

## SUPPLEMENTAL TABLE 1

Characteristics of cohort and case-control studies included in the systematic review on the association between maternal folate/folic acid intake and the risk of asthma and other allergic outcomes in childhood

Author, year	Study design; Study location; Study population; Study name; Study time period	Exposure: assessment method, type, and dose	Timing of Exposure	Exposure	Outcome (timing)	Adj. <sup>1</sup> effect measure (95% CI)	SS Change in Risk	Adjustments
Litonjua, 2006 (1)	Cohort; US; Boston, MA; 1,290 mother-child pairs; Project Viva; Mothers enrolled 1999-2002	FFQ – total folate intake in 1 <sup>st</sup> and 2 <sup>nd</sup> trimester; Analyzed in quartiles (ranges not given)	1 <sup>st</sup> and 2 <sup>nd</sup> trimester	Total folate (Q4:Q1)	Any wheezing (in first 2 y)	OR: 0.89 (0.60, 1.31)		Any wheezing in first 2 y: Sex, maternal age, maternal asthma, paternal asthma, family income, passive smoke exposure, breastfeeding, and other children <12 y old in the home.
					Recurrent wheezing (in first 2 y) Eczema (at 2 y)	OR: 0.68 (0.38, 1.22) No association (Data not reported)		
Granell, 2008 (2)	Cohort; UK; 14,541 pregnant women and 14,062 live born children; Avon Longitudinal Study of Parents and Children (ALSPAC); Maternal expected delivery date 1991 – 1992	FFQ – at 32 weeks of pregnancy for maternal dietary folate (Mean 255.8 µg/day; SD: 70.1);  Maternal self-report for folic acid supplements at 18 and 32 wk of pregnancy (vs. no use)	3 <sup>rd</sup> trimester	Dietary folate (per 100 µg/day ↑)	Childhood atopy (at 7-8 y)	OR: 0.98 (0.88, 1.10)		Dietary folate: mother's folate supplementation at 32 wk, prenatal and postnatal smoking, maternal education and social class.
			3 <sup>rd</sup> trimester 3 <sup>rd</sup> trimester	FA SUP (vs. no use, 18 wk) FA SUP (vs. no use, 32 wk)	Childhood atopy at (at 7-8 y) Childhood atopy at (at 7-8 y)	OR: 0.99 (0.78, 1.25) OR: 1.15 (0.98, 1.35)		
Haberg, 2009 (3)	Cohort; Norway; 32,077 children; Norwegian Mother and Child Study (MoBa); born between 2000 and 2005	Folic acid supplement assessed from wk 0 to 30 in pregnancy; Categorized as first trimester or after first trimester exposure	1 <sup>st</sup> trimester	FA SUP (vs. no use)	Wheeze (at 6-18 mo)	RR:1.06 (1.03, 1.10)	↑ ↑ ↑ ↑	Other vitamin supplements and cod liver oil in pregnancy, vitamin supplements and cod liver oil at 6 mo of age, 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; Exposures in first and after first trimester also adjusted for each other
			2 <sup>nd</sup> /3 <sup>rd</sup> trimester	FA SUP (vs. no use)	LRTI (at 0-18 mo) Hospitalized for LRTI (at 0-18 mo) Wheeze (at 6-18 mo)	RR:1.09 (1.02, 1.15) RR:1.24 (1.09, 1.41) RR: 1.00 (0.97, 1.03)		
			Anytime	FA SUP (vs. no use)	LRTI (at 0-18 mo) Hospitalized for LRTI (at 0-18 mo) Wheeze (at 6-18 mo) LRTI (at 0-18 mo) Hospitalized for LRTI (at 0-18 mo)	RR: 0.98 (0.92, 1.04) RR: 0.86 (0.75, 0.97) RR:1.07 (1.02, 1.12) RR:1.07 (0.98, 1.16) RR:1.08 (0.90, 1.29)		

Author, year	Study design; Study location; Study population; Study name; Study time period	Exposure: assessment method, type, and dose	Timing of Exposure	Exposure	Outcome (timing)	Adj. <sup>1</sup> effect measure (95% CI)	SS Change in Risk	Adjustments
Whitrow, 2009 (4)	Cohort; Australia; 490 mother/child pairs at 3.5 y / 423 at 5.5 y Generation One Cohort Study; women and children recruited 1998 – 2000	FFQ x 2 - early and late pregnancy for dietary folate;	Pre-pregnancy	PP FA SUP (vs. no use)	Asthma at 3.5 y	RR: 1.22 (0.70, 2.15)		All models adjusted for “a” (maternal education, maternal age, parity, gravida, gestational age, maternal asthma status, and breastfeeding (partial or full for <3 months)). Pre- and early pregnancy models adjusted for “a” and vitamin A, vitamin E, vitamin D, zinc from diet and supplements in early pregnancy, and maternal smoking during early pregnancy. Late pregnancy model adjusted for “a” and vitamin A, vitamin E, vitamin D, zinc from diet and supplements in late pregnancy, and maternal smoking during late pregnancy. Early and late pregnancy combined model adjusted for all the potential confounders listed above.
			1 <sup>st</sup> + 2 <sup>nd</sup> trimester	EP FA SUP (per 1,000 µg)	Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y	RR: 1.00 (0.59, 1.72) RR: 1.16 (0.55, 2.46) RR: 0.92 (0.79, 1.08)		
		Maternal self-report of for FA SUP	3 <sup>rd</sup> trimester	LP FA SUP (per 1,000 µg)	Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y	RR: 0.92 (0.77, 1.10) RR: 0.88 (0.67, 1.14) RR: 1.26 (1.09, 1.47)	↑	
			1 <sup>st</sup> – 3 <sup>rd</sup> trimester	E+L, Early FA SUP (per 1,000 µg)	Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y	RR: 1.16 (0.94, 1.43) RR: 1.32 (1.03, 1.69) RR: 0.88 (0.74, 1.05)	↑	
		Timing: (1) Pre-pregnancy (PP) (2) Early pregnancy (EP) (<16 wks) (3) Late pregnancy (LP) (30-34 wks) (4) Early + Late (E+L) pregnancy	1 <sup>st</sup> – 3 <sup>rd</sup> trimester	E+L, Late FA SUP (per 1,000 µg)	Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y	RR: 0.90 (0.74, 1.10) RR: 0.83 (0.61, 1.14) RR: 1.32 (1.14, 1.53)	↑	
			1 <sup>st</sup> + 2 <sup>nd</sup> trimester	EP diet (per 100 µg)	Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y	RR: 1.18 (0.96, 1.45) RR: 1.38 (1.06, 1.79) RR: 1.09 (0.78, 1.51)	↑	
		3 <sup>rd</sup> trimester	LP diet (per 100 µg)	Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y	RR: 0.97 (0.63, 1.50) RR: 1.00 (0.56, 1.79) RR: 1.03 (0.66, 1.60) RR: 0.86 (0.57, 1.28) RR: 0.83 (0.46, 1.49) RR: 1.15 (0.82, 1.61)			
		1 <sup>st</sup> – 3 <sup>rd</sup> trimester	E+L, early diet (per 100 µg)	Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y	RR: 1.08 (0.72, 1.60) RR: 1.19 (0.73, 1.94) RR: 0.94 (0.63, 1.40)			
		1 <sup>st</sup> + 2 <sup>nd</sup> trimester	EP diet + FA SUP (total) (per 1,000 µg)	Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y	RR: 0.80 (0.51, 1.24) RR: 0.71 (0.38, 1.35) RR: 0.93 (0.97, 1.08)			
		3 <sup>rd</sup> trimester	LP diet + FA SUP (total) (per 1,000 µg)	Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y) Asthma at 3.5 y	RR: 0.92 (0.77, 1.11) RR: 0.88 (0.67, 1.15) RR: 1.26 (1.09, 1.47)	↑		
				Asthma at 5.5 y Persistent asthma (3.5 & 5.5 y)	RR: 1.16 (0.94, 1.43) RR: 1.32 (1.02, 1.69)	↑		

Author, year	Study design; Study location; Study population; Study name; Study time period	Exposure: assessment method, type, and dose	Timing of Exposure	Exposure	Outcome (timing)	Adj. <sup>1</sup> effect measure (95% CI)	SS Change in Risk	Adjustments
Binkley, 2011 (5)	Case-control; Canada; 1,300 cases with peanut allergy, 113 controls with shellfish allergy; Anaphylaxis Canada Registry; 2007	Folic acid supplement; Self-report of initiation before pregnancy, initiation after pregnancy, or taken anytime during pregnancy	Initiated PreC	FA SUP (vs. no use)	Peanut allergy (any age)	OR: 1.48 (0.99, 2.20)		N/A
			Initiated PostC	FA SUP (vs. no use)	Peanut allergy (any age)	OR: 0.78 (0.27, 2.24)		
			Anytime	FA SUP (vs. no use)	Peanut allergy (any age)	OR: 0.53 (0.19, 1.48)		
Haberg, 2011 (6)	Nested case-control; Norway; Cases: 507 children with asthma at 3 y Controls: 1,455 children; Norwegian Mother and Child Cohort Study (MoBa); 2002-2003	Nonfasting plasma folate concentrations measured in 2nd trimester (median 18 weeks)  Median plasma folate (nmol/L): 9.1; 25 <sup>th</sup> percentile 6.2; 75 <sup>th</sup> percentile 16.1  Quintiles: Q1: <5.54 Q5: >17.84	2 <sup>nd</sup> trimester	Plasma folate (Q5:Q1)	Asthma risk (at 3 y)	OR: 1.66 (1.16, 2.37) <sup>2</sup>	↑	Maternal educational level, maternal age, parity, maternal atopy, maternal body mass index, maternal smoking in pregnancy, maternal smoking at age 3 y, and supplement use at age 3 y
Magdelijns et al., 2011. (7)	Nested case-control; Netherlands; 2,834 healthy pregnant women recruited in weeks 10-14 of pregnancy; 2,640 children included in study; conducted within KOALA Birth Cohort study; 2000	Questionnaire- Folic Acid supplement use (yes/no) and start date  RBC folates at 35 weeks of pregnancy Q1: ≤480 nmol/L Q5: ≥1140 nmol/L	PeriC	FA SUP (vs. no use)	Eczema (until 6-7 y)	OR: 1.12 (0.86, 1.46)		Recruitment group, maternal antibiotic, smoking and alcohol use during pregnancy, mode and place of delivery, birth weight, gender, treatment with antibiotics during the first 6 months of life, exposure to environmental tobacco smoke and domestic animals, breastfeeding, maternal education level, family history of atopy, siblings, day care attendance, and multivitamin or other supplement use during pregnancy
			Anytime	FA SUP (vs. no use)	Atopic dermatitis (at 2 y)	OR: 1.15 (0.60, 2.20)		
					Increased total IgE (at 2 y)	OR: 0.72 (0.46, 1.12)		
					Increased specific IgE (at 2 y)	OR: 1.02 (0.62, 1.67)		
					Wheeze (until 6-7 y)	OR: 1.00 (0.79, 1.26)		
					Asthma (at 6-7 y)	OR: 1.27 (0.67, 2.41)		
					Lung function - % FEV (at 6-7 y)	OR: 1.96 (-3.37, 7.28)		
			3 <sup>rd</sup> trimester	RBC folate (Q5:Q1)	Lung function - % FVC (at 6-7 y)	OR: 1.08 (-3.78, 5.95)		
					Eczema (until 6-7 y)	OR: 1.16 (0.90, 1.46)		
					Atopic dermatitis (at 2 y)	OR: 1.15 (0.63, 2.10)		
					Increased total IgE (at 2 y)	OR: 0.71 (0.47, 1.07)		
					Increased specific IgE (at 2 y)	OR: 1.06 (0.67, 1.68)		
Wheeze (until 6-7 y)	OR: 0.99 (0.80, 1.23)							
		Asthma (at 6-7 y)	OR: 1.19 (0.65, 2.20)					
		Lung function - % FEV (at 6-7 y)	β: 0.55 (-4.50, 5.61)					
		Lung function - % FVC (at 6-7 y)	β: 0.34 (-4.21, 4.90)					
		Eczema (until 6-7 y)	OR: 1.35 (0.87, 2.09)					
		Atopic dermatitis (at 2 y)	OR: 0.94 (0.33, 2.67)					
		Increased total IgE (at 2 y)	OR: 1.33 (0.64, 2.80)					
		Allergic sensitization (at 2 y)	OR: 0.70 (0.32, 1.51)					
		Wheeze (until 6-7 y)	OR: 1.01 (0.69, 1.49)					
		Asthma (at 6-7 y)	OR: 0.31 (0.09, 1.10) <sup>2</sup>					
		Lung function - % FEV (at 6-7 y)	β: -0.92 (-6.82, 6.64)					
		Lung function - % FVC (at 6-7 y)	β: -0.65 (-6.68, 5.39)					
					↓			

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Miyake et al., 2011 (8)	Cohort; Japan; 763 Japanese mother-child pairs; Osaka Maternal and Child Health Study; mothers recruited 2001-2003	Dietary History Questionnaire - maternal intake of dietary folate at 5-39 wk pregnancy  Dietary folate (Mean 284 µg; SD 82.2) Quartiles (Median): Q1: 206.8 µg/day Q4: 370.6 µg/day	Anytime	Dietary folate (Q4:Q1)	Wheeze (at 16-24 mo) Eczema (at 16-24 mo)	OR: 1.28 (0.65, 2.50) OR: 1.01 (0.51, 2.00)		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 older 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 β-carotene during pregnancy.
Nwaru, 2011 (9)	Cohort; Finland; 2,441 children; Finnish Type 1 Diabetes Prediction and Prevention study; 1997-2004	FFQ (8 <sup>th</sup> month of pregnancy); FA SUP (mean 364µg; SD 113)	3 <sup>rd</sup> trimester	Dietary folate (continuous)	Asthma (at 5 y) Allergic rhinitis (at 5 y) Atopic eczema (up to 5yr) Wheeze (at 5 y)	HR: 1.04 (0.71, 1.52) HR: 0.95 (0.79, 1.15) HR: 0.91 (0.75, 1.09) No association (data not reported)		Sex of child, place of birth (Southern or Northern Finland), season of birth (winter, spring, summer, autumn), gestational age at birth (in quartiles), maternal age at birth (<25 years, 25–29 years, 30–34 years, ≥35 years), maternal basic education (less than high school, high school graduate), maternal smoking during pregnancy (no, yes, no information), mode of delivery (vaginal, forceps or suction, cesarean section), number of siblings (none, one, two or more), parental asthma (no, yes, no information), parental allergic rhinitis (no, yes, no information), pets at home at 1 year of age (no, yes), and

Author, year	Study design; Study location; Study population; Study name; Study time period	Exposure: assessment method, type, and dose	Timing of Exposure	Exposure	Outcome (timing)	Adj. <sup>1</sup> effect measure (95% CI)	SS Change in Risk	Adjustments
Triche, 2011 (10)	Cohort; US (Massachusetts and Connecticut); Asthma in Pregnancy (AIP) Study and the Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM)	Maternal self-report of folic acid supplements Q1: <270 µg Q5: ≥700 µg	1 <sup>st</sup> trimester	FA SUP (trend test)	Recurrent wheeze (at 1 y) Active asthma (at 6 y)	P-value = .002 P-value = .01	↓ ↓	atopic eczema by 6 months of age (no, yes)  N/A
Bekkers, 2012 (11)	Cohort; Netherlands; 3,786 children; Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study; Children born 1996-1997	Questionnaire completed during pregnancy (80% during wk 30-36); FA containing supplements (200, 400 or 500 µg doses) vs. no use of FA containing supplements	3 <sup>rd</sup> trimester	FA SUP (vs. no use)	Wheeze (at 1 y) Wheeze (at 1-8 y) Asthma symptoms (at 3-8 y) Upper RTI (at 1-8 y) Lower RTI (at 1-8 y) Frequent RTI (at 1-8 y) Eczema (at 1-8 y) Sensitization (at 8 y)	PR: 1.20 (1.04, 1.39) PR: 1.07 (0.96, 1.20) PR: 1.03 (0.92, 1.16) PR: 1.04 (1.00, 1.09) PR: 0.94 (0.83, 1.06) PR: 1.01 (0.89, 1.13) PR: 0.98 (0.87, 1.09) PR: 0.86 (0.73, 1.01)	↑	Maternal education, maternal allergy, maternal smoking during pregnancy and number of older siblings
Dunstan, 2012 (12)	Cohort; Australia; Convenience sample of women (70% known to be "sensitized allergic mother"), 484 offspring examined	Semi-quantitative FFQ for intake of dietary folate and folic acid supplements; Maternal blood measurements  Folic Acid Supplement (Median 668.0 µg DFEs/d; IQR 95.4-1210.8) T1: <200 µg/day T2: 200-500 µg/day T3: >500 µg/day  Dietary folate (Median 277.9 µg DFE/d; IQR 217.4-341.4)  Maternal serum folate: (median 37.2	3 <sup>rd</sup> trimester  3 <sup>rd</sup> trimester  3 <sup>rd</sup> trimester	FA SUP (T3:T1)  Maternal serum folate  Cord blood folate (T1:T2)	Any allergic disease Sensitized (at 1 y) Recurrent wheeze (at 1 y) Eczema (at 1 y) Food reactions (at 1 y) IgE-mediated food allergy (at 1 y) Sensitized to food allergens (at 1 y) Any outcome (at 1 y)  Any allergic disease Sensitized (at 1 y) Recurrent wheeze (at 1 y) Eczema (at 1 y) Food allergy (at 1 y) IgE-mediated food allergy (at 1 y) Sensitized to food allergens (at 1 y) Any allergic disease Sensitized (at 1 y) Recurrent wheeze (at 1 y) Eczema (at 1 y) Food allergy (at 1 y)	OR: 1.4 (0.9, 2.4) OR: 1.2 (0.7, 2.1) OR: 1.1 (0.6, 2.3) OR: 1.7 (1.0, 2.8) OR: 1.2 (0.6, 2.3) OR: 1.1 (0.5, 2.4) OR: 1.1 (0.6, 2.0) No association (data not reported) OR: 1.4 (0.7, 2.9) OR: 2.7 (1.1, 7.0) OR: 0.8 (0.3, 2.1) OR: 0.9 (0.3, 2.4) OR: 1.5 (0.5, 4.4) OR: 1.7 (0.5, 5.6) OR: 2.2 (0.9, 5.6) OR 1.8 (0.9, 3.6) OR: 3.3 (1.3, 8.0) OR: 0.9 (0.3, 2.4) OR: 0.8 (0.3, 2.2) OR: 2.3 (0.9, 6.5)	↑  ↑  ↑	Maternal allergy and infant postnatal diet (pets, siblings, and day care did not change the relationships and were not included)

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		nmol/L; IQR 25.6-50.5)			IgE-mediated food allergy (at 1 y) Sensitized to food allergens (at 1 y)	OR: 2.6 (0.9, 8.1) OR: 1.1 (0.5, 2.4)		
		Cord serum folate (Median 63.2 nmol/L; IQR 46.8-79.1) T1: <50.3 nmol/L T2: 50.3–75.1 nmol/L (reference) T3: >75.1 nmol/L						
Kiefte-de Jong, 2012 (13)	Cohort; Netherlands; 8,742 children; Embedded in Generation R Study; Children born 2002-2006	Folic acid supplement (between 400 and 500 µg/d): self-reported on questionnaire – No use (ref.), Start within 10 weeks of conception (1 <sup>st</sup> trimester), or periconceptional use (started before conception) Maternal plasma folate (1 <sup>st</sup> trim): Q1: ≤10.30 nmol/L Q4: ≥23.21 nmol/L	1 <sup>st</sup> trimester  Periconcep.  1 <sup>st</sup> trimester	FA SUP (vs. no use)  FA SUP (vs. no use)  Plasma folate (Q4:Q1)	Wheeze (up to 4 y) Shortness of breath (up to 4 y) Atopic dermatitis (up to 4 y) Wheeze (up to 4 y) Shortness of breath (up to 4 y) Atopic dermatitis (up to 4 y) Wheeze (up to 4 y) Shortness of breath (up to 4 y) Atopic dermatitis (up to 4 y)	OR: 1.02 (0.90,1.16) OR: 1.16 (0.85,1.57) OR: 1.15 (0.90,1.47) OR: 0.99 (0.89,1.09) OR: 1.04 (0.84,1.29) OR: 1.17 (0.97,1.40) OR: 1.02 (0.89,1.18) OR: 0.98 (0.79,1.22) OR: 1.18 (1.05,1.33)	↑	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 estimating equations
Martinussen, 2012 (14)	Nested case-control; US (Massachusetts and Connecticut); 1,499 mother/child pairs (case-control) (Cases: mothers with asthma diagnosis, mothers who had symptoms or took asthma medications during pregnancy; controls: mothers without a history of asthma); Perinatal Risk of Asthma in Infants of Asthmatic Mothers (PRAM); 2003-2007	Pregnancy Questionnaire assessed before 24 wks  Folic acid supplement in first trimester (Mean 497 µg; SD 301);  No individual first trimester month was significant in stratified findings	Month PreC Month PreC Month PreC 1 <sup>st</sup> trimester 1 <sup>st</sup> trimester 1 <sup>st</sup> trimester	FA SUP (vs. no use) FA SUP (per 100 µg ↑) FA SUP (No use vs. >800 µg/d) FA SUP (vs. no use) FA SUP (per 100 µg ↑) FA SUP (No use vs. >800 µg/d)	Asthma (at 6 y) Asthma (at 6 y) Asthma (at 6 y) Asthma (at 6 y) Asthma (at 6 y) Asthma (at 6 y)	OR: 0.95 (0.68, 1.32) OR: 0.98 (0.94, 1.03) OR: 1.02 (0.44, 2.40) OR: 1.23 (0.73, 2.07) OR: 0.98 (0.93, 1.04) OR: 0.73 (0.28, 1.87)		Household annual income (<41,000 USD vs. > 40,000 USD), maternal marital status (married vs. not married), and physician-diagnosed maternal asthma (yes/no)

<sup>1</sup>Adj, adjusted; DFE, Dietary Folate Equivalent; FA, Folic Acid; FEV, Forced Expiratory Volume; FFQ, Food Frequency Questionnaire; FVC, Forced Vital Capacity; IgE, immunoglobulin-E; LRTI, Lower Respiratory Tract Infection; PeriC, Periconception; PreC, Preconception; PostC, Postconception; RBC, Red Blood Cell; RTI, Respiratory Tract Infection; SS, Statistically Significant; SUP, Supplement; Tri, Trimester; Vit A, Vitamin A

<sup>2</sup>P for trend statistically significant ( $\leq 0.05$ ) (data not shown)

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