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## **Online data supplement**

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

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## **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

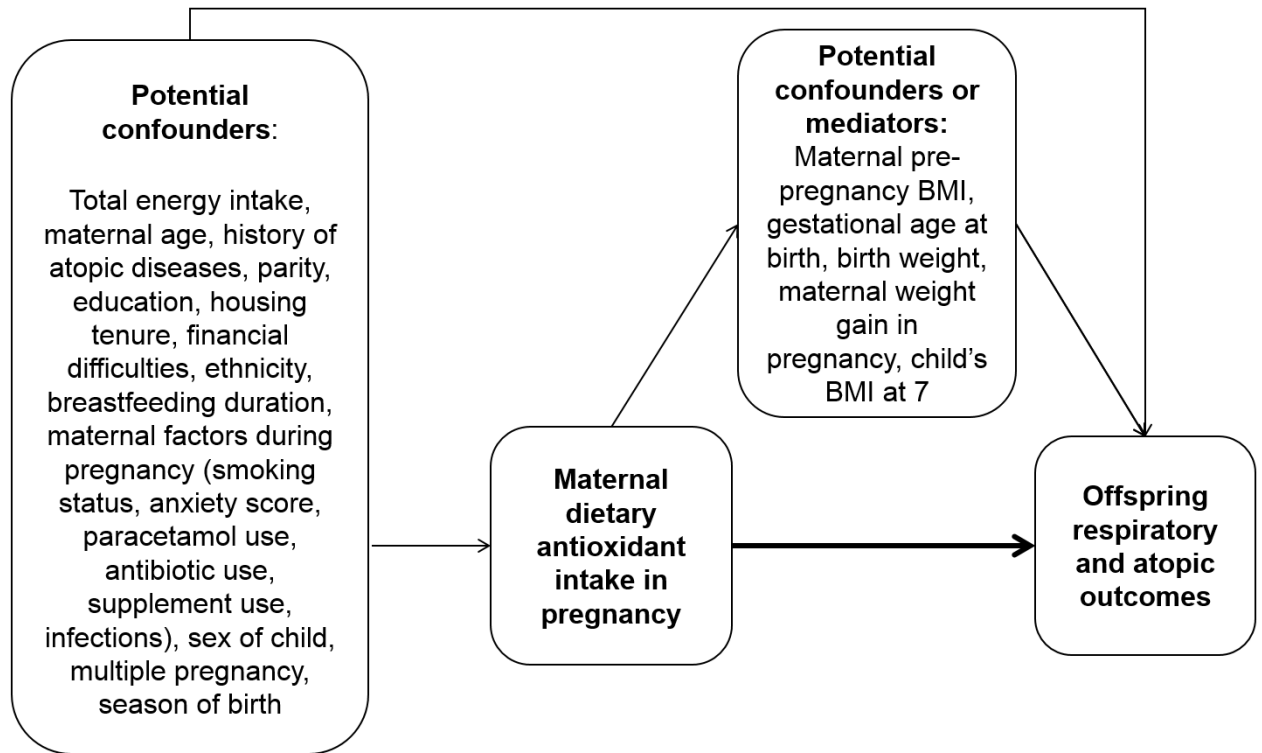
characteristics for which differences between excluded and included women were found to be statistically significant, including the exposure – see online Table E1) and assigning her a weight that is the inverse of that probability.

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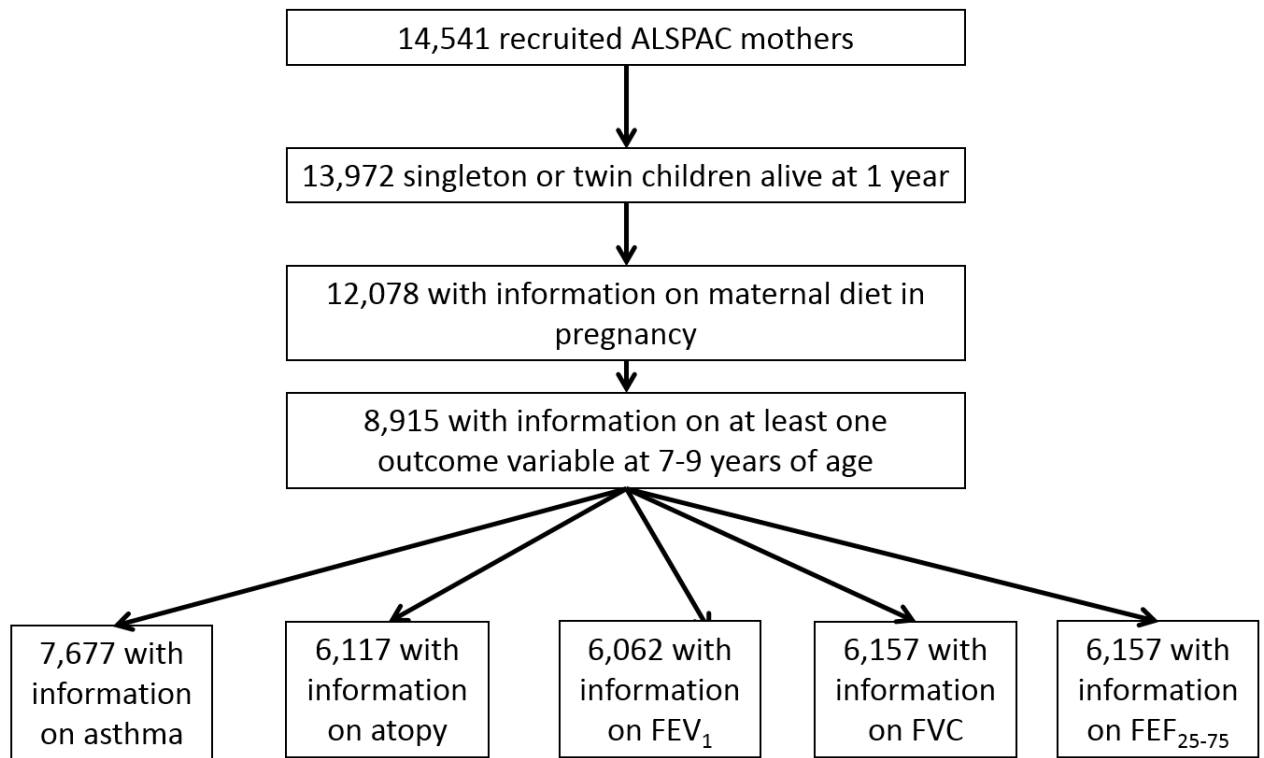
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**Online Figure 1.** Directed acyclic graph showing potential confounders and mediators of the associations between maternal dietary antioxidant intake in pregnancy and offspring respiratory and atopic outcomes



**Online Figure 2.** Participant flow





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

	<b>Included (n=8,915)</b>	<b>Excluded (n=3,163)</b>	<b>P</b>
<b>Maternal fruit intake in pregnancy (g/day)</b>	671 (390)	557 (392)	< .001
<b>Maternal vegetable intake in pregnancy (g/day)</b>	949 (474)	888 (505)	< .001
<b>Mother's age (years), m (sd)</b>	28.9 (4.6)	26.5 (5.1)	< .001
<b>Parity, %</b>			
0	45.5	42.8	
1	36.1	34.1	< .001
≥2	18.5	23.0	
<b>Sex of child, %</b>			
Male	51.1	52.2	0.28
Female	48.9	47.8	
<b>Multiple pregnancy, %</b>			
Singleton	97.6	97.1	0.14
Twin	2.4	2.9	
<b>Season of birth, %</b>			
Winter	16.2	15.8	
Spring	26.9	26.7	0.65
Summer	30.1	31.3	
Autumn	26.7	26.2	
<b>Breastfeeding duration, %</b>			
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	
<b>Mother's educational level, %</b>			
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	
<b>Maternal ethnicity, %</b>			
White	98.1	95.5	< .001
Non-white	1.9	4.5	
<b>Housing tenure, %</b>			
Owned/mortgaged	83.7	62.5	
Council rented	9.4	24.0	< .001
Non-council rented	6.9	13.5	
<b>Financial difficulties, %</b>			
Yes	17.1	22.9	< .001
<b>Maternal history of atopic diseases, %</b>			
Yes	68.3	68.9	0.62
<b>Maternal anxiety score in pregnancy, %</b>			
0-9	21.3	16.9	
10-14	25.7	21.6	< .001

15-20	25.9	24.6	
≥20	27.2	36.9	
<b>Maximum maternal tobacco exposure, %</b>			
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	
<b>Maternal paracetamol use during pregnancy, %</b>			
Yes	62.4	64.6	0.03
<b>Maternal antibiotic use during pregnancy, %</b>			
Yes	16.1	14.5	0.04
<b>Maternal supplement use during pregnancy, %</b>			
Yes	56.9	59.0	0.04
<b>Maternal infections in pregnancy, %</b>			
Yes	45.8	46.9	0.27
<b>Total energy intake (kJ/day), m (sd)</b>	7260 (1966)	7162 (2153)	0.02
<b>Maternal pre-pregnancy BMI, %</b>			
<18.50 kg/m <sup>2</sup>	4.3	6.4	
18.50-24.99 kg/m <sup>2</sup>	75.4	72.8	< .001
25.00-29.99 kg/m <sup>2</sup>	15.1	14.8	
≥30.00 kg/m <sup>2</sup>	5.2	6.0	
<b>Birth weight, %</b>			
<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	
<b>Gestational age (weeks), m (sd)</b>	39.5 (1.8)	39.4 (1.8)	0.03
<b>Child's BMI at 7, %</b>			
<15.00 kg/m <sup>2</sup>	28.1	29.6	
15.00-17.49 kg/m <sup>2</sup>	52.5	45.5	0.51
17.50-20.49 kg/m <sup>2</sup>	15.2	19.3	
≥20.50 kg/m <sup>2</sup>	4.2	5.7	
<b>Maternal weight gain during pregnancy, %</b>			
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	

**Online Table 2.** Associations between maternal smoking during pregnancy and childhood FEF<sub>25-75</sub> stratified by maternal dietary antioxidant intake in pregnancy (n=6,157)

Stratification variable	Below median		Above median		<i>P</i> interaction <sup>‡</sup>
	$\beta^*$ (95% CI)	<i>P</i> trend	$\beta^*$ (95% CI)	<i>P</i> trend	
<b>Fruit intake</b>	-0.06 (-0.10, -0.02)	0.004	-0.04 (-0.06, -0.01)	0.02	0.63
<b>Vegetable intake</b>	-0.05 (-0.08, -0.01)	0.009	-0.04 (-0.07, -0.01)	0.02	0.19
<b>Vitamin C intake</b>	-0.06 (-0.10, -0.03)	0.0002	-0.03 (-0.06, 0.01)	0.13	0.26
<b>Vitamin E intake</b>	-0.06 (-0.09, -0.03)	0.0002	-0.03 (-0.06, 0.01)	0.10	0.39
<b>Zinc intake</b>	-0.04 (-0.08, -0.01)	0.01	-0.04 (-0.08, -0.01)	0.01	0.83
<b>Selenium intake</b>	-0.04 (-0.07, -0.01)	0.01	-0.05 (-0.08, -0.02)	0.004	0.69
<b>Carotene intake</b>	-0.05 (-0.08, -0.02)	0.004	-0.04 (-0.07, -0.01)	0.02	0.52

$\beta$ : 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

<sup>‡</sup> treating both smoking and dietary exposures as continuous variables

**Online Table 3.** Associations between maternal selenium intake and childhood outcomes stratified by maternal GPX<sub>4</sub> genotype

<b>GPX<sub>4</sub>, rs713041</b>	<b>Asthma (n=4,953)</b>		<b>Atopy (n=3,911)</b>		<b>FEV<sub>1</sub> (n=4,011)</b>		<b>FVC (n=4,080)</b>		<b>FEF<sub>25-75</sub> (n=4,080)</b>	
	OR* (95% CI)	<i>P</i> trend	OR* (95% CI)	<i>P</i> trend	β * (95% CI)	<i>P</i> trend	β * (95% CI)	<i>P</i> trend	β* (95% CI)	<u><i>P</i> trend</u>
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
<i>P</i> 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