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Maternal dietary antioxidant intake in pregnancy and childhood respiratory and atopic outcomes: birth cohort study

Annabelle Bédard[1], PhD, Kate Northstone[2], PhD, John W Holloway[3], PhD, A John Henderson[2*], MD, Seif O Shaheen[1*], PhD

[1]Centre for Primary Care and Public Health, Barts and The London School of Medicine and Dentistry, London, Queen Mary University of London, UK

[2] Population Health Sciences, Bristol Medical School, University of Bristol, UK

[3] Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK.

[*] Joint senior authors

Corresponding author:

Prof. Seif Shaheen, Centre for Primary Care and Public Health, Blizard Institute, Barts and The London School of Medicine and Dentistry, 58 Turner Street, London E1 2AB.
Email: s.shaheen@qmul.ac.uk

Tel: +44 (0)20 7882 2480; Fax: +44 (0)20 7882 2252

ABSTRACT

Evidence for a possible protective effect of maternal dietary antioxidant intake during pregnancy on childhood asthma and other atopic outcomes is conflicting, and associations with childhood lung function have been little studied. In the Avon Longitudinal Study of Parents and Children, we analysed associations between maternal intake of fruits, vegetables, vitamins C and E, carotene, zinc, and selenium in pregnancy, and current doctor-diagnosed asthma, atopy, and lung function in 8,915 children at 7-9 years. Potential modification of associations by maternal smoking and common maternal antioxidant gene polymorphisms was explored to strengthen causal inference. After controlling for confounders, positive associations were observed between maternal intake of zinc and childhood forced expiratory volume in 1 second (FEV_1), and forced vital capacity (FVC) (difference in age, height and gender adjusted standard deviation units per quartile increase in maternal dietary zinc intake β (95% CI): 0.05 (0.01,0.08), p-trend=0.01 and 0.05 (0.02,0.09), p-trend=0.005, respectively). Weak evidence was found for an interaction between maternal zinc intake and maternal *GSTM1* genotype on childhood FVC (p-interaction=0.05); association among the *GSTM1* null group β: 0.11 (0.05,0.17), p-trend=0.001. Our results suggest that a higher maternal intake of zinc during pregnancy may be associated with better lung function in the offspring.

Keywords: Respiratory epidemiology; Prenatal; Antioxidants; Lung function; Nutrition; Gene-environment interaction

Background

A declining dietary intake of antioxidants has been proposed as a possible explanation for the large increase in the prevalence of asthma and atopy seen in the West in recent decades [1], and this has led to interest in the role of maternal antioxidant dietary intake in pregnancy in the aetiology of childhood asthma and atopic diseases. Although some studies have suggested a possible protective effect of maternal intake of vitamin E, zinc, fruits and vegetables during pregnancy [2–4], the evidence overall is conflicting. A recent meta-analysis concluded that, whilst there is some evidence for a protective effect of maternal intake of zinc and vitamin E on childhood wheeze, evidence regarding asthma and other atopic outcomes is inconclusive [5]. Evidence regarding childhood lung function is limited to one study [2].

A concern with all observational studies, and particularly in nutritional epidemiology, is that findings may be confounded [6]. One way to strengthen causal inference is to demonstrate biologically plausible interactions. Researchers have hypothesized that a diet low in antioxidants may increase susceptibility to oxidant injury and airway inflammation [7]. Maternal smoking during pregnancy has been associated with adverse respiratory outcomes in children [8, 9], and in the Avon Longitudinal Study of Parents and Children (ALSPAC), maternal smoking during pregnancy was associated with reduced mid-expiratory flows in childhood [10]. A recent randomized clinical trial (RCT) suggested that vitamin C supplementation in pregnant, smoking women may reduce the deleterious effect of maternal smoking on infant pulmonary function [11]. However, to our knowledge, no observational study has investigated potential interactions between maternal dietary antioxidant intake and maternal smoking during pregnancy on respiratory and atopic outcomes in later childhood. Similarly, interactions between maternal diet and common antioxidant gene polymorphisms have not been explored, although a few studies conducted in children have investigated

possible interactions between common glutathione-S-transferease (GST) polymorphisms and antioxidant intake on atopic and respiratory outcomes [12–14].

The aim of this study was to investigate the associations between maternal intake of dietary antioxidants in pregnancy and childhood respiratory and atopic outcomes (including lung function), and to explore whether these associations were modified by maternal smoking during pregnancy and common maternal antioxidant gene polymorphisms, which could potentially strengthen causal inference.

Methods

Participants

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a population-based birth cohort that recruited 14,541 predominantly white pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992. These pregnancies resulted in 13,613 singletons who were alive at one year of age. The cohort has been followed since birth with annual questionnaires and, since age 7 years, with objective measures in annual research clinics. The study protocol has been described previously [15, 16] and further information can be found at: http://www.alspac.bris.ac.uk, which contains details of all the data that are available: http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. Ethics approval was obtained from the ALSPAC Ethics and Law Committee (IRB 00003312) and the Local NHS Research Ethics Committees

Outcome assessment

Children were defined as having current doctor-diagnosed asthma at 7.5 years (primary outcome) if mothers responded positively to the question 'Has a doctor *ever* actually *said* that your study child has asthma?' and positively to one or both of the questions 'Has your child had any of the following in the past 12 months: wheezing with whistling; asthma?'. Parental reports of a doctor's diagnosis of asthma agree well with a GP-recorded diagnosis in ALSPAC [17]. Atopy at 7 years was defined as a positive reaction (maximum diameter of any detectable weal) to *D.pteronyssinus*, cat or grass (after subtracting positive saline reactions from histamine and allergen weals, and excluding children unreactive to 1% histamine). Lung function was measured by spirometry (Vitalograph 2120) at age 8½ years after withholding short-acting bronchodilators for at least 6 hours and long-acting

bronchodilators and theophyllines for at least 24 hours. The best of three reproducible flow-volume curves was used to measure forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and maximal mid-expiratory flow (FEF_{25-75}). Lung function measurements were transformed to age, height and gender adjusted standard deviation units[18]. The tests adhered to American Thoracic Society (ATS) criteria for standardisation and reproducibility of flow-volume measurement[19], with the exception of ATS recommendations for duration of expiration, since many young children cannot sustain exhalation for 6s to establish FVC[20]. We therefore used no volume change over >1s to define the plateau phase of the flow-volume curve as the end-of-test criterion in those unable to blow >6s. Lung function at 15 years was also considered as a secondary outcome of interest in *post hoc* analyses (see below).

Exposures of interest

Data on maternal diet in pregnancy were collected by a food frequency questionnaire (FFQ) sent out at 32 weeks gestation to mothers, covering all the main foods consumed in Britain[21]. The questionnaire included questions about the weekly frequency of consumption of 43 food groups and food items, with the possibility for respondents to tick one of the following options: never or rarely, once in 2 weeks, 1-3 times a week, 4-7 times a week, more than once a day. One question on the weekly frequency of fresh fruit consumption and six questions on the weekly frequency of vegetables (peas, sweetcorn, broad beans; cabbage, brussel sprouts, kale and other green leafy vegetables; other green vegetables; carrots; other root vegetables; salad) were used to estimate weekly intake of fruits and vegetables, respectively, using standard portions [22]. The FFQ was used to estimate daily nutrient intakes for each woman, by multiplying the daily frequency of consumption of a food by the nutrient content [23] of a standard portion [22] of that food, and summing this

for all the foods consumed. Daily intakes of vitamins C and E, zinc, selenium and carotene were estimated in this way. To ensure consistency, all dietary exposure variables were categorized in quartiles. A maternal dietary antioxidant score was derived for each mother by adding the intake quartile for each of the five antioxidant nutrients, thus ranging from 5 to 20. Information on the child's intake of antioxidants at 3 years, and maternal and paternal antioxidant intake at 4 years post-partum, was collected using a similar FFQ.

Maternal smoking during pregnancy

Maternal smoking habits during the 3 months before pregnancy and at several time points during pregnancy were recorded using self-reported questionnaires on an ordinal categorical scale (never, passive smoking only, 1-9 cigarettes per day, 10-19 cigarettes per day, ≥20 cigarettes per day). The highest category reported at any time during pre-pregnancy or pregnancy was used in the analysis.

Genotypes of interest

Maternal DNA was a mixture of samples extracted from blood collected during pregnancy and from lymphoblastoid cell lines. The majority of the children's DNA samples were extracted from cord blood or venous blood collected at age 7 years, with a small number extracted from venous blood collected at 43 to 61 months. The *GSTT1* and *GSTM1* gene deletion genotyping was performed using a real-time PCR method described previously [24]. Two single nucleotide polymorphisms (SNPs) were typed in mothers and children by LGC Genomics Ltd (formerly KBiosciences Ltd, Hoddesdon, Herts, United Kingdom), using a competitive allele-specific PCR system (KASPar), namely, a SNP in *GSTP1* (G313A, Ile105Val, rs1695) and a SNP in *GPX4* (rs713041, at position 718). The *GST* polymorphisms are common and we have previously investigated their role (and interactions) in childhood

asthma in ALSPAC [25, 26]. We have also reported interactions between prenatal selenium status and childhood *GPX4* genotype on childhood asthma (GPX4 is a selenium-dependent enzyme)[27].

Potential confounders

We selected potential confounding factors which are known (from existing literature) to be associated with one or more of the outcomes of interest [28]. These included maternal age at delivery, sex of child, multiple pregnancy, season of birth, maternal history of atopic diseases (hay fever, asthma, eczema, allergies, or attacks of wheezing with whistling on the chest or attacks of breathlessness in the past two years), parity, highest educational qualification, housing tenure, financial difficulties, ethnicity, breastfeeding duration, and maternal factors during pregnancy (smoking status, anxiety score [Crown-Crisp Experiential Index][29], paracetamol use, antibiotic use, infections [urinary infection, influenza, rubella, thrush, genital herpes, other], supplement use and total energy intake [kJ/day]).

Statistical analyses

Logistic regression and linear regression were used to analyse associations between dietary exposure variables and binary and continuous outcomes, respectively. Dietary exposure variables were analysed in quartiles, first as a categorical variable using the lowest quartile as reference to allow for a non-linear pattern of association, and second as a continuous variable to test for linear trend (i.e. per increasing quartile effect). For all regression analyses, two stages of adjustment were used. In Model 1, we adjusted for total energy intake only. In Model 2, we adjusted additionally for all potential confounders listed above.

Sensitivity analyses

When evidence for associations persisted after adjustment for potential confounders, we conducted a number of additional analyses: 1) additional adjustment for potential mediators (ie. gestational age at delivery[30, 31], birth weight [32, 33], maternal pre-pregnancy body mass index (BMI) and weight gain during pregnancy [34–36] and child's BMI at 7 [37, 38]; see Online Figure 1 for directed acyclic graph), 2) additional adjustment for maternal dietary intake of total polyunsaturated fatty acids (PUFAs) [5], 3) mutual adjustment for maternal dietary intake of antioxidants that were found to be associated with the same childhood outcome, 4) exclusion of mothers taking supplements in pregnancy (vitamins/zinc) and 5) exclusion of mothers with implausible energy intakes (<2500 or >25000kJ/day [39]).

Further investigation of confounding

We also used two approaches to further investigate potential confounding of associations with prenatal exposures: first, we controlled additionally for child's intake of the same exposure at 3 years of age, and second, we used a parental comparison approach to investigate potential unmeasured confounding by genetic or shared environmental or lifestyle factors [40, 41] (see further details online). To correct for potential loss to follow-up bias, we used inverse probability weighting and assigned to each woman a weight that is the inverse of the probability of her selection for given values of covariates (see further details online) [42].

Exploration of interactions

To explore potential modification of dietary associations by maternal smoking we stratified by maternal smoking history (dichotomised) and tested for interaction. Maternal smoking during pregnancy has been found to be associated with reduced childhood FEF_{25-75} in ALSPAC [10]. To explore potential modification of this association by maternal dietary

antioxidant exposures, we stratified by antioxidant intake (above versus below median) and tested for interaction. Distributions of allele frequencies for each polymorphism in mothers and children were formally tested for deviation from Hardy-Weinberg equilibrium using a likelihood ratio test. To investigate whether associations between dietary exposures and childhood outcomes were modified by maternal antioxidant genotype, we stratified by maternal *GSTM1* and *GSTT1* null genotypes, and by *GSTP1* genotype. We also stratified the associations between maternal dietary selenium intake and outcomes by maternal *GPX4* genotype (GPX4 is a selenium-dependent enzyme). All statistical analyses were carried out using Stata version 12.1 (StataCorp LP, USA).

Results

Of the 13,972 singletons and twins alive at one year of age, information on maternal diet during pregnancy was available for 12,078, of whom there was information on at least one of the outcomes of interest for 8,915 children (Online Figure 2). Characteristics of the 8,915 mother-child pairs who were included in the analyses, and those of the 3,163 mother-child pairs with information on maternal diet who were excluded because of incomplete outcome data, are compared in Table 1.

After controlling for energy intake only, maternal intakes of fruit and vitamin C during pregnancy were negatively associated with childhood asthma. However, these associations attenuated towards the null after further adjustment for potential confounders (Table 2). No other association was found between other dietary antioxidant exposures and childhood asthma or atopy (Table 2). After controlling for energy intake and all other potential confounders, there was weak evidence for a positive association between maternal intake of vegetables and childhood FEV_1 and FEF_{25-75} (Table 3). Positive associations were observed between maternal intake of zinc and childhood FEV_1 and FVC, with evidence of a dose-response relationship. There was weaker evidence for positive associations between maternal carotene intake and childhood FEV_1 and FVC, and between maternal selenium intake and childhood FVC (Table 3). Positive associations were observed between the maternal antioxidant score and childhood FEV_1 and FVC, with evidence of a dose-response relationship (Table 3). If zinc intake was omitted from the antioxidant score, the latter was no longer significantly associated with childhood lung function (data not shown).

The significant associations observed between maternal zinc intake and the maternal antioxidant score during pregnancy and childhood FEV_1 and FVC remained unattenuated in all the sensitivity analyses (see statistical methods), whereas associations with the other dietary exposures weakened (data not shown). The significant associations observed between

maternal zinc intake and the maternal antioxidant score and childhood FEV_1 and FVC also remained unattenuated after adjusting for child's dietary zinc intake and antioxidant score, respectively, at age 3 years. In subsets of the cohort with complete data for paternal (respectively maternal) zinc intake after pregnancy, no association was found between paternal (respectively maternal) zinc intake or antioxidant score after pregnancy and childhood lung function (data not shown). The inverse probability weighting analysis did not alter the main results (data not shown). *Post hoc* analyses of the associations between maternal zinc intake and childhood FEV_1 and FVC at 15 years (n=3,669) showed similar findings to those observed at 8 years (difference in age, height and gender adjusted standard deviation units per quartile increase in maternal dietary zinc intake β (95% CI): 0.06 (0.01,0.11), p-trend=0.01 and 0.06 (0.01,0.10), p-trend=0.02, respectively). However, no association was found between the maternal antioxidant score and childhood FEV_1 and FVC at 15 years (data not shown).

When we stratified maternal dietary associations by maternal smoking, there was no evidence of effect modification by smoking on any childhood outcome (Table 4). Conversely, when we stratified the association between maternal smoking during pregnancy and childhood FEF_{25-75} (β per smoking category increase in the whole cohort: 0.05 (-0.07, -0.02), *P* trend=0.0001) by maternal intake (above and below median) of dietary antioxidants, associations between maternal smoking and child mid-expiratory flows were stronger for mothers with below median intakes of fruit, vitamin C, vitamin E and the maternal antioxidant score, although there was no statistical evidence of interaction (online Table 1).

When the study population was restricted to mother-child pairs with complete data on maternal genotype, the main findings described above were similar (results not shown). Maternal and child genotype frequencies did not deviate significantly from Hardy-Weinberg equilibrium. When we stratified associations between maternal intake of fruit and vegetables

during pregnancy and childhood outcomes by maternal *GST* polymorphisms, there was weak evidence for an interaction between vegetable intake and *GSTM1* genotype on FVC (P interaction 0.07), with a positive association only if mothers were *GSTM1* null (Table 5). When we investigated interactions between maternal intake of other antioxidants and maternal *GST* polymorphisms on childhood outcomes, weak evidence was found for an interaction between zinc and *GSTM1* on childhood FVC (β: 0.11 (0.05, 0.17), *P* trend=0.001, and 0.02 (-0.05, 0.08), *P* trend=0.57, for the null and non-null maternal *GSTM1* genotype groups, respectively; p-interaction=0.05). No interaction was found between maternal intake of other antioxidant nutrients or the antioxidant score and *GST* polymorphisms on any childhood outcome (data not shown). No interaction was found between maternal intake of selenium during pregnancy and maternal *GPX4* genotype on childhood outcomes (online Table 2). As a *post hoc* analysis, we studied the associations between maternal zinc intake and childhood FVC, stratified by combinations of maternal and child *GSTM1* genotypes. We observed positive associations if mothers were *GSTM1* null, regardless of the child's *GSTM1* genotype (Table 6). *Post hoc* analysis did not show evidence of an interaction between maternal zinc intake and maternal *GSTM1* on childhood FVC at 15 years (p-interaction=0.16).

Discussion

In this large, population-based, birth cohort study, we found that a higher maternal zinc intake during pregnancy was associated, in a dose-response fashion, with higher FEV_1 and FVC in the offspring, after controlling for potential confounders. To the best of our knowledge this is a novel finding. Only one other birth cohort study has investigated the relation between maternal diet in pregnancy and childhood lung function, and did not report any association between maternal zinc intake and lung function in the offspring at age 5 [2], but the sample size was much smaller than ours. We also found weak evidence for an interaction between maternal zinc intake during pregnancy and maternal *GSTM1* genotype on childhood FVC. Interactions between maternal intake of antioxidants and antioxidant genotype on childhood lung function and other respiratory and atopic outcomes have not previously been investigated. The graded nature of the associations between maternal zinc intake and lung function is in keeping with a causal effect on lung growth and development, and persistence of the association from childhood to adolescence strengthens causal inference further. Whilst we also found positive associations between the maternal antioxidant score during pregnancy (derived from five antioxidant nutrients) and childhood lung function, these were largely explained by maternal zinc intake.

A surprising observation was the lack of interaction between maternal intake of antioxidants and maternal smoking on childhood outcomes. We hypothesized that a higher intake of antioxidants might be particularly beneficial if the fetus was exposed to tobacco smoke, a source of oxidative stress, but no such effect modification was seen. To our knowledge, this has not been investigated before. On the other hand, when we examined the detrimental effect of maternal smoking on mid-expiratory flows, we found that effect estimates were generally larger if mothers had below average intakes of antioxidants, especially vitamin C and vitamin E, than if their intakes were above average. Whilst these

differences were not statistically significant on formal testing for interaction, they are in keeping with a trial in pregnant smokers which showed that the detrimental effect of smoking on infant lung function was reduced by vitamin C supplementation in pregnancy [11]. One possible explanation for why we did not see a statistically significant interaction between antioxidant intake and smoking is that the maximum vitamin C intake from food alone in ALSPAC pregnant women was 256mg/day, which is much lower than the 500mg daily intake of vitamin C taken by mothers in the trial [11], although approximately 20% of ALSPAC women were also taking vitamin supplements.

Whilst some studies have suggested a possible protective effect of maternal intake of vitamin E, zinc, fruits and vegetables during pregnancy on childhood asthma and atopy [2–4], we found no evidence to support this, nor were the other antioxidant nutrients associated with these outcomes, which is concordant with two recent systematic reviews and meta-analyses [5, 43]. Given the size of our study, we therefore believe that the new totality of evidence (including ALSPAC) indicates that there is unlikely to be a causal relation between dietary antioxidant intake in pregnancy and risk of childhood asthma and atopy.

Mechanisms

A plausible explanation for the associations we observed between maternal zinc intake during pregnancy and childhood lung function, and especially FVC, could be that prenatal zinc status influences growth and development of fetal lungs. In support of this hypothesis, zinc deficiency has been associated with impaired fetal lung growth in rats [44]. According to the FFQ completed in pregnancy, the main sources of dietary zinc were red meat and poultry in ALSPAC pregnant women. Although zinc is generally considered to be an antioxidant, it can serve such a function only indirectly, and the term ‘pro-antioxidant’ is

more appropriate [45]. Whilst the interaction between maternal zinc intake and maternal *GSTM1* genotype on childhood FVC is in keeping with a pro-antioxidant effect of zinc on prenatal lung growth (stronger association if the mother was *GSTM1* null and therefore had compromised enzymatic antioxidant defences), the lack of effect modification by maternal smoking, and the lack of effect modification by maternal *GSTM1* genotype on FVC in adolescence, does not support such an interpretation. However, zinc influences growth through multiple, complex pathways[46], and effects on fetal lung growth may not involve its pro-antioxidant properties.

Strengths and limitations

Strengths of the ALSPAC birth cohort include its population-based prospective design, rich information on numerous potential confounders, and detailed phenotypic outcome measurements. ALSPAC's size gave us greater statistical power than previous, smaller birth cohorts which have investigated this research question. Another major strength of the ALSPAC birth cohort is that maternal DNA was collected, enabling maternal genotyping and exploration of interactions with prenatal exposures, which is not possible in most other birth cohort studies.

Although the FFQ that we used had not been formally calibrated against other instruments such as diet diaries, it was based on the one used by Yarnell et al which has been validated against weighed dietary records [47], and modified in the light of a more recent weighed dietary survey [21]. Whilst there will have been some misclassification of dietary exposures, this is likely to be non-differential with respect to the outcomes of interest, and would be expected to bias effect estimates towards the null; in other words, the magnitude of associations may have been underestimated, and small or modest effects may have been

missed. The possibility of uncontrolled or residual confounding cannot be ruled out. However, we think that confounding of the main findings by lifestyle or other aspects of maternal diet in pregnancy is unlikely, as we controlled for numerous potential confounders in the analyses, including postnatal zinc intake. The null findings for maternal and paternal zinc intakes after pregnancy make confounding by unmeasured familial behaviours linked to zinc intake and offspring lung function a less likely explanation for the main findings.

As with any longitudinal study, we cannot rule out the possibility that exclusion of mother-child pairs without complete information might have biased our findings. However, it could be argued that, for our results to be totally spurious for maternal zinc intake and childhood lung function in those included in our analysis (and for the associations to be truly null in the population as a whole), associations in the excluded mother-child pairs would have to be at least of equal magnitude in the opposite direction, which seems unlikely. Furthermore, loss to follow-up bias has been shown to only slightly modify associations in longitudinal studies, including in ALSPAC [48], and the results of our inverse probability weighting analysis confirmed that loss to follow-up is unlikely to have biased our results. In view of the multiple analyses carried out, we cannot exclude the possibility that the main findings occurred by chance; hence they should be interpreted with caution and require replication in another birth cohort study. Given the *a priori* nature of the general hypothesis being tested, and the fact that some outcomes of interest were highly correlated, it did not seem appropriate to correct for multiple testing.

Conclusions

We conclude that a higher maternal intake of zinc during pregnancy may improve lung function, and especially FVC, in the offspring, but further studies are needed to confirm

these results. A Mendelian randomisation approach could be used to strengthen causal inference. If the association with prenatal zinc status is causal, this may have greater implications in developing countries where zinc deficiency is a bigger problem today than it is in the West [49]. In contrast, we found no evidence that maternal dietary antioxidant intake in pregnancy is associated with risk of childhood asthma or atopy, suggesting that intervening in pregnancy to increase antioxidant intake would be unlikely to succeed as a strategy to prevent these conditions.

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Author's contributions:

AB and SS conceived the study and drafted the manuscript. All authors were involved in the analysis strategy, KN gave advice on the dietary data, and AB performed the statistical analyses. AJH was responsible for all clinical respiratory and allergy data collection. JWH was responsible for generation of the genotyping data. All authors participated in the interpretation of the findings, reviewed the manuscript and revised it critically before submission. All authors have seen and approved the final version of the manuscript.

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Table 1. Characteristics of mothers and offspring who were included in analyses and those who were excluded (n=12,078)

	Included (n=8,915)	**Excluded (n=3,163)**	***P****
Maternal vitamin C intake in pregnancy (mg/day), m(sd)	82 (35)	74 (36)	< .001
Maternal vitamin E intake in pregnancy (mg/day), m(sd)	8.7 (4.1)	8.0 (4.1)	< .001
Maternal zinc intake in pregnancy (mg/day), m(sd)	8.3 (2.4)	7.8 (2.4)	< .001
Maternal selenium intake in pregnancy (µg/day), m(sd)	72.2 (27.9)	66.1 (27.2)	< .001
Maternal carotene intake in pregnancy (µg/day), m(sd)	2170 (1176)	2018 (1175)	< .001
Maternal fruit intake in pregnancy (g/week), m(sd)	671 (390)	557 (392)	< .001
Maternal vegetable intake in pregnancy (g/week), m(sd)	949 (474)	888 (505)	< .001
Mother's age (years), m (sd)	28.9 (4.6)	26.5 (5.1)	< .001
Parity, %			
0	45.5	42.8	
1	36.1	34.1	< .001
≥2	18.5	23.0	
Sex of child, %			
Male	51.1	52.2	0.28
Female	48.9	47.8	
Multiple pregnancy, %			
Singleton	97.6	97.1	0.14
Twin	2.4	2.9	
Season of birth, %			
Winter	16.2	15.8	
Spring	26.9	26.7	0.65
Summer	30.1	31.3	
Autumn	26.7	26.2	
Breastfeeding duration, %			
Never	21.2	35.4	
<3 months	31.5	32.9	< .001
3-6 months	13.8	10.4	
≥6 months	33.5	21.3	
Mother's educational level, %			
Certificate of Secondary Education	15.4	32.7	
Vocational	9.0	12.2	< .001
Ordinary level	35.4	32.6	
Advanced level	25.1	15.6	
Degree	15.1	6.8	
Maternal ethnicity, %			
White	98.1	95.5	< .001
Non-white	1.9	4.5	
Housing tenure, %			

Owned/mortgaged	83.7	62.5	
Council rented	9.4	24.0	< .001
Non-council rented	6.9	13.5	
Financial difficulties, %			
Yes	17.1	22.9	< .001
Maternal history of atopic diseases, %			
Yes	68.3	68.9	0.62
Maternal anxiety score in pregnancy, %			
0-9	21.3	16.9	
10-14	25.7	21.6	< .001
15-20	25.9	24.6	
≥20	27.2	36.9	
Maximum maternal tobacco exposure, %			
None	26.5	17.5	
Passive only	46.0	36.1	< .001
1-9 cig/day	8.0	9.5	
10-19 cig/day	11.3	19.9	
20+ cig/day	8.2	17.1	
Maternal paracetamol use during pregnancy, %			
Yes	62.4	64.6	0.03
Maternal antibiotic use during pregnancy, %			
Yes	16.1	14.5	0.04
Maternal vitamin/zinc supplement use during pregnancy, %	21.6	20.0	0.06
Yes			
Maternal infections in pregnancy, %			
Yes	45.8	46.9	0.27
Total energy intake (kJ/day), m (sd)	7260 (1966)	7162 (2153)	0.02
Maternal pre-pregnancy BMI, %			
<18.50 kg/m²	4.3	6.4	
18.50-24.99 kg/m²	75.4	72.8	< .001
25.00-29.99 kg/m²	15.1	14.8	
≥30.00 kg/m²	5.2	6.0	
Birth weight, %			
<2500 g	4.3	5.7	
2500-2999 g	13.8	15.2	< .001
3000-3499 g	35.4	36.6	
3500-3999 g	33.2	30.8	
≥4000 g	13.3	11.7	
Gestational age (weeks), m (sd)	39.5 (1.8)	39.4 (1.8)	0.03
Child's BMI at 7, %			
<15.00 kg/m²	28.1	29.6	
15.00-17.49 kg/m²	52.5	45.5	0.51
17.50-20.49 kg/m²	15.2	19.3	
≥20.50 kg/m²	4.2	5.7	

Maternal weight gain during pregnancy, %			
Quartile 1	25.3	28.4	
Quartile 2	24.8	24.4	< .001
Quartile 3	25.6	22.0	
Quartile 4	24.4	25.2	

m (sd) : mean (standard deviation)

*Chi-square tests were used for categorical variables, t-tests and Wilcoxon tests were used for non-skewed- and skewed-distributed continuous variables, respectively.

Table 2. Associations between maternal dietary antioxidant intake and childhood asthma and atopy

	OR (95% CI)			
	Asthma (n=7,677)		**Atopy** (n=6,117)	
	M1	M2	M1	M2
Total fruit				
Q1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	0.80 (0.61, 1.05)	0.87 (0.66, 1.15)	0.89 (0.68, 1.16)	0.84 (0.63, 1.10)
Q3	0.73 (0.57, 0.94)	0.86 (0.66, 1.12)	1.06 (0.82, 1.36)	0.92 (0.70, 1.20)
Q4	0.68 (0.52, 0.88)	0.82 (0.62, 1.10)	1.06 (0.82, 1.37)	0.85 (0.65, 1.13)
Per quartile	0.90 (0.83, 0.97)	0.95 (0.88, 1.04)	1.06 (0.99, 1.13)	0.98 (0.91, 1.06)
P for trend	0.004	0.26	0.12	0.58
Total vegetable				
Q1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	0.94 (0.77, 1.15)	0.96 (0.79, 1.18)	0.98 (0.82, 1.18)	0.94 (0.78, 1.14)
Q3	0.90 (0.75, 1.09)	0.93 (0.77, 1.14)	0.96 (0.81, 1.15)	0.90 (0.75, 1.08)
Q4	0.84 (0.69, 1.02)	0.88 (0.71, 1.08)	1.07 (0.89, 1.28)	0.96 (0.79, 1.15)
Per quartile	0.95 (0.89, 1.01)	0.96 (0.90, 1.02)	1.02 (0.96, 1.08)	0.98 (0.93, 1.04)
P for trend	0.08	0.22	0.52	0.57
Vitamin C				
Q1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	0.83 (0.68, 1.02)	0.90 (0.74, 1.11)	1.03 (0.85, 1.24)	0.94 (0.78, 1.14)
Q3	0.86 (0.70, 1.04)	0.98 (0.79, 1.20)	1.06 (0.88, 1.28)	0.93 (0.76, 1.13)
Q4	0.77 (0.63, 0.95)	0.89 (0.71, 1.11)	1.20 (0.99, 1.44)	0.98 (0.80, 1.20)
Per quartile	0.93 (0.87, 0.99)	0.97 (0.91, 1.05)	1.06 (1.00, 1.13)	1.00 (0.93, 1.06)
P for trend	0.03	0.46	0.05	0.93
Vitamin E				
Q1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	0.83 (0.67, 1.02)	0.90 (0.73, 1.12)	1.03 (0.86, 1.25)	0.97 (0.80, 1.17)
Q3	1.06 (0.87, 1.31)	1.18 (0.95, 1.46)	1.10 (0.91, 1.32)	1.00 (0.82, 1.22)

Q4	0.88 (0.70, 1.10)	0.99 (0.78, 1.26)	1.12 (0.91, 1.37)	0.99 (0.80, 1.22)
Per quartile	0.99 (0.92, 1.06)	1.03 (0.95, 1.11)	1.04 (0.98, 1.11)	1.00 (0.94, 1.07)
P for trend	0.80	0.46	0.23	0.98
Zinc				
Q1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	1.05 (0.85, 1.30)	1.15 (0.92, 1.43)	1.00 (0.82, 1.21)	0.91 (0.75, 1.11)
Q3	1.01 (0.80, 1.27)	1.15 (0.90, 1.47)	1.13 (0.92, 1.40)	0.98 (0.78, 1.22)
Q4	0.97 (0.73, 1.30)	1.15 (0.85, 1.57)	1.07 (0.82, 1.38)	0.85 (0.64, 1.12)
Per quartile	0.99 (0.90, 1.08)	1.04 (0.94, 1.15)	1.04 (0.95, 1.13)	0.96 (0.88, 1.05)
P for trend	0.78	0.42	0.39	0.41
Selenium				
Q1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	0.95 (0.77, 1.17)	1.04 (0.84, 1.29)	1.09 (0.90, 1.31)	1.00 (0.83, 1.22)
Q3	0.95 (0.77, 1.18)	1.04 (0.83, 1.31)	1.14 (0.94, 1.39)	0.99 (0.80, 1.21)
Q4	0.90 (0.71, 1.15)	1.03 (0.79, 1.35)	1.07 (0.86, 1.33)	0.87 (0.68, 1.10)
Per quartile	0.97 (0.90, 1.05)	1.01 (0.93, 1.10)	1.02 (0.95, 1.10)	0.95 (0.89, 1.03)
P for trend	0.44	0.83	0.53	0.23
Carotene				
Q1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	0.95 (0.78, 1.15)	0.94 (0.77, 1.15)	0.91 (0.76, 1.09)	0.91 (0.75, 1.09)
Q3	0.91 (0.74, 1.10)	0.94 (0.77, 1.16)	1.03 (0.87, 1.23)	1.01 (0.84, 1.21)
Q4	0.89 (0.73, 1.09)	0.93 (0.75, 1.14)	1.00 (0.84, 1.20)	0.93 (0.77, 1.12)
Per quartile	0.96 (0.90, 1.02)	0.98 (0.91, 1.05)	1.01 (0.96, 1.07)	0.99 (0.93, 1.05)
P for trend	0.23	0.51	0.67	0.68
Antioxidant score				
Q1	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2	0.98 (0.79, 1.21)	1.09 (0.88, 1.36)	1.04 (0.85, 1.27)	0.94 (0.76, 1.15)
Q3	0.91 (0.72, 1.15)	1.06 (0.83, 1.37)	1.20 (0.96, 1.48)	1.00 (0.80, 1.26)
Q4	0.81 (0.62, 1.05)	0.98 (0.74, 1.31)	1.19 (0.94, 1.51)	0.92 (0.71, 1.20)
Per quartile	0.93 (0.86, 1.01)	0.98 (0.90, 1.08)	1.07 (0.99, 1.15)	0.98 (0.91, 1.07)

P for trend	0.07	0.72	0.08	0.70

OR: odds ratio

M1: Model controlling for energy intake only
M2: Model controlling for energy intake, smoking, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, history of atopic diseases, anxiety; sex of child, season of birth, multiple pregnancy, breastfeeding duration

Table 3. Associations between maternal dietary antioxidant intake and childhood lung function

	β (95% CI)					
	FEV_1 (n=6,062)		**FVC** (n=6,157)		**FEF_{25-75}** (n=6,157)	
	M1	M2	M1	M2	M1	M2
Total fruit						
Q1	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)
Q2	-0.02 (-0.13, 0.09)	-0.03 (-0.14, 0.08)	-0.01 (-0.11, 0.08)	-0.04 (-0.15, 0.07)	-0.01 (-0.12, 0.10)	-0.03 (-0.14, 0.08)
Q3	0.04 (-0.06, 0.15)	0.02 (-0.09, 0.12)	-0.01 (-0.10, 0.07)	-0.03 (-0.14, 0.08)	0.07 (-0.04, 0.17)	0.04 (-0.07, 0.14)
Q4	0.06 (-0.05, 0.17)	0.03 (-0.09, 0.14)	0.04 (-0.05, 0.13)	0.02 (-0.10, 0.13)	0.05 (-0.06, 0.15)	0.01 (-0.10, 0.13)
Per quartile	0.03 (0.00, 0.06)	0.02 (-0.01, 0.05)	0.02 (0.00, 0.05)	0.02 (-0.01, 0.05)	0.02 (-0.01, 0.05)	0.01 (-0.02, 0.04)
P for trend	0.04	0.25	0.09	0.26	0.12	0.41
Total vegetable						
Q1	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)
Q2	0.06 (-0.01, 0.14)	0.05 (-0.03, 0.13)	0.02 (-0.05, 0.10)	0.02 (-0.06, 0.09)	0.08 (0.00, 0.15)	0.06 (-0.02, 0.14)
Q3	0.02 (-0.05, 0.09)	0.01 (-0.07, 0.08)	-0.01 (-0.08, 0.06)	-0.02 (-0.09, 0.05)	0.06 (-0.01, 0.13)	0.05 (-0.03, 0.12)
Q4	0.10 (0.03, 0.17)	0.08 (0.01, 0.16)	0.07 (0.00, 0.15)	0.06 (-0.01, 0.14)	0.10 (0.03, 0.18)	0.09 (0.01, 0.16)
Per quartile	0.03 (0.00, 0.05)	0.02 (0.00, 0.05)	0.02 (0.00, 0.04)	0.01 (-0.01, 0.04)	0.03 (0.01, 0.05)	0.02 (0.00, 0.05)
P for trend	0.03	0.09	0.12	0.22	0.01	0.05
Vitamin C						
Q1	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)
Q2	0.05 (-0.02, 0.13)	0.04 (-0.04, 0.12)	0.06 (-0.01, 0.14)	0.05 (-0.02, 0.13)	0.02 (-0.05, 0.10)	0.01 (-0.07, 0.09)
Q3	0.05 (-0.03, 0.12)	0.02 (-0.05, 0.10)	0.05 (-0.02, 0.12)	0.03 (-0.04, 0.11)	0.02 (-0.05, 0.10)	0.00 (-0.07, 0.08)
Q4	0.06 (-0.02, 0.14)	0.04 (-0.05, 0.12)	0.05 (-0.02, 0.13)	0.04 (-0.05, 0.12)	0.05 (-0.02, 0.13)	0.03 (-0.05, 0.12)
Per quartile	0.02 (-0.01, 0.04)	0.01 (-0.02, 0.03)	0.01 (-0.01, 0.04)	0.01 (-0.02, 0.03)	0.02 (-0.01, 0.04)	0.01 (-0.02, 0.04)
P for trend	0.17	0.53	0.30	0.62	0.19	0.45
Vitamin E						
Q1	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)
Q2	-0.03 (-0.10, 0.05)	-0.03 (-0.11, 0.04)	0.00 (-0.07, 0.08)	0.01 (-0.07, 0.08)	-0.02 (-0.09, 0.06)	-0.04 (-0.11, 0.04)
Q3	-0.02 (-0.10, 0.06)	-0.03 (-0.11, 0.05)	0.02 (-0.06, 0.10)	0.02 (-0.06, 0.10)	-0.02 (-0.10, 0.05)	-0.05 (-0.13, 0.03)
Q4	0.01 (-0.07, 0.10)	-0.01 (-0.09, 0.08)	0.04 (-0.04, 0.13)	0.04 (-0.04, 0.13)	0.00 (-0.08, 0.09)	-0.03 (-0.12, 0.05)

Per quartile	0.01 (-0.02, 0.03)	0.00 (-0.03, 0.03)	0.01 (-0.01, 0.04)	0.01 (-0.01, 0.04)	0.00 (-0.02, 0.03)	-0.01 (-0.04, 0.02)
P for trend	0.63	0.98	0.26	0.28	0.90	0.48
Zinc						
Q1	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)
Q2	0.05 (-0.03, 0.13)	0.04 (-0.04, 0.12)	0.04 (-0.04, 0.12)	0.03 (-0.05, 0.11)	0.05 (-0.03, 0.13)	0.03 (-0.05, 0.11)
Q3	0.11 (0.02, 0.20)	0.08 (-0.01, 0.17)	0.13 (0.04, 0.21)	0.11 (0.02, 0.20)	0.06 (-0.03, 0.15)	0.02 (-0.07, 0.11)
Q4	0.18 (0.07, 0.29)	0.14 (0.03, 0.25)	0.16 (0.05, 0.26)	0.14 (0.03, 0.25)	0.13 (0.02, 0.23)	0.07 (-0.04, 0.18)
Per quartile	0.06 (0.03, 0.09)	0.05 (0.01, 0.08)	0.06 (0.02, 0.09)	0.05 (0.02, 0.09)	0.04 (0.00, 0.07)	0.02 (-0.02, 0.06)
P for trend	0.001	0.01	0.001	0.005	0.03	0.28
Selenium						
Q1	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)
Q2	0.05 (-0.03, 0.13)	0.03 (-0.05, 0.11)	0.05 (-0.03, 0.13)	0.05 (-0.03, 0.13)	0.04 (-0.04, 0.12)	0.00 (-0.07, 0.08)
Q3	0.06 (-0.02, 0.14)	0.04 (-0.04, 0.13)	0.05 (-0.03, 0.13)	0.05 (-0.04, 0.18)	0.06 (-0.02, 0.14)	0.02 (-0.07, 0.10)
Q4	0.09 (0.00, 0.18)	0.06 (-0.03, 0.16)	0.11 (0.02, 0.20)	0.10 (0.01, 0.20)	0.05 (-0.04, 0.14)	-0.01 (-0.10, 0.09)
Per quartile	0.03 (0.00, 0.06)	0.02 (-0.01, 0.05)	0.03 (0.00, 0.06)	0.03 (0.00, 0.06)	0.02 (-0.01, 0.05)	0.00 (-0.03, 0.03)
P for trend	0.05	0.22	0.03	0.06	0.25	0.95
Carotene						
Q1	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)
Q2	0.01 (-0.07, 0.08)	-0.01 (-0.09, 0.06)	0.02 (-0.05, 0.09)	0.01 (-0.06, 0.09)	-0.02 (-0.09, 0.05)	-0.05 (-0.12, 0.02)
Q3	0.05 (-0.02, 0.12)	0.03 (-0.05, 0.10)	0.02 (-0.05, 0.10)	0.01 (-0.06, 0.09)	0.03 (-0.04, 0.11)	0.00 (-0.07, 0.07)
Q4	0.10 (0.03, 0.18)	0.08 (0.01, 0.16)	0.08 (0.01, 0.16)	0.08 (0.00, 0.15)	0.07 (0.00, 0.15)	0.04 (-0.03, 0.12)
Per quartile	0.04 (0.01, 0.06)	0.03 (0.00, 0.05)	0.03 (0.00, 0.05)	0.02 (0.00, 0.05)	0.03 (0.00, 0.05)	0.02 (-0.01, 0.04)
P for trend	0.004	0.02	0.03	0.05	0.03	0.17
Antioxidant score						
Q1	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)	0.00 (ref)
Q2	-0.01 (-0.09, 0.07)	-0.03 (-0.11, 0.06)	0.01 (-0.07, 0.09)	0.02 (-0.06, 0.10)	-0.01 (-0.09, 0.07)	-0.04 (-0.13, 0.04)
Q3	0.03 (-0.06, 0.12)	0.01 (-0.09, 0.10)	0.03 (-0.05, 0.12)	0.04 (-0.06, 0.13)	0.04 (-0.05, 0.12)	-0.01 (-0.10, 0.09)
Q4	0.12 (0.02, 0.22)	0.08 (-0.02, 0.19)	0.13 (0.03, 0.22)	0.12 (0.02, 0.23)	0.07 (-0.03, 0.17)	0.01 (-0.10, 0.12)
Per quartile	0.04 (0.01, 0.08)	0.03 (0.00, 0.07)	0.04 (0.01, 0.07)	0.04 (0.01, 0.07)	0.03 (0.00, 0.06)	0.01 (-0.02, 0.04)
P for trend	0.004	0.04	0.005	0.01	0.06	0.52

β: difference in age, height and gender adjusted standard deviation units

M1: Model controlling for energy intake only
M2: Model controlling for energy intake, smoking, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, history of atopic diseases, anxiety; sex of child, season of birth, multiple pregnancy, breastfeeding duration

Table 4. Associations between maternal dietary antioxidant intake and childhood outcomes stratified by maternal smoking during pregnancy

	Asthma (n=7,677)		**Atopy** (n=6,117)		**FEV_1** (n=6,062)		**FVC** (n=6,157)		**FEF_{25-75}** (n=6,157)	
	OR* (95% CI)	*P* trend	OR* (95% CI)	*P* trend	β * (95% CI)	*P* trend	β * (95% CI)	*P* trend	β* (95% CI)	*P* trend
Total fruit intake										
Non/passive smokers	0.99 (0.89, 1.09)	0.81	1.02 (0.93, 1.12)	0.61	0.02 (-0.02, 0.05)	0.41	0.02 (-0.02, 0.05)	0.35	0.01 (-0.02, 0.05)	0.43
Active smokers	0.90 (0.78, 1.04)	0.16	0.87 (0.76, 1.01)	0.07	0.02 (-0.04, 0.08)	0.49	0.02 (-0.04, 0.08)	0.45	0.00 (-0.06, 0.06)	1.00
P interaction [a]	0.59		0.14		0.60		0.90		0.93	
Total vegetable intake										
Non/passive smokers	1.00 (0.92, 1.08)	0.91	0.99 (0.93, 1.06)	0.85	0.02 (-0.01, 0.05)	0.15	0.02 (-0.01, 0.05)	0.16	0.02 (-0.01, 0.04)	0.23
Active smokers	0.88 (0.78, 1.00)	0.05	0.94 (0.83, 1.07)	0.34	0.02 (-0.03, 0.07)	0.36	0.00 (-0.05, 0.05)	0.96	0.04 (0.00, 0.09)	0.07
P interaction [a]	0.18		0.70		0.96		0.35		0.25	
Vitamin C intake										
Non/passive smokers	1.00 (0.92, 1.09)	0.99	1.01 (0.94, 1.09)	0.75	0.00 (-0.03, 0.03)	0.81	0.01 (-0.02, 0.04)	0.53	0.00 (-0.03, 0.03)	0.86
Active smokers	0.92 (0.81, 1.05)	0.23	0.93 (0.82, 1.06)	0.30	0.02 (-0.03, 0.07)	0.49	0.00 (-0.05, 0.05)	0.95	0.02 (-0.03, 0.07)	0.41
P interaction [a]	0.54		0.57		0.55		0.65		0.30	
Vitamin E intake										
Non/passive smokers	1.06 (0.97, 1.16)	0.19	0.97 (0.90, 1.05)	0.44	0.00 (-0.03, 0.03)	0.96	0.02 (-0.01, 0.05)	0.25	-0.01 (-0.05, 0.02)	0.38
Active smokers	0.96 (0.84, 1.11)	0.60	1.12 (0.98, 1.28)	0.11	0.00 (-0.06, 0.05)	0.91	0.00 (-0.05, 0.05)	0.95	0.00 (-0.05, 0.06)	0.94
P interaction [a]	0.39		0.09		0.83		0.51		0.53	
Zinc intake										
Non/passive smokers	1.06 (0.94, 1.19)	0.36	0.96 (0.86, 1.06)	0.39	0.04 (0.00, 0.08)	0.05	0.05 (0.01, 0.09)	0.02	0.01 (-0.03, 0.05)	0.58
Active smokers	1.01 (0.85, 1.21)	0.90	1.01 (0.85, 1.21)	0.90	0.05 (-0.02 0.12)	0.15	0.05 (-0.02, 0.12)	0.14	0.04 (-0.03, 0.11)	0.30
P interaction [a]	0.92		0.61		0.74		0.72		0.76	
Selenium intake										
Non/passive smokers	0.99 (0.90, 1.10)	0.87	0.93 (0.86, 1.02)	0.12	0.03 (-0.01, 0.06)	0.13	0.03 (0.00, 0.07)	0.07	0.01 (-0.03, 0.04)	0.76
Active smokers	1.05 (0.90, 1.22)	0.56	1.03 (0.89, 1.19)	0.72	0.00 (-0.06, 0.06)	0.93	0.03 (-0.03, 0.08)	0.40	-0.01 (-0.07, 0.04)	0.64
P interaction [a]	0.50		0.31		0.32		0.52		0.67	
Carotene intake										
Non/passive smokers	0.98 (0.91, 1.07)	0.70	0.98 (0.91, 1.05)	0.53	0.02 (0.00, 0.05)	0.10	0.02 (-0.01, 0.05)	0.12	0.01 (-0.02, 0.04)	0.52

Active smokers	0.97 (0.85, 1.10)	0.59	1.02 (0.90, 1.15)	0.78	0.04 (-0.01, 0.09)	0.11	0.03 (-0.02, 0.08)	0.25	0.04 (-0.01, 0.08)	0.15
P interaction [a]	0.83		0.47		0.75		0.85		0.32	
Antioxidant score										
Non/passive smokers	1.01 (0.91, 1.13)	0.85	0.96 (0.87, 1.05)	0.35	0.03 (-0.01, 0.07)	0.18	0.04 (0.00, 0.08)	0.03	0.00 (-0.04, 0.04)	0.93
Active smokers	0.94 (0.80, 1.11)	0.44	1.08 (0.92, 1.27)	0.37	0.05 (-0.01, 0.11)	0.13	0.04 (-0.03, 0.10)	0.23	0.04 (-0.02, 0.10)	0.22
P interaction [a]	0.70		0.25		0.86		0.64		0.35	

OR: odds ratio; β: difference in age, height and gender adjusted standard deviation units

* per category/quartile of dietary intake, controlling for energy intake, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, history of atopic diseases, anxiety; sex of child, season of birth, multiple pregnancy, breastfeeding duration

[a] treating smoking as a binary variable and dietary exposures as continuous variables

Table 5. Associations between maternal fruit and vegetable intake and childhood outcomes stratified by maternal *GST* polymorphisms

	Asthma (n=4,953)		**Atopy** (n=3,911)		**FEV_1** (n=4,011)		**FVC** (n=4,080)		**FEF_{25-75}** (n=4,080)	
	OR* (95% CI)	*P* trend	OR* (95% CI)	*P* trend	β * (95% CI)	*P* trend	β * (95% CI)	*P* trend	β* (95% CI)	*P* trend
Total fruit intake										
GSTT1										
Non-null (n=4,376)	0.91 (0.81, 1.02)	0.10	1.01 (0.90, 1.12)	0.92	0.01 (-0.03, 0.06)	0.52	0.02 (-0.02, 0.06)	0.39	0.00 (-0.04, 0.04)	0.95
Null (n=870)	1.00 (0.77, 1.30)	0.99	0.92 (0.71, 1.18)	0.49	0.04 (-0.06, 0.14)	0.42	0.04 (-0.06, 0.13)	0.48	0.04 (-0.06, 0.14)	0.46
P interaction	0.71		0.47		0.44		0.50		0.48	
GSTM1										
Non-null (n=2,476)	0.84 (0.72, 0.98)	0.03	1.01 (0.87, 1.17)	0.93	0.01 (-0.05, 0.06)	0.77	0.03 (-0.03, 0.08)	0.30	-0.03 (-0.09, 0.03)	0.29
Null (n=2,799)	0.94 (0.82, 1.09)	0.44	0.98 (0.85, 1.12)	0.73	0.04 (-0.02, 0.09)	0.20	0.02 (-0.03, 0.08)	0.46	0.04 (-0.01, 0.10)	0.13
P interaction	0.12		0.54		0.53		0.87		0.26	
GSTP1, rs947894										
A:A (n=2,289)	0.96 (0.81, 1.13)	0.61	0.99 (0.85, 1.16)	0.94	0.01 (-0.05, 0.07)	0.66	0.01 (-0.05, 0.07)	0.75	0.02 (-0.04, 0.08)	0.47
G:A (n=2,529)	0.91 (0.78, 1.06)	0.23	0.98 (0.85, 1.13)	0.76	0.02 (-0.04, 0.08)	0.55	0.02 (-0.04, 0.08)	0.46	0.00 (-0.06, 0.06)	0.97
G:G (n=670)	0.83 (0.61, 1.13)	0.25	0.80 (0.59, 1.10)	0.17	0.00 (-0.11, 0.12)	0.94	0.01 (-0.10, 0.12)	0.83	0.01 (-0.11, 0.13)	0.85
P interaction	0.60		0.94		0.59		0.87		0.31	
Total vegetable intake										
GSTT1										
Non-null (n=4,376)	0.91 (0.83, 1.00)	0.05	1.01 (0.93, 1.10)	0.85	0.04 (0.00, 0.07)	0.03	0.05 (0.01, 0.07)	0.006	0.02 (-0.01, 0.05)	0.21
Null (n=870)	1.00 (0.80, 1.25)	0.98	0.99 (0.80, 1.23)	0.95	0.01 (-0.07, 0.09)	0.84	-0.03 (-0.11, 0.05)	0.46	0.04 (-0.04, 0.12)	0.30
P interaction	0.25		0.98		0.81		0.22		0.68	
GSTM1										
Non-null (n=2,476)	0.90 (0.79, 1.02)	0.09	0.96 (0.86, 1.08)	0.54	0.01 (-0.03, 0.06)	0.54	0.01 (-0.03, 0.05)	0.59	0.03 (-0.01, 0.07)	0.19
Null (n=2,799)	0.94 (0.84, 1.06)	0.32	1.05 (0.95, 1.17)	0.33	0.06 (0.01, 0.10)	0.01	0.06 (0.02, 0.10)	0.004	0.02 (-0.02, 0.06)	0.41
P interaction	0.52		0.15		0.24		0.07		0.41	
GSTP1, rs947894										
A:A (n=2,289)	0.98 (0.86, 1.12)	0.76	1.02 (0.90, 1.15)	0.77	0.06 (0.01, 0.11)	0.01	0.06 (0.02, 0.11)	0.008	0.04 (-0.01, 0.08)	0.12

G:A (n=2,529)	0.98 (0.87, 1.10)	0.72	1.06 (0.94, 1.18)	0.33	0.02 (-0.03, 0.06)	0.41	0.02 (-0.02, 0.07)	0.27	0.00 (-0.04, 0.05)	0.88
G:G (n=670)	0.89 (0.69, 1.15)	0.37	0.81 (0.64, 1.02)	0.08	0.01 (-0.07, 0.10)	0.78	-0.01 (-0.10, 0.07)	0.76	0.06 (-0.03, 0.15)	0.21
P interaction	0.42		0.19		0.35		0.18		0.82	

OR: odds ratio; β: difference in age, height and gender adjusted standard deviation units

* per category/quartile of fruits/vegetables intake, controlling for energy intake, smoking, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, history of atopic diseases, anxiety; sex of child, season of birth, multiple pregnancy, breastfeeding duration

Table 6. Associations between maternal zinc intake and childhood FVC stratified by combinations of maternal and child GSTM1 genotypes

GSTM1			**FVC** (n=3,014)	
Mother	**Child**	N	β* (95% CI)	*P* trend
Zinc				
Non-null	Non-null	956	-0.04 (-0.12, 0.05)	0.41
Non-null	Null	452	0.04 (-0.11, 0.18)	0.60
Null	Non-null	439	0.13 (-0.01, 0.27)	0.07
Null	Null	1,167	0.15 (0.07, 0.23)	0.0002

β: difference in age, height and gender adjusted standard deviation units

* per quartile of zinc intake, controlling for energy intake, smoking, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, history of atopic diseases, anxiety; sex of child, season of birth, multiple pregnancy, breastfeeding duration

Online data supplement

Supplementary methods

Parental comparison approach

Proof of concept has been illustrated in ALSPAC with maternal smoking in pregnancy, which is strongly associated with lower offspring birth weight, whereas paternal smoking is only weakly associated (and not associated at all after mutual adjustment). In contrast, paternal and maternal smoking in pregnancy are similarly associated with offspring BMI, even after mutual adjustment, suggesting that these associations are non-causal and generated by confounding [1]. We have also used this approach to investigate the likely causal role of prenatal paracetamol exposure in the development of asthma in ALSPAC[2].

In the current study, effect estimates for maternal intake of a particular antioxidant in pregnancy were compared with those for maternal and paternal antioxidant intake after pregnancy. If there is a causal intra-uterine effect, one would expect a stronger association with maternal intake in pregnancy than with maternal postnatal intake or paternal intake (the latter two exposures cannot have a direct biological effect on offspring outcome risk).

Inverse probability weighting

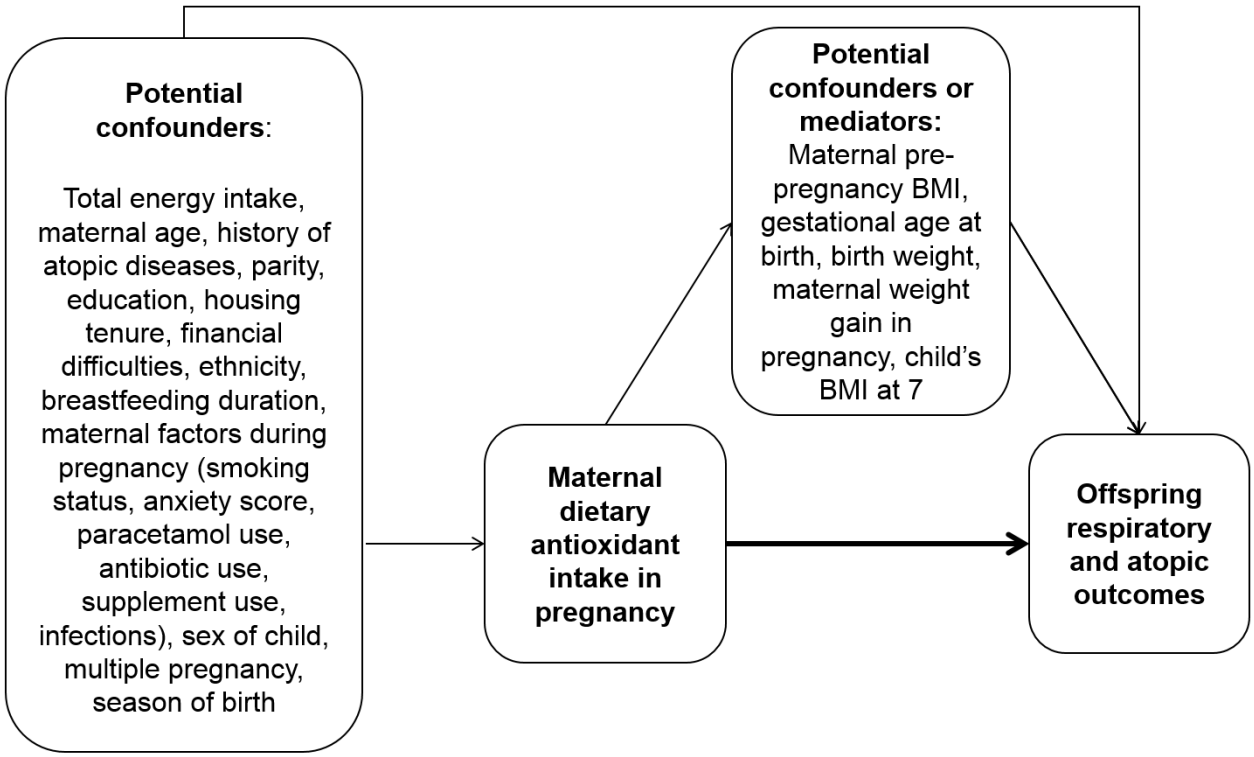
Inverse probability weighting has been proposed as a way to correct for selection bias [3]. By assigning to each subject a weight that is the inverse of the probability of his/her selection based on a given set of covariates and exposure, inverse probability weighting creates a pseudo-population in which effect measures are not affected by selection bias (provided that the outcome in the uncensored subjects truly represents the outcome in the censored subjects

for the same values of covariates and exposure). We used this approach by estimating for each woman, the probability of her selection for given values of covariates (ie. the characteristics for which differences between excluded and included women were found to be statistically significant, including the exposure – see Table 1) and assigning her a weight that is the inverse of that probability.

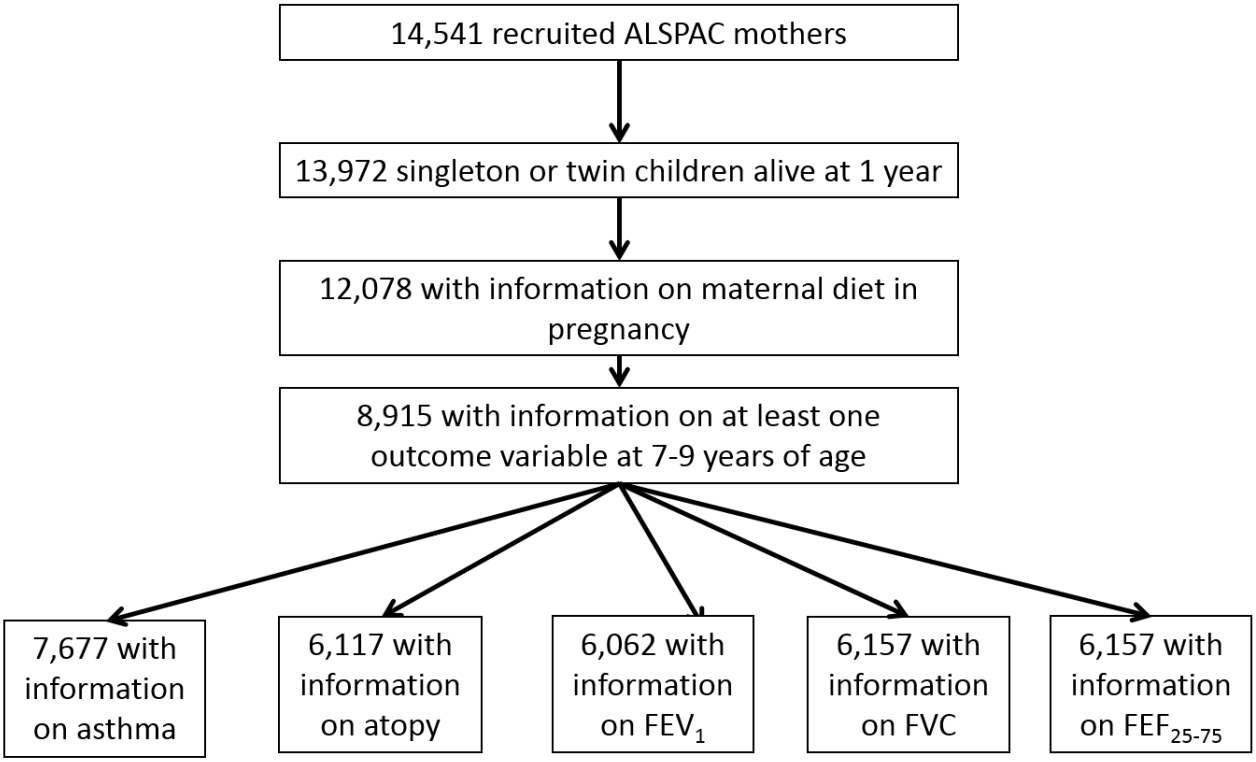
References

1. Smith GD. Assessing intrauterine influences on offspring health outcomes: Can epidemiological studies yield robust findings? *Basic Clin. Pharmacol. Toxicol.* 2008; 102: 245–256.
2. Shaheen SO, Newson RB, Smith GD, Henderson AJ. Prenatal paracetamol exposure and asthma: Further evidence against confounding. *Int. J. Epidemiol.* 2010; 39: 790–794.
3. Hernán MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004; 15: 615–625.

Online Figure 1. Directed acyclic graph showing potential confounders and mediators of the associations between maternal dietary antioxidant intake in pregnancy and offspring respiratory and atopic outcomes



Online Figure 2. Participant flow



Online Table 1. Associations between maternal smoking during pregnancy and childhood FEF_{25-75} stratified by maternal dietary antioxidant intake in pregnancy (n=6,157)

Stratification variable	**Below median**		**Above median**		*P* interaction[±]
	β* (95% CI)	*P* trend	β* (95% CI)	*P* trend	
Fruit intake	-0.06 (-0.10, -0.02)	0.004	-0.04 (-0.06, -0.01)	0.02	0.63
Vegetable intake	-0.05 (-0.08, -0.01)	0.009	-0.04 (-0.07, -0.01)	0.02	0.19
Vitamin C intake	-0.06 (-0.10, -0.03)	0.0002	-0.03 (-0.06, 0.01)	0.13	0.26
Vitamin E intake	-0.06 (-0.09, -0.03)	0.0002	-0.03 (-0.06, 0.01)	0.10	0.39
Zinc intake	-0.04 (-0.08, -0.01)	0.01	-0.04 (-0.08, -0.01)	0.01	0.83
Selenium intake	-0.04 (-0.07, -0.01)	0.01	-0.05 (-0.08, -0.02)	0.004	0.69
Carotene intake	-0.05 (-0.08, -0.02)	0.004	-0.04 (-0.07, -0.01)	0.02	0.52
Antioxidant score	-0.05 (-0.09, -0.02)	0.001	-0.03 (-0.07, 0.00)	0.06	0.48

β: difference in age, height and gender adjusted standard deviation units

* per smoking category, controlling for energy intake, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, history of atopic diseases, anxiety; sex of child, season of birth, multiple pregnancy, breastfeeding duration

[±] treating both smoking and dietary exposures as continuous variables

Online Table 2. Associations between maternal selenium intake and childhood outcomes stratified by maternal GPX_4 genotype

	Asthma (n=4,953)		**Atopy** (n=3,911)		**FEV_1** (n=4,011)		**FVC** (n=4,080)		**FEF_{25-75}** (n=4,080)	
GPX_4, rs713041	OR* (95% CI)	*P* trend	OR* (95% CI)	*P* trend	β * (95% CI)	*P* trend	β * (95% CI)	*P* trend	β* (95% CI)	*P* trend
C:C (n=1,722)	1.02 (0.84, 1.23)	0.84	1.03 (0.87, 1.22)	0.75	0.03 (-0.04, 0.10)	0.42	0.03 (-0.03, 0.10)	0.33	0.00 (-0.07, 0.07)	0.99
C:T (n=2,717)	1.06 (0.91, 1.24)	0.44	1.01 (0.88, 1.15)	0.92	0.05 (0.00, 0.11)	0.05	0.06 (0.01, 0.11)	0.03	0.02 (-0.03, 0.08)	0.38
T:T (n=1,069)	1.07 (0.84, 1.36)	0.59	0.78 (0.62, 0.99)	0.04	0.00 (-0.09, 0.10)	0.93	0.06 (-0.04, 0.15)	0.25	-0.05 (-0.14, 0.05)	0.33
P interaction	0.88		0.60		0.81		0.95		0.48	

OR: odds ratio; β: difference in age, height and gender adjusted standard deviation units

* per quartile of selenium intake, controlling for energy intake, smoking, infections, supplements, antibiotics and paracetamol use during pregnancy; maternal educational level, housing tenure, financial difficulties, ethnicity, age, parity, history of atopic diseases, anxiety; sex of child, season of birth, multiple pregnancy, breastfeeding duration