

Table S1. The characteristics of studies included in the systematic review on the relationship between folate status and asthma, wheeze or other allergic diseases (cohort study)

Study	Study Design; follow-up time	Definition of Outcomes	Measurement of Folate/ Folic Acid Status	Main Findings	Study Limitations	Adjusted Factors	Quality Assessment Score
Kim 2014 ¹	Birth cohort study of 917 children in South Korea, carried out from 2006-2011, embedded in the MOCEH study; 2 yr	Asthma: physician-diagnosed or treatment for asthma in past year AD: physician-diagnosed or treatment for AD in past year	Serum folate level	Increased maternal folate level during mid-pregnancy was associated with a decreased risk of LRTIs at 6 mo and AD at 24 mo	Potential selection bias due to the substantial loss of folate (~50%) at 24 mo, no assessment of maternal folate status in the early pregnancy	Baby's sex, birth weight, gestational age, and duration of breastfeeding, and maternal age, the history of allergic diseases such as AD, asthma, allergic rhinitis, and allergic conjunctivitis, the urinary cotinine levels in mid- and late-pregnancy, and the prepregnancy BMI	7
van der Valk 2013 ²	Birth cohort study of 2001 children in Netherlands, carried out from 2002-2006, embedded in the Generation R study; 6 yr	Asthma: physician-diagnosed Wheeze: using questions from the ISAAC Eczema: physician-diagnosed or self-reported	Cord blood folate, <i>MTHFR</i> C677T polymorphism	No significant association between folate level at birth and wheeze or eczema until 4 yr, or asthma and eczema ever. Genetic mutations in <i>MTHFR</i> C677T and higher folate levels were associated with increased risk of eczema until 4 yr	Lack of data on maternal folate status, potential selection bias due to missing cord blood samples	Maternal age, BMI, educational level at intake, history of maternal atopy or asthma, parity, smoking, folic acid supplement use and pet keeping during pregnancy, and children's sex, gestational age, birth weight and day care attendance, based on the significance of their associations with repeated wheezing ($P < 0.05$), or a change in effect estimate of $> 10\%$	8
Okupa 2013 ³	Cohort study of 138 children (2-9 yr) in USA, carried out from 1998, embedded in the COAST study; 8 yr	Asthma: physician-diagnosed and/or the use of asthma medication Sensitization: 1 or more positive (> 0.34) specific IgE results	Plasma folate level	Higher plasma folate levels at or before age 6 yr were associated with allergic sensitization but not with IgE production, wheeze, or asthma at age 6 yr	Small sample size, no assessment of dietary intake, and limited adjustment for covariates	Gender and socioeconomic status	6
Lin 2013 ⁴	Cohort study of 150 children (5-17 yr) in USA; 1 yr	Asthma: long-term controller medication for asthma or meeting National Asthma Education and Prevention Program guideline Atopy: at least 1 positive skin prick test (SPT) result	Serum folate level	Serum folate level was not significantly associated with FENO, the number of positive SPTs, lung function, or hospitalizations for asthma. A folate level in the second quartile was associated with increased total IgE when compared with the lowest folate level. Increased serum folate level was associated with less exercise-related symptoms	Small sample size, no assessment of dietary intake, lack of multiple testing corrections, and limited adjustment for covariates	Age, sex, and education	6

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Study	Study Design; follow-up time	Definition of Outcomes	Measurement of Folate/ Folic Acid Status	Main Findings	Study Limitations	Adjusted Factors	Quality Assessment Score
Martinussen 2012 ⁵	Birth cohort study of 1,499 children in USA, carried out from 1997-2000, embedded in the AIP and later the PRAM study; 6 yr	Asthma: physician diagnosed and current symptoms	Maternal folic acid supplement	No significant association between maternal folate supplement in the first trimester and childhood asthma at 6 age yr	Lack of date on maternal dietary intake	Maternal marital status, family income, and maternal asthma.	9
Bekkers 2012 ⁶	Birth cohort of 3,786 children in Netherlands, carried out from 1996-1997, embedded in the PIAMA study; 8 yr	Asthma: symptoms and/or doctor-diagnosed Wheeze: at least one attack of wheeze Eczema: an itchy rash that came and went on typical eczema sites Sensitization: serum IgE ≥ 0.70 IU/mL ⁻¹	Maternal folic acid supplement	Maternal folic acid use was associated with wheeze at age 1 yr and eczema at age 7 yr. No overall (from 1 to 8 yr of age) associations between maternal folic acid supplementation and (frequent) asthma symptoms, wheeze, LRIs and eczema	Lack of data on maternal dietary intake	Maternal education, maternal allergy, maternal smoking during pregnancy and number of older siblings	9
Kieffe-de 2012 ⁷	Birth cohort study of 8,742 children in Netherlands, carried out from 2002-2006, embedded in the Generation R study; 4 yr	Wheeze: symptoms, ISAAC AD: doctor-diagnosed	Maternal <i>MTHFR</i> C677T polymorphism, maternal folic acid supplement, and maternal plasma folate	Higher maternal plasma folate level in early pregnancy was associated with increased prevalence of AD but not with wheeze and shortness of breath at age 4 yr	No assessment of maternal dietary intake, and measured plasma folate level at a very early stage in pregnancy (13 ± 2.0 wk of gestation)	Time, maternal ethnicity, parental atopic constitution, parity, maternal BMI, maternal age, breastfeeding duration, daycare attendance, maternal educational level, maternal smoking and alcohol consumption, and fetal gender and birth weight SD score derived from generalized estimation equations.	8
Dunstan 2012 ⁸	Birth cohort of 484 children in Australia; 1 yr	Asthma: recurrent wheeze to be responsive to bronchodilator medications Eczema: typical skin lesions Food Allergy: IgE-mediated food allergy and a positive SPT to the implicated food Sensitization: SPT positive	Folate consumption from foods and folic acid supplement, maternal and cord blood serum folate level	Maternal folate taken as a supplement in higher doses during the third trimester was significant associated with eczema at age 1 yr. With cord folate levels <50 nmol/L and >75 nmol/L was associated with greater sensitization risk than levels between 50 and 75 nmol/L	Short duration of follow-up and limited adjustment of covariates	Maternal allergy and infant postnatal diet	6

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Study	Study Design; follow-up time	Definition of Outcomes	Measurement of Folate/Folic Acid Status	Main Findings	Study Limitations	Adjusted Factors	Quality Assessment Score
Magdelijns 2011 ⁹	Birth cohort of 2,640 children in Netherlands, carried out from 2000, embedded in the KOALA Birth Cohort Study; 6-7 yr	Asthma: physician-diagnosed with clinical symptoms and/or asthma medication use Wheeze: parents report Eczema: parents report AD: symptoms, UK Working Party criteria Sensitization: sIgE >0.3 IU/mL for ≥ 1 of the tested allergens	Maternal folic acid supplement and intracellular folic acid level	No significant association between maternal folic acid supplement use during pregnancy and AD and sensitization at age 2 yr; or wheeze, lung function, asthma, and eczema at age 6-7 yr. Maternal folate level in erythrocytes in late pregnancy was inversely associated with asthma at age 6-7 yr. ($P=0.05$)	No assessment of maternal dietary intake, potential selection bias due to loss of follow-up, and no assessment of folate level in early pregnancy	Maternal antibiotic use during pregnancy, maternal smoking during pregnancy, maternal alcohol consumption during pregnancy, mode and place of delivery, birthweight, gender of the child, treatment with antibiotics during the first 6 mo of life, breastfeeding during the first 2 yr of life, exposure to domestic animals during pregnancy and the first 2 yr of life, exposure to environmental tobacco smoke in the first 6 to 7 yr of life, siblings, family history, recruitment group, maternal education level, daycare, and other supplement use during pregnancy.	8
Nwaru 2011 ¹⁰	Birth cohort of 2,441 children in Finland, carried out from 1996-1997, embedded in the Finnish Type 1 Diabetes Prediction and Prevention study; 5 yr	Asthma: physician-diagnosed plus either any wheezing symptom or asthma medication use in the past 12 mo, ISAAC Eczema: parents report	Maternal folate consumption from foods and folic acid supplement	No significant associations between maternal folate intake and eczema at age 5 yr	Potential recall bias	Sex of child, place of birth, season of birth, gestational age at birth, maternal age at birth, maternal basic education, maternal smoking during pregnancy, mode of delivery, number of siblings, parental asthma, parental allergic rhinitis, pets at home at 1 yr of age, and atopic eczema by 6 mo of age.	9
Miyake 2011 ¹¹	Birth cohort of 763 children in Japan, carried out from 2001-2003, embedded in the OMCHS study; 16-24 mo	Wheeze: had symptom 12 mo pre based on the International Study of Asthma and Allergies in Childhood (ISAAC) criteria Eczema: had symptom, ISAAC	Maternal folate consumption from foods	No significant association between maternal consumption of folate during pregnancy and wheeze or eczema at age 16-24 mo	No assessment of maternal folate supplementation, lack of analysis of folate intake at different stage of pregnancy, and potential selection bias	Maternal age, gestation at baseline, residential municipality at baseline, family income, maternal and paternal education, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, changes in maternal diet in the previous 1 mo, season when data at baseline were collected, maternal smoking during pregnancy, baby's old-ter siblings, baby's sex, baby's birth weight, household smoking in same room as infant, breastfeeding duration, age at which solid foods were introduced, age of 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.	8

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Study	Study Design; follow-up time	Definition of Outcomes	Measurement of Folate/Folic Acid Status	Main Findings	Study Limitations	Adjusted Factors	Quality Assessment Score
Thuesen 2010 ¹²	Cohort study of 6,784 adults (30-60 yr) in Denmark, carried out from 1999-2001, embedded in the Inter99 study; 5 yr	Asthma: self-reported doctor-diagnosed Atopy: specific IgE \geq 0.35kU/l to at least one of the four allergens	Dietary intake of folate, serum folate level and <i>MTHFR</i> C677T polymorphism	Low serum folate level and the TT genotype of the <i>MTHFR</i> C677T polymorphism were associated with increased prevalence of self-reported doctor-diagnosed asthma at baseline	Lack of data on vitamin supplements, limited analysis of longitudinal data with 5-yr follow-up, and potential bias due to loss of follow-up	Age, sex, total energy intake, smoking, alcohol intake, BMI, and socioeconomic status	7
Whitrow 2009 ¹³	Birth cohort study of 557 children in Australia, carried out from 1998-2000, embedded in the Generation 1 cohort study; 5.5 yr	Asthma: physician-diagnosed	Maternal folate consumption from foods and folic acid supplement	Maternal folic acid supplementation in late pregnancy significantly increase the risk of asthma 3.5 yr and of persistent asthma at 3.5 and 5.5 yr	No assessment of folate level, and potential selection bias due to loss of follow-up	Maternal education, maternal age, parity, gravida, gestational age, maternal asthma status, and breastfeeding (partial or full for <3 mo)	9
Haber 2009 ¹⁴	Birth cohort study of 32,077 children in Norway, carried out from 2000-2005, embedded in the MoBa study; 1.5 yr	Wheeze: had symptom	Maternal folic acid supplement	Maternal folate supplementation in the first trimester was associated with increased risk of wheeze and LRI up to 18 mo of age	No assessment of dietary intake	Other vitamin supplements and cod liver oil in pregnancy, vitamin supplements and cod liver oil at 6 mo of age, and for maternal age, maternal atopy, maternal smoking in pregnancy, maternal educational level, postnatal parental smoking, sex, parity, birth weight, season born, breast-feeding and type of day care	7
Granel 2008 ¹⁵	Birth cohort study of 5,364 children in UK, carried out from 1991-1992, embedded in the ALSPAC study; 7-8 yr	Asthma: physician-diagnosed and current symptom Atopy: SPT positive	Maternal and child <i>MTHFR</i> C677T polymorphism, Maternal and child folate consumption from foods, and maternal folic acid supplement	No significant association between <i>MTHFR</i> C677T genotype and asthma or atopy in mothers or children	No assessment of dietary intake in early pregnancy, and potential selection bias due to loss of follow-up	Exposure to pre-natal and post-natal smoking, maternal education and social class	7
Litonjua 2006 ¹⁶	Birth cohort of 1,290 children in USA, carried out from 1999-2002, embedded in the Project Viva study; 2 yr	Wheeze: mother-reported symptom Eczema: health care professional diagnosed	Maternal folate consumption from foods and folic acid supplement	No significant association between maternal folate intake in the first and second trimesters of pregnancy and wheeze or eczema at age 2 yr	Limited assessment of folate status at different stage of pregnancy, and potential selection bias due to loss of follow-up	Sex, maternal age, maternal asthma, paternal asthma, family income, passive smoke exposure, breastfeeding, and other	8

MOCEH, Mothers and Children's Environmental Health study; AD, Atopic dermatitis; BMI, body mass index; *MTHFR*, methylene-tetrahydrofolate reductase; ISAAC, International Study of Asthma and Allergies in Childhood; COAST, Childhood Origins of Asthma project; AIP, Asthma in Pregnancy; PRAM, Perinatal Risk of Asthma in Infants of Asthmatic Mothers; PLAMA, Prevention and Incidence of Asthma and Mite Allergy; OMCHS, Osaka Maternal and Child Health Study; MoBa, Norwegian Mother and Child Cohort Study; ALSPAC, Avon Longitudinal Study of Parents and Children