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Folate Levels in Pregnancy and Offspring Food Allergy and Eczema.

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Abstract

Background

High folate status in pregnancy has been implicated in the increased prevalence of allergic disease but there are no published data relating directly measured folate status in pregnancy to challenge-proven food allergy among offspring. The study aim was to examine the association between red blood cell (RBC) folate status in trimester three of pregnancy and allergic disease among offspring.

Methods

RBC folate levels were measured at 28-32 weeks gestation in a prospective birth cohort (n=1074). Food allergy outcomes were assessed in 1-year-old infants by skin prick testing and subsequent food challenge. Eczema was assessed by questionnaire and clinical review. High trimester three RBC folate was defined as greater than (>) 1360 nmol/L. Binomial regression was used to examine associations between trimester three RBC folate and allergic outcomes, adjusting for potential confounders.

Results

RBC folate levels were measured in 88% (894/1064) of pregnant women. The mean concentration was 1695.6 nmol/L (Standard Deviation 415.4) with 82% (731/894) >1360 nmol/L. There was no evidence of either linear or non-linear relationships between trimester three RBC folate and allergic outcomes, nor evidence of associations between high RBC folate and food allergy (adjusted risk ratio (aRR)

2.89, 95% CI 0.90-9.35), food sensitisation (aRR 1.72, 95% CI 0.85-3.49) or eczema (aRR 0.97, 95% CI 0.67-1.38).

Conclusion

The majority of pregnant women in this study had high RBC folate levels. There was no evidence of associations between trimester three RBC folate and food allergy, food sensitisation or eczema among the offspring, although larger studies are required.

Key words: cohort, eczema, folic acid, food allergy, paediatrics

Introduction

Folic acid supplementation during the periconception period has been recommended since the 1980's to reduce the risk of neural tube defects (NTDS) among offspring.[1] Recognising that a substantial proportion of pregnancies are unplanned,[2] over recent decades several countries have also introduced voluntary fortification of foodstuffs with folic acid [3] and mandatory fortification of cereal grains and wheat flour.[4] These strategies have resulted in a substantial decrease in population folate deficiency,[5] with an associated decrease in NTDS.[4] However, folate status is now supraphysiological in many women.[6] This is noteworthy given concerns regarding the potential relationship between high folate intake during pregnancy and the increase in allergic disease among infants and children in developed countries. [7]

Folate is a key methyl donor in the one carbon metabolic pathway, essential for multiple biological processes, including the epigenetic regulation genes crucial to immune development and function.[8] However, evidence linking maternal folate status throughout pregnancy to allergic disease and asthma in the offspring is conflicting.[9-12] High serum folate in pregnancy has been linked with offspring food sensitisation [7] but there are currently no data regarding the more clinically relevant outcome of

challenge-proven food allergy. Further, the majority of folate-allergy studies have relied on either questionnaire data [9, 11] or serum/plasma measures of folate status [10], which are highly sensitive to recent dietary intake.[13] In contrast, red blood cell (RBC) folate, provides an estimate of folate status over the preceding four months and may be a more reliable estimate of long term folate status.[13]

The aims of this study were to utilise a population-derived birth cohort, with detailed measurement of relevant covariates and extensive offspring allergy data, to evaluate the relationship between RBC folate status during late pregnancy and allergic disease in offspring, with a primary outcome of challenge-proven IgE mediated food allergy.

Methods

Study design

The aims and methodology of the Barwon Infant Study (BIS) have been described previously.[14] Briefly, a cohort of 1074 mother-infant pairs (including ten sets of twins) was assembled in the southeast of Australia using an unselected antenatal sampling frame. Mother-infant pairs were reviewed at regular intervals during pregnancy and the first year of life. Maternal blood was collected at 28-32 weeks of pregnancy. Food sensitisation and challenge-proven food allergy status were determined at 1 year of age. Eczema symptoms and signs were recorded at each review. Relationships were investigated between maternal RBC folate, folic acid supplementation during pregnancy and infant challenge-proven food allergy, food sensitisation and eczema, assessed at 1 year of age.

Exposure measures

Red blood cell folate

RBC folate was measured by the ADVIA Centaur XP Immunoassay System (Siemens Healthineers, Australia). The reference range for this chemiluminescent assay was defined as 634 to 1792 nmol/L.[15] RBC folate was investigated as a continuous variable in the primary analysis. In secondary analyses we defined RBC folate >1360 nmol/L as 'high', in accordance with the 97th centile reported from the 1999-2004 NHANES.[16] Low RBC folate (based on a sufficient level to maximise reduction of

risk of NTDS [17]) was defined as <906 nmol/L, and folate deficiency was defined as <340 nmol/L.[18]

Dietary folate

Daily dietary folate intake in mothers was estimated using the Dietary Questionnaire for Epidemiological Studies V.2 (DQES) [19] developed by the Cancer Council, Victoria, Australia. The DQES estimate of dietary folate intake does not take into account the mandatory fortification of bread flour in Australia (2009) [19] and the questionnaire analysis could not be modified. To account for the different bioavailability and absorption of folic acid and natural folates, the folate intake estimations from dietary sources and folic acid supplementation were converted to dietary folate equivalents (DFE = 1 mcg dietary folate or 0.6 mcg folic acid) units. [20] The recommended daily total intake of folate for women during pregnancy in Australia is at least 600 mcg/day expressed as DFE's.[20]

Folic acid supplementation

Maternal folate supplementation was recorded in trimester 1 and 2 questionnaires. The amount of folic acid supplement ingested daily was estimated from the constituents of the supplement brand combined with the daily supplement tablet intake. This estimate then was divided into < 500 mcg/day, 500-999 mcg/day and ≥1000 mcg/day, based on guidelines for recommended folic acid supplementation in pregnancy.[20]

Outcome measures

Food sensitisation

At the 1 year review, infants underwent a skin prick test (SPT) to five foods: cow's milk, egg, peanut, cashew and sesame (ALK-Abelló, Madrid, Spain) with a positive (10 mg/ml histamine) and negative control (saline). Quintip® lancets (Hollister-Stier Laboratories, Spokane, WA) were used to perform SPTs on infant's backs. Studies have used a definition of a wheal size of 2 mm (rather than 3 mm) or greater than (≥) the negative control in infants for food sensitisation, as smaller wheals are common in this age group and may more appropriately reflect allergic sensitisation.[21] We used 2

mm as a threshold for sensitisation in primary analyses [21] and 3 mm as a threshold in a secondary analysis.

Food allergy status

All participants with SPT wheals ≥ 1 mm than the negative control were offered an in-hospital open food challenge.[14] Open food challenges (including raw egg) were performed under clinical supervision using a validated protocol.[21] A positive challenge was defined as one or more of the following criteria occurring within 2 hours of ingesting a dose of challenge food; three or more concurrent non-contact urticaria for five minutes or longer; vomiting or diarrhoea; angioedema; anaphylaxis (circulatory or respiratory compromise). [21]

Eczema status

Questionnaires collecting information on eczema were administered at 1, 3, 6, 9 months and 1 year in addition to clinical assessments conducted at 1 month, 6 months and 1 year. Eczema was defined according to the modified UK working party criteria for infants under 12 months.[22] All infants with eczema had to have a history of itchy skin, plus at least three of the following: a history of dry skin, a family history of allergy, a history of skin rash affecting the flexures or outer surfaces of the limbs or the head or cheeks, visible dermatitis assessed during a study visit at either 1 month, 6 months or 1 year. The Scoring Atopic Dermatitis Scale (SCORAD) was used to quantify eczema severity.[23]

Statistical analysis

The relationships between maternal covariates and RBC folate were investigated using multivariate linear regression. Log-link binomial regression models were fitted to estimate risk ratios (RR) for associations between the exposures, RBC folate status, folic acid supplementation and allergic outcomes. Linear regression was used to examine the relationship between RBC folate and offspring SPT wheal size as continuous variables. Ethnicity, family history of allergy and number of siblings were included as potential confounders in the models, as each has been linked to both folate and risk of allergic disease. Other potential confounders included the maternal factors: smoking in pregnancy, markers of socioeconomic status (SES) (Socio-Economic Indexes for Areas (SEIFA), [24] parental education, household income), alcohol consumption in pregnancy, folic acid supplementation, maternal age, pet ownership in

pregnancy and the infant factors of birth weight and sex. These covariates were retained in the model if they made a greater than 10% change to the risk ratio point estimate. An interaction term was generated to investigate whether the relative risk relationship between RBC folate in pregnancy and offspring food allergy was modified by infant eczema status. Analyses were performed using Stata (version 14.1, College Station, Texas, United States of America (USA)).

Ethics

The study was approved by Barwon Health Human Research and Ethics Committee (HREC 10/24). Parents or guardians provided written informed consent for this study.

Results:

RBC folate status in pregnancy

The majority of participants were Caucasian, with middle to high SES status, and most infants were born at term (Table 1). RBC folate was measured in 88% (894/1064) of women. The mean RBC folate concentration was 1695.6 nmol/L (Standard Deviation (SD) 415.4) with a median of 1633.5 nmol/L (Interquartile range (IQR) 1424-1908 nmol/L) (Figure 1). Only 1% (10/894) of women had folate levels below the threshold associated with increased risk of NTDs (906 nmol/L); and only one woman was below the threshold for deficiency (<340 nmol/L). In contrast, 82% (731/894) of women had a folate level greater than the 97th centile in the NHANES survey (>1360 nmol/L) , and 34% (306/894) had levels above the assay's upper limit of normal (1792 nmol/L). RBC folate levels were lower among younger women less than 25 years but were independent of SES, cigarette smoking or alcohol intake during pregnancy (Table 2).

Maternal dietary folate intake and folic acid supplementation

The mean estimated maternal dietary folate intake was 267.4 mcg/day (SD 95.0). Sixty-nine per cent (581/848) had an estimated intake of less than half of the recommended daily intake (RDI) for pregnancy (600 mcg/day), whereas only 0.08% (7/848) had an estimated intake above the RDI. More than 90% (819/894) of mothers

reported taking a supplement containing folic acid. Among these, 71% (580/819) ingested a folic acid supplement throughout the first and second trimester and 98% (570/580) were taking at least 500 mcg/day (Table 1). The estimated dietary folate intake was weakly associated with maternal RBC folate measures, but folic acid supplementation did not show any association (Table 2). .

Pregnancy red blood cell folate status and offspring allergy

Among the inception birth cohort 83% (863/1074) participated in the 1 year review. The prevalence of food sensitisation and challenge-proven food allergy at 1 year was 11.6% (95% Confidence Intervals (CI) 9.5-13.9%) and 7.7% (95% CI 6.0-9.8%) respectively. The prevalence of eczema over the first year for the inception cohort was 24.2% (95% CI 21.2–27.3%) with an average SCORAD at 6 months and 1 year of 9.9 and 6.6 respectively.

There was no evidence of linear or non-linear associations between RBC folate and challenge-proven food allergy (Figure 2) (Supplemental Table 1). Similarly, RBC folate was unrelated to food sensitisation defined at either ≥2 or ≥3 mm wheal size (Supplemental Table 1); nor was there evidence of association when both RBC folate and SPT wheal size were treated as continuous measures (p=0.271).

There was no evidence of associations between 'high' RBC folate in pregnancy >1360 nmol/L and offspring food allergy (aRR 2.89, 95% CI 0.90-9.35) (Figure 3) (Supplemental Table 2), food sensitisation ≥2 mm (adjusted risk ratio (aRR) 1.72, 95% CI 0.85-3.49) (Figure 3) (Supplemental Table 2) or ≥3 mm wheal size (aRR 3.17, 95% CI 0.99-10.13) (Supplemental Table 2). There was no association between RBC folate >1360 nmol/L and eczema (aRR 0.97, 95% CI 0.67-1.38) (Figure 3) (Supplemental Table 2). There was no evidence of an association between folic acid supplementation in pregnancy and allergic outcomes in offspring (Supplemental Table 3). The relationship between high RBC folate and food allergy was not modified by eczema status (p=0.75).

Discussion

In a prospective birth cohort exposed to mandatory folic acid fortification of wheat flour and high levels of folic acid supplementation in pregnancy, over 80% of women tested had high RBC folate concentrations (>1360 nmol/L) in late pregnancy. There

was no compelling or consistent relationship between folate status in pregnancy and offspring allergy.

High folic acid supplementation is prevalent during pregnancy in developed countries such as the USA [6] and Canada, [25] but variable in Australia.[26, 27] In our study, the majority of women reported supplementing throughout the first and second trimester. Consistent with this, in NHANES in the USA, folic acid supplementation was reported by 60-80% of women in the first and second trimester with a mean daily intake of >800 mcg/day.[6] Similarly, in the PREFORM study from Canada, 90% of participants reported folic acid supplementation in pregnancy, with the majority taking greater than 1000 mcg/day.[25] Thus many women are taking doses in excess of the Australian recommendation for standard risk pregnancies of 400 mcg/day.[20]

Maternal RBC folate status in BIS was comparable to some Australian surveys in women of childbearing age.[27] Consistent with findings from the NHANES, maternal RBC folate status in BIS was lower in women under 25 years compared to older women.[6] Interestingly, RBC folate levels were independent of self-reported folic acid supplementation and traditional risk factors for low maternal folate status including low SES, cigarette smoking and alcohol intake during pregnancy.[28] Similarly, in PREFORM folate levels were independent of folic acid supplementation and SES. [25] Folic acid supplementation in pregnancy appears to be less common in low SES groups, among whom folic acid fortification of foodstuffs to prevent folate insufficiency may be of greater importance.[29] Unfortunately we were unable to adequately assess the impact of folic acid fortified foods, as the dietary assessment tool used in our study predated mandatory fortification.[19]

Despite the importance of folate status to epigenetic regulation, including DNA methylation, [8] and mounting evidence for a role of epigenetic dysregulation in food allergy,[30] evidence from human studies regarding folate status in pregnancy and offspring allergy remains limited and conflicting. Serum or plasma folate status in pregnancy has been positively associated with offspring atopic dermatitis [10] and allergic sensitisation, but not food allergy nor eczema.[7] The only previous allergy study to measure RBC folate in pregnancy found no evidence of association with offspring allergic sensitisation or asthma.[12] Important limitations of current evidence

include small study sample sizes and variation in the timing of folate status measurement in pregnancy. Additionally, there is still considerable variation among studies regarding optimal assays used to assess folate status and consequential misinterpretation of folate status remains an issue. [31]

Although folate status was only measured among mothers in BIS, several studies have included both maternal and infant measures. In an Australian cohort (n=484 infants), maternal serum and cord blood serum folate were correlated ($r = 0.472$, $P < 0.001$).[7] Higher and lower infant folate status was associated with allergic sensitization at 1 year of age but there was no effect of directly measured maternal folate status on allergic outcomes.[7] In a USA birth cohort (n=1,394), maternal folate concentrations correlated poorly with unmetabolized folic acid (UMFA) in cord blood. Interestingly though, higher cord blood UMFA, but not maternal serum folate, associated with food allergy.[32] Further studies are needed to investigate the relationship between folate metabolites during late pregnancy and early infancy and subsequent allergy.

We found evidence of an association between maternal RBC folate >1360 nmol/L and food allergy and sensitisation but exploratory analysis revealed that the evidence was highly sensitive to the use of different thresholds/definitions of 'high' RBC folate. In the absence of a consistent or biologically plausible pattern across quintiles, a threshold level of greater than 1360 nmol/L for high folate must be interpreted with considerable caution.

Strengths of the current study include a longitudinal design with good retention rates, detailed measurement of relevant covariates, measurement of RBC rather than serum folate status and robust study outcomes, including challenge-proven food allergy. Limitations include the single measure of folate status and the absence of data on intake of folic acid fortified foods. We also did not have any information on genetic polymorphisms that may affect folate metabolism, such as methylenetetrahydrofolate reductase within our cohort population.[33] The timing of folate commencement during pregnancy may be relevant to the offspring's risk of allergic disease.[34] However, as more than 90% of mothers in the BIS cohort began folic acid supplementation in the first trimester, we were unable to investigate the importance of folate commencement later in pregnancy. The predominantly Caucasian cohort limits generalisability but assists internal validity. Most notably, the low prevalence of folate deficiency in the cohort and the small number of food allergy cases limited the statistical power. Thus

the confidence intervals around the key estimates include magnitudes of association that would be considered clinically important.

In conclusion, in a population of women exposed to mandatory folic acid fortification, most of whom also take folic acid supplements during pregnancy, virtually all had a RBC folate level above that required to reduce the risk of offspring NTDS (906 nmol/L), and the majority had levels well above the NHANES 97th percentile of 1360 nmol/L. Although we did not find compelling evidence that high folate status in pregnancy is associated with an increased risk of allergic outcomes in offspring, additional studies are required to identify optimal measurement of folate status and exclude potential harmful effects. In the meantime, given the striking biological activity of folate, it may be appropriate to aim for levels which are only modestly higher than 906 nmol/L.

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Table 1: Participant baseline characteristics

Characteristic	Inception birth cohort (n =1074) n (%)	Participants with Maternal RBC folate (n=903) n (%)	Food allergic (n=61) n (%)	Eczema (n=192) n (%)
Twins	20 (1.9%)	18 (1.9%)	2 (3.2%)	4 (2.1%)
Sex of child				
– Male	557 (51.9%)	470 (52.0%)	34 (55.7%)	107 (55.7%)
– Female	517 (48.1%)	433 (48.0%)	27 (44.3%)	85 (44.3%)
Maternal country of birth				
– Australia	946 (88%)	793 (88.0%)	56 (91.8%)	177 (92.2%)
– Other	107 (10%)	91 (8.8%)	5 (8.2%)	13 (6.7%)
– unknown	21 (2%)	19 (2.1%)	0 (0.0%)	2 (1.1%)
Paternal country of birth				
– Australia	923 (85.9%)	767 (84.9%)	49 (80.3%)	169 (88.0%)
– other	109 (10.2%)	89 (9.9%)	8 (13.1%)	17 (8.9%)
– unknown	42 (3.9%)	47 (5.2%)	4 (6.6%)	6 (3.1%)
Participant Caucasian ethnicity				
– yes	772 (71.9%)	657 (72.8%)	43 (70.5%)	139 (72.4%)
– no	299 (27.8%)	246 (27.2%)	17 (27.9%)	52 (27.1%)
– unknown	3 (0.3%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Number of siblings				
– 0	453 (42.2%)	371 (41.1%)	22 (36.2%)	78 (40.6%)
– 1	383 (35.7%)	327 (36.2%)	28 (45.9%)	71 (37.0%)
– 2	183 (17.0%)	156 (17.3%)	10 (16.3%)	37 (19.3%)
– 3 or more	55 (5.1%)	49 (5.4%)	1 (1.6%)	6 (3.1%)
Family history in a first degree relative of				
– asthma	542 (50.5%)	454 (50.3%)	43 (70.5%)	124 (64.6%)
– hay fever	674 (62.8%)	577 (63.9%)	47 (77.1%)	143 (74.5%)
– eczema	480 (44.7%)	410 (45.4%)	40 (65.6%)	128 (66.7%)
– food allergy	265 (24.7%)	225 (24.9%)	16 (26.2%)	55 (28.7%)
Delivery via caesarean	332 (30.9%)	271 (30.0%)	20 (32.8%)	64 (33.3%)

section

Birth weight (kg), mean (SD)	3.53 (0.525)	3.54 (0.527)	3.51 (0.459)	3.57 (0.504)
Smoking				
– yes	165 (15.4%)	131 (14.5%)	9 (14.8%)	28 (14.6%)
– no	891 (83.0%)	755 (83.6%)	52 (85.2%)	162 (84.4%)
– unknown	18 (1.6%)	17 (1.9%)	0 (0.0%)	2 (1.0%)
[#]SEIFA				
– low	268 (25.0%)	231 (25.6%)	15 (24.6%)	44 (22.9%)
– middle	204 (19%)	166 (18.4%)	9 (14.8%)	36 (18.7%)
– high	582 (54.2%)	488 (54.0%)	35 (57.4%)	109 (56.8%)
– unknown	20 (1.9%)	18 (2.0%)	2 (3.2%)	3 (1.6%)
Household income				
less than 25.000	26 (2.4%)	20 (2.2 %)	0 (0.0%)	1 (0.5%)
25,000 to 49,999	99 (9.2%)	83 (9.2%)	4 (6.6%)	14 (7.3%)
50,000 to 74,999	186 (17.3%)	167 (18.5%)	7 (11.5%)	23 (12.0%)
75,000 to 99,999	266 (24.8%)	231 (25.6%)	18 (29.5%)	48 (25.0%)
100,000 to 149,999	343 (31.9%)	271 (30.1%)	23 (37.7%)	79 (41.2%)
More than 150,000	121 (11.3%)	97 (10.7%)	8 (13.1%)	21 (10.9%)
unknown	33 (3.1%)	33 (3.6%)	1 (1.6%)	6 (3.1%)
Maternal Alcohol consumption-trimester 2				
– none	738 (68.7%)	614 (68.0%)	45 (73.8%)	130 (67.7%)
– <1 per wk	274 (25.5%)	234 (25.9%)	12 (19.7%)	53 (27.6%)
– 1-6 per wk	50 (4.7%)	43 (4.8%)	4 (6.6%)	7 (3.7%)
– 1-3 per day	3 (0.3%)	3 (0.3%)	0 (0.0%)	1 (0.5%)
– 4+ per day	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
– unknown	9 (0.8%)	9 (1.0%)	0 (0.0%)	0 (0.0%)
Infant feeding (at twelve months)				
– breastfed	271 (25.2%)	222 (24.6%)	18 (29.5%)	58 (30.2%)
– formula fed	354 (33.0%)	292 (32.3%)	23 (37.7%)	75 (39.1%)
– mixed	260 (24.2%)	235 (26.0%)	18 (29.5%)	51 (26.6%)
– unknown	189 (17.6%)	154 (17.1%)	2 (3.3%)	8 (4.1%)

Maternal Folate supplementation				
– yes	987 (91.9%)	828 (91.7%)	56 (91.8%)	179 (93.2%)
– No	31 (2.9%)	26 (2.9%)	3 (4.9%)	5 (2.6%)
– unknown	56 (5.2%)	49 (5.4%)	2 (3.3%)	8 (4.2%)
Folate supplementation levels in women supplemented throughout T1 and T2.				
– unknown	211 (19.6%)	188 (20.8%)	13 (21.3%)	36 (18.7%)
– <500mcg/day	47 (4.4%)	41 (4.6%)	4 (6.6 %)	7 (3.7%)
– 500-999 mcg/day	626 (58.3%)	504 (55.8%)	34 (55.7%)	120 (62.5%)
– ≥1000mcg/day	190 (17.7%)	170 (18.8%)	10 (16.4%)	29 (15.1%)

#SEIFA, Socio-Economic Indexes for Areas (Tertiles).

Table 2: Relationship between maternal exposures and maternal RBC folate in the BIS cohort

Maternal exposure	Regression coefficient	(95% CI)	P value
Family history of allergy	48.3	-40.8, 137.4	0.28
Caucasian ethnicity	6.9	-61.4, 75.3	0.84
Maternal age<25 years	-166.1	-288.9, -43.2	**0.008**
Household income			
-0 to 49,999	Ref (0)		
-50,000 to 74,999	21.2	-96.1, 138.6	0.72
-75,000 to 99,999	61.7	-47.9, 171.3	0.27
-100,000 to 149,999	29.72	-81.6, 141.1	0.60
-more than 150,000	-32.7	-165.2, 99.9	0.63
Maternal smoking	-49.2	-142.2, 43.8	0.30
Maternal alcohol consumption in pregnancy trimester 2	Ref (0)		
-none			
<1 per week	-22.0	-88.5, 44.4	0.51
>1 per week	-67.2	-189.7, 55.4	0.28
Folic acid supplementation in pregnancy	120.4	-28.8, 269.6	0.114
Dietary folate	0.30	0.01, 0.60	0.04
Number of siblings-none	Ref (0)		
-one	6.5	-64.9, 77.9	0.86
-two	-104.6	-185.1, -24.2	0.01
-three or more	- 66.1	-194.3, 62.1	0.31

Family history of allergy, maternal age, ethnicity, household income, maternal smoking, maternal alcohol intake in pregnancy, folic acid supplementation in pregnancy, dietary folate intake and number of siblings were included in the model.

Figure 1: Distribution of maternal RBC folate levels in the BIS cohort.

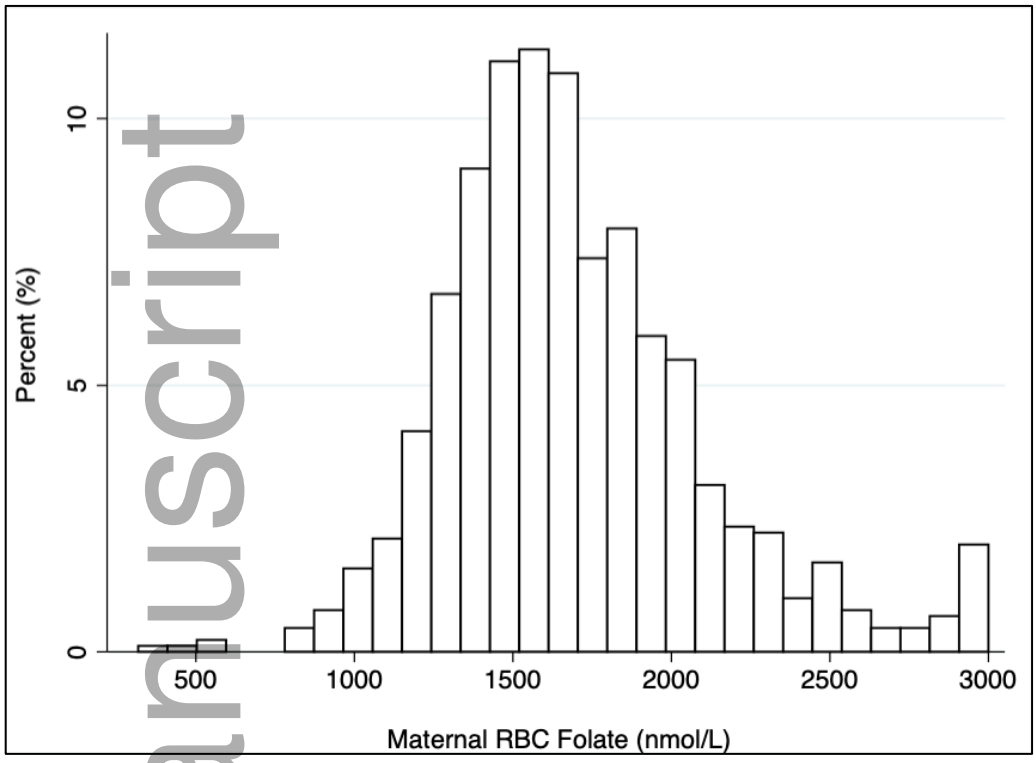
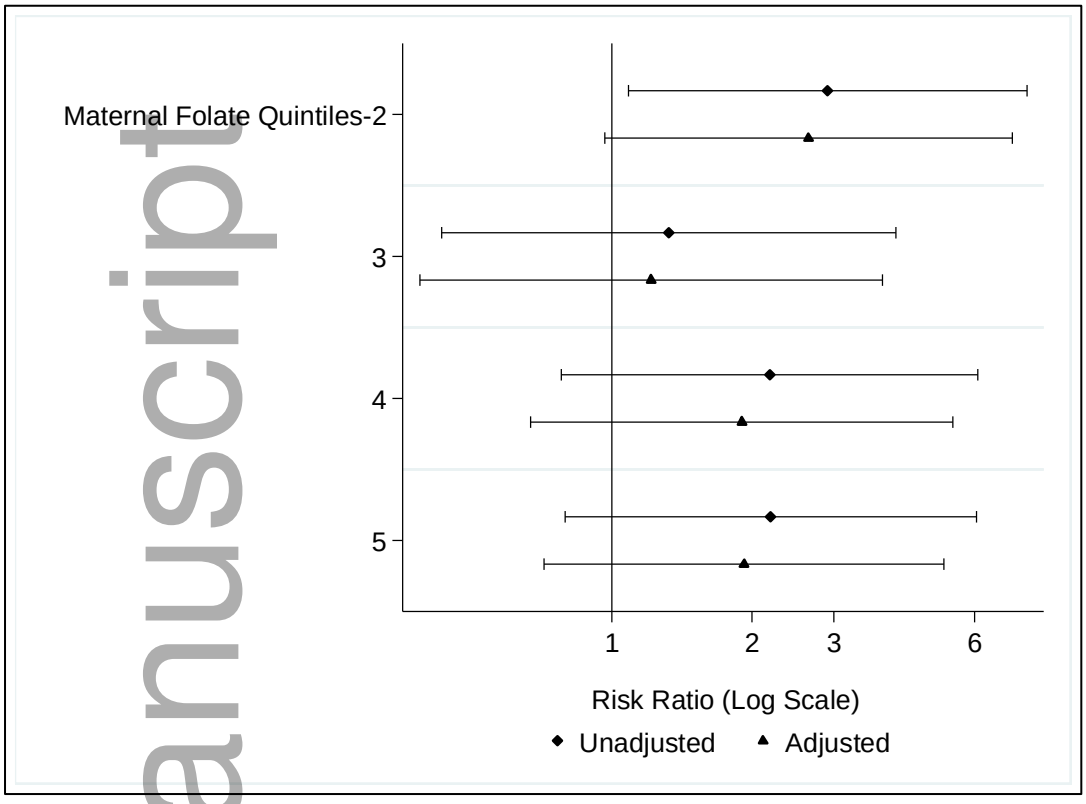
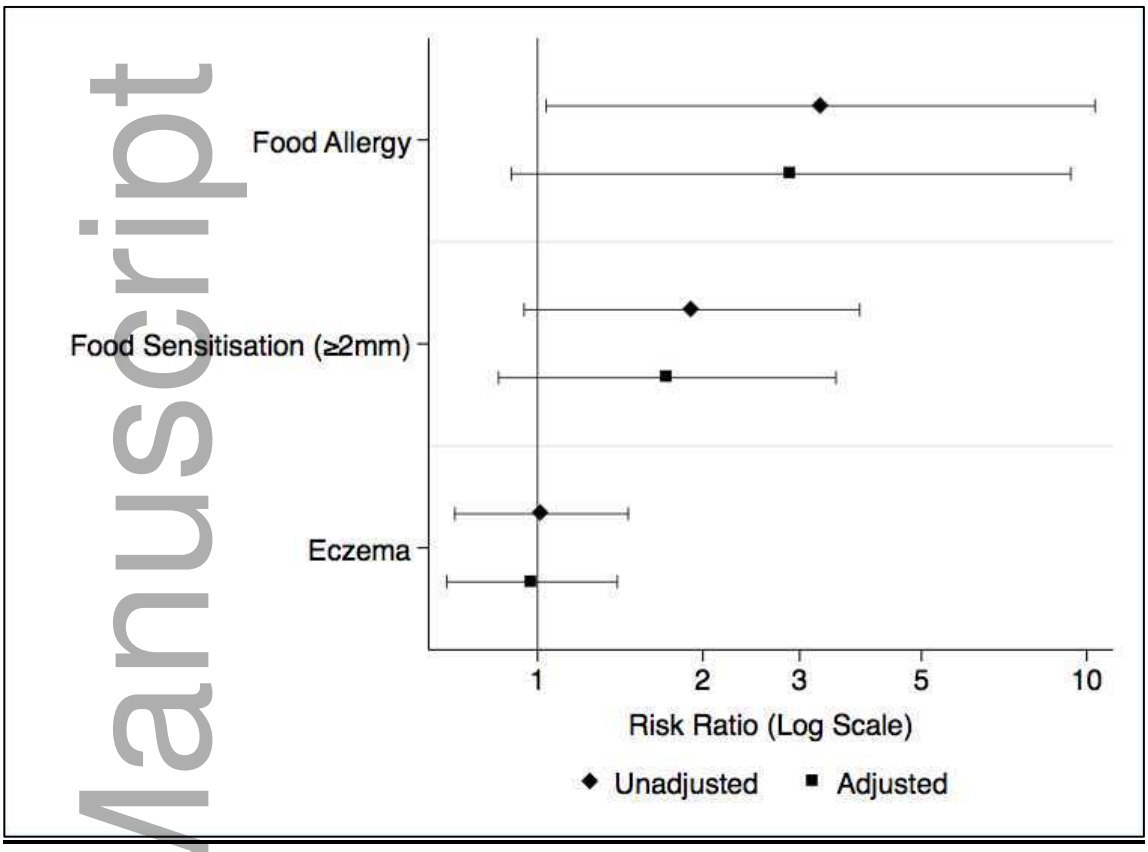


Figure 2: Association between maternal RBC folate quintiles and food allergy among the offspring.



Quintile 1 (lowest) has been used as the reference group. The covariates included in the adjusted estimates were: family history of allergy, ethnicity, number of siblings and socioeconomic status.

Figure 3: Association between maternal RBC folate >1360 nmol/L and allergic outcomes among the offspring.



Adjusted for family history of allergy, ethnicity, number of siblings and SES in food allergy and food sensitisation model. Adjusted for ethnicity, number of siblings and SES in eczema model.

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