more physician-diagnosed allergies (skin including eczema, food, drug, or hay fever) at 3.5 years only (atopy questions not asked at 5.5 years).

Results

42.1.A Asthma at 3.5 Years

Population: Generation 1 Cohort, 1998-2005
Exposure: Maternal intake of folate during pregnancy
Outcome: Asthma at 3.5 Years
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
Prepregnancy-- Supplement	-	1.22 (0.7, 2.15)	
Early pregnancy-- Diet	-	1.09 (0.78, 1.51)	
Early pregnancy-- Supplement	-	0.92 (0.79, 1.08)	
Early pregnancy--Combination	-	0.93 (0.79, 1.08)	
Late pregnancy-- Diet	-	1.03 (0.66, 1.6)	
Late pregnancy-- Supplement	-	1.26 (1.09, 1.47)	0.05
Late pregnancy-- Combination	-	1.26 (1.09, 1.47)	0.05
Early & Late Combined Models- 'Early Diet'	-	1.15 (0.82, 1.61)	
Early & Late Combined Models- 'Early Supplement'	-	0.88 (0.74, 1.05)	
Early & Late Combined Models- 'Late Diet'	-	0.94 (0.63, 1.4)	
Early & Late Combined Models- 'Late Supplement'	-	1.32 (1.14, 1.53)	0.05

42.1.B Asthma at 5.5 years

Population: Generation 1 Cohort, 1998-2005
Exposure: Maternal intake of folate during pregnancy
Outcome: Asthma at 5.5 years
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
Prepregnancy-- Supplement	-	1.0 (0.59, 1.72)	
Early pregnancy-- Diet	-	0.97 (0.63, 1.5)	
Early pregnancy-- Supplement	-	0.92 (0.77, 1.1)	
Early pregnancy--Combination	-	0.92 (0.77, 1.11)	
Late pregnancy-- Diet	-	0.86 (0.57, 1.28)	
Late pregnancy-- Supplement	-	1.16 (0.94, 1.43)	
Late pregnancy-- Combination	-	1.16 (0.94, 1.43)	
Early & Late Combined Models- 'Early Diet'	-	1.08 (0.72, 1.6)	
Early & Late Combined Models- 'Early Supplement'	-	0.9 (0.74, 1.1)	
Early & Late Combined Models- 'Late Diet'	-	0.8 (0.51, 1.24)	
Early & Late Combined Models- 'Late Supplement'	-	1.18 (0.96, 1.45)	

42.1.C Persistent asthma at 3.5 Years and 5.5 Years

Population: Generation 1 Cohort, 1998-2005
Exposure: Maternal intake of folate during pregnancy
Outcome: Persistent asthma at 3.5 Years and 5.5 Years
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
Prepregnancy-- Supplement	-	1.16 (0.55, 2.46)	
Early pregnancy-- Diet	-	1.0 (0.56, 1.79)	
Early pregnancy-- Supplement	-	0.88 (0.67, 1.14)	
Early pregnancy--Combination	-	0.88 (0.67, 1.15)	
Late pregnancy-- Diet	-	0.83 (0.46, 1.49)	
Late pregnancy-- Supplement	-	1.32 (1.03, 1.69)	0.05
Late pregnancy-- Combination	-	1.32 (1.02, 1.69)	0.05
Early & Late Combined Models- 'Early Diet'	-	1.19 (0.73, 1.94)	
Early & Late Combined Models- 'Early Supplement'	-	0.83 (0.61, 1.14)	
Early & Late Combined Models- 'Late Diet'	-	0.71 (0.38, 1.35)	
Early & Late Combined Models- 'Late Supplement'	-	1.38 (1.06, 1.79)	0.05

Statistical Method(s)

Endpoints: Asthma at 5.5 years; Asthma at 3.5 Years; Persistent asthma at 3.5 Years and 5.5 Years
Adjustment factors: breastfeeding (partial or full for less than 3 months), gestational age, gravida, maternal age, maternal asthma, maternal education, maternal intake of vitamin A, maternal intake of vitamin D, maternal intake of vitamin E, maternal intake of zinc, maternal smoking during early pregnancy, maternal smoking during late pregnancy, parity, socioeconomic status
Statistical metric: adjusted relative risk
Statistical metric description: The association between maternal folic acid and folate intake (assessed as continuous variables) at each of the 4 time points (pre-, early, late, and early + late pregnancy) and each

asthma outcome (3.5 years, 5.5 years, persistent) was investigated by using a Poisson regression model. In early and late pregnancy, folic acid and folate were initially included in the models as separate continuous variables because of their different bioavailability (11). Models were then rerun with the sum of folic acid and folate (continuous variable).

43. ZETSTRA-VAN DER WOUDE, 2014

Full citation: Zetstra-van der Woude PA, De Walle HE, Hoek A, Bos HJ, Boezen HM, Koppelman GH, de Jong-van den Berg LT, Scholtens S. 2014. Maternal high-dose folic acid during pregnancy and asthma medication in the offspring. Pharmacoepidemiol Drug Saf 23(10): 1059-1065.

Funding: No external funding was used for this study.

IADB.NL PRESCRIPTION DATABASE, NETHERLANDS, 1994-2001

Age: no information about children's age; maternal age in high-dose vs referent: 31.0+/-4.71; 30.4+/-4.69 and were statistically diff	**Study design:** Retrospective (**n =** 35604)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Netherlands **Region:** **State:**
Inclusion criteria: mothers taking high-dose folic acid supplements during pregnancy	**Exclusion critieria:**

43.1. Exposure: Maternal high-dose folic acid prescription during pregnancy

Method	Description	Analysis
prescription	used data from the IADB.nl, a population-based pharmacy prescription database; all prescriptions would be registered at a single pharmacy for a single patient, all high-dose folic acid supplements would be prescribed (not acquired over-the-counter)	Exposure to maternal high-dose folic acid was defined as at least one dispension of high-dose folic acid during pregnancy (coded according to the World Health Organization classification system with the anatomical therapeutically chemical [ATC] code: B03BB01 and on the basis of the preparation dispensed [folic acid 5 mg] or the number of defined daily doses prescribed and the number of days prescribed for).

Outcomes

	Outcome	Diagnostic Description
A	Any asthma medication (medical records)	Dispension of asthma medication for the child was taken as a proxy for childhood asthma. Four outcome parameters were defined: (i) at least one dispension of any asthma medication (ATC code R03); (ii) at least two dispensions of any asthma medication, (iii) at least one dispension of an inhalation corticosteroid (ICS, ATC code R03BA); and (iv) at least two dispensions of ICSs
B	Any inhalation corticosteroid (medical records)	Dispension of asthma medication for the child was taken as a proxy for childhood asthma. Four outcome parameters were defined: (i) at least one dispension of any asthma medication (ATC code R03); (ii) at least two dispensions of any asthma medication, (iii) at least one

	Outcome	Diagnostic Description
		dispension of an inhalation corticosteroid (ICS, ATC code R03BA); and (iv) at least two dispensions of ICSs
C	Recurrent asthma medication (medical records)	Dispension of asthma medication for the child was taken as a proxy for childhood asthma. Four outcome parameters were defined: (i) at least one dispension of any asthma medication (ATC code R03); (ii) at least two dispensions of any asthma medication, (iii) at least one dispension of an inhalation corticosteroid (ICS, ATC code R03BA); and (iv) at least two dispensions of ICSs
D	Recurrent inhalation corticosteroid (medical records)	Dispension of asthma medication for the child was taken as a proxy for childhood asthma. Four outcome parameters were defined: (i) at least one dispension of any asthma medication (ATC code R03); (ii) at least two dispensions of any asthma medication, (iii) at least one dispension of an inhalation corticosteroid (ICS, ATC code R03BA); and (iv) at least two dispensions of ICSs

Results

43.1.A Any asthma medication

Population: IADB.nl prescription database, Netherlands, 1994-2001
Exposure: Maternal high-dose folic acid prescription during pregnancy
Outcome: Any asthma medication
Statistical metric: adjusted incidence rate ratio

Group	N	adjIRR 95% CI (low, high)	*p*-value
No prescription of high-dose folic acid during pregnancy	34296	-	
Prescription of high-dose folic acid during pregnancy	1308	1.03 (0.92, 1.16)	

43.1.B Any inhalation corticosteroid

Population: IADB.nl prescription database, Netherlands, 1994-2001
Exposure: Maternal high-dose folic acid prescription during pregnancy
Outcome: Any inhalation corticosteroid
Statistical metric: adjusted incidence rate ratio

Group	N	adjIRR 95% CI (low, high)	*p*-value
No prescription of high-dose folic acid during pregnancy	34296	-	
Prescription of high-dose folic acid during pregnancy	1308	1.22 (1.06, 1.4)	0.05

43.1.C Recurrent asthma medication

Population: IADB.nl prescription database, Netherlands, 1994-2001
Exposure: Maternal high-dose folic acid prescription during pregnancy
Outcome: Recurrent asthma medication
Statistical metric: adjusted incidence rate ratio

Group	N	adjIRR 95% CI (low, high)	*p*-value
No prescription of high-dose folic acid during pregnancy	34296	-	

Group	N	adjIRR 95% CI (low, high)	*p*-value
Prescription of high-dose folic acid during pregnancy	1308	1.14 (1.0, 1.3)	0.05

43.1.D Recurrent inhalation corticosteroid

Population: IADB.nl prescription database, Netherlands, 1994-2001
Exposure: Maternal high-dose folic acid prescription during pregnancy
Outcome: Recurrent inhalation corticosteroid
Statistical metric: adjusted incidence rate ratio

Group	N	adjIRR 95% CI (low, high)	*p*-value
No prescription of high-dose folic acid during pregnancy	34296	-	
Prescription of high-dose folic acid during pregnancy	1308	1.26 (1.07, 1.47)	0.05

Statistical Method(s)

Endpoints: Any asthma medication ; Recurrent inhalation corticosteroid ; Any inhalation corticosteroid ; Recurrent asthma medication
Adjustment factors: dispension of benzodiazepines during pregnancy, maternal age, maternal dispension of asthma medication
Statistical metric: adjusted incidence rate ratio
Statistical metric description: Crude and adjusted IR ratios (IRRs) and 95% confidence intervals (CIs) were calculated for the exposure compared with the reference group. As possible confounders, we took into account the following: age of the mother, single or multiple pregnancy, maternal asthma medication, and paternal asthma medication. In addition, confounding by medication associated with high-dose folic acid supplementation was evaluated. We assessed dispension of iron supplements, antifolate medication (anti-epileptics, sulphonamides, and trimethoprim), antidepressants, antihypertensives, antidiabetics, and benzodiazepines during pregnancy, because prenatal exposure to these drugs or to the underlying condition might possibly be related to the development of childhood asthma and may confound the association. Differences between the exposed and reference group were tested at a level of significance of 0.05, using the Student's t-test for maternal age and the Pearson's chi-squared test for the other possible confounding factors.