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 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.

Figure S1. Directed acyclic graph showing potential confounders and mediators of the associations between maternal dietary antioxidant intake in pregnancy and offspring respiratory and atopic outcomes

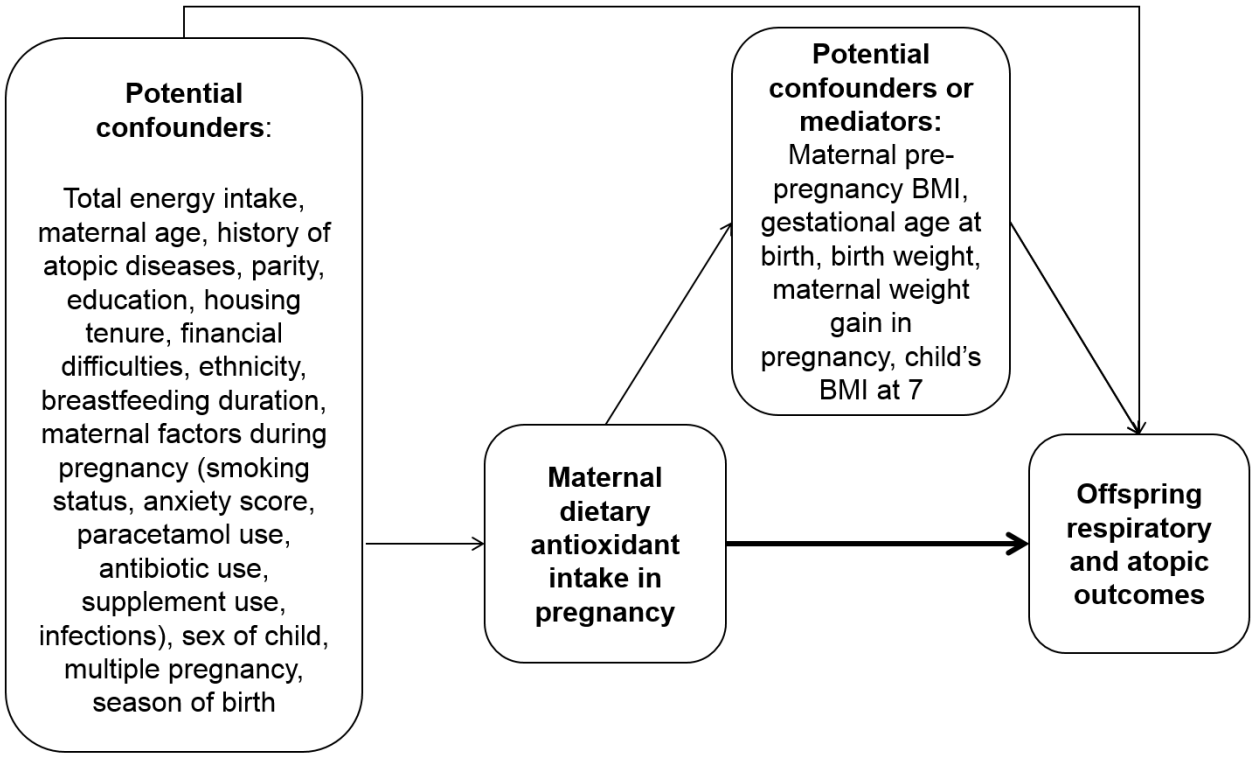

Figure S2. Participant flow

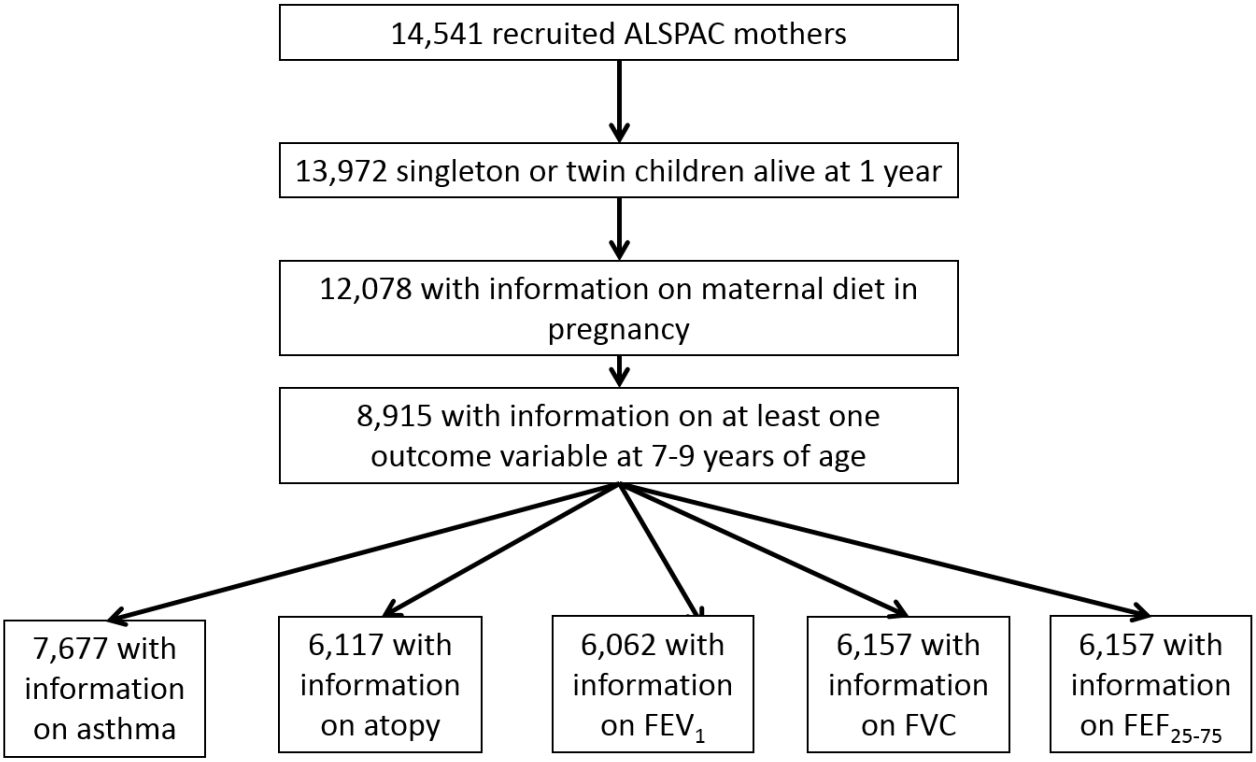

Table S1. Associations between maternal smoking during pregnancy and childhood FEF_{25-75} stratified by maternal dietary antioxidant intake in pregnancy (n=6,157)

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

Table S2. 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