

**Do maternal dietary antioxidants modify the relationship between binge drinking and small for gestational age? Findings from a longitudinal cohort study**

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**Funding**

This project was funded by an Oxford Brookes University PhD scholarship. The UK Medical Research Council, Wellcome Trust (grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC.

## Abstract

**Background:** Vitamin C, vitamin E and carotenoids are potent dietary antioxidants that have been shown to attenuate ethanol-induced harm in animal models of fetal alcohol spectrum disorder. A diet low in antioxidant-rich foods may induce a state of oxidative stress in the context of maternal alcohol consumption during pregnancy, potentially causing growth restriction in the developing fetus.

**Methods:** We conducted a secondary analysis of a longitudinal UK birth cohort. The sample comprised 9,699 women and their babies in Avon, UK, with an estimated delivery date between 1<sup>st</sup> April 1991 and 31<sup>st</sup> December 1992. Alcohol consumption data was self-reported at 18 weeks' gestation via a postal questionnaire. Women reported any binge drinking ( $\geq 4$  UK units/occasion) during the past month. Dietary data was self-reported at 32 weeks' gestation using a food frequency questionnaire. Estimated intakes of vitamins C and, E and carotenoids were categorised into quartiles. Logistic regression models with interaction terms were used to investigate relationships between maternal binge drinking, dietary antioxidants and fetal growth. Models were adjusted for maternal socio-demographic and lifestyle characteristics. Small for gestational age ( $<10^{\text{th}}$  percentile) was defined using customised birth centiles.

**Results:** In the unadjusted models, binge drinking was associated with higher risk of SGA birth (OR 1.38 [1.10, 1.72]  $p=0.005$ ), and higher maternal intakes of vitamin C (OR=0.90, 95% CI [0.84, 0.96]  $p=0.002$ ) and vitamin E (OR=0.90, 95% CI [0.84, 0.95]  $p<0.0001$ ) were associated with lower risk of SGA birth. However, addition of potentially confounding variables attenuated these relationships. Likelihood ratio tests indicated that interaction terms were not significant for vitamin C ( $p=0.116$ ), vitamin E ( $p=0.059$ ) or carotenoid intakes ( $p=0.174$ ).

**Conclusions:** There was no evidence of maternal intake of dietary antioxidants modifying the relationship between maternal binge drinking and SGA birth.

## Keywords:

Alcohol; pregnancy; dietary antioxidants; SGA; ALSPAC

## Background

Being born small for gestational age (SGA) is associated with higher rates of neonatal morbidity and mortality(Ho 2001), as well as increased risks of type 2 diabetes, cardiovascular disease(Nafee et al. 2008; Waterland 2009), and mental health problems during adulthood(Schlottz et al. 2010).

Women who reported drinking  $\geq 10$ g of ethanol per day during pregnancy showed an increased risk of SGA birth compared with intakes below this level, and increased risk with greater levels of exposure(Patra, Bakker, Irving, V. W. V Jaddoe, et al. 2011). Evidence for the effects of different patterns of alcohol consumption on fetal growth is less consistent(Patra, Bakker, Irving, V. Jaddoe, et al. 2011; Henderson et al. 2007; Mamluk et al. 2017). The timing, dose and duration of exposure to ethanol are all factors that determine the severity of symptoms observed in offspring. Heavy episodic alcohol consumption ‘binge drinking’ may result in greater harm to the fetus compared to similar quantities consumed relatively evenly over a longer period resulting in lower peak blood alcohol concentrations(Pierce & West 1986).

Maternal diet is also a determinant of fetal growth(da Silva Lopes et al. 2017). Oxidative stress (OS) – a state of imbalance between the production of reactive oxygen species (ROS) and antioxidant defences – is considered one of the major routes of harm(Brocardo et al. 2011; Ornoy & Ergaz 2010). Ethanol can induce oxidative stress in a number of ways. Its metabolism produces ROS, which then react with cellular components, such as surrounding proteins, lipids and DNA,(Cohen-kerem & Koren 2003) and reduces antioxidant defences(Bailey et al. 2001; Fernandez-Checa et al. 1991). For example, elevated levels of ethanol-induced oxidative stress in animal models of fetal alcohol spectrum disorders (FASD) are associated with increased lipid peroxidation and decreased levels of the antioxidant, glutathione(Brocardo et al. 2016; Dembele et al. 2006).

Vitamin C, vitamin E and carotenoids are potent dietary antioxidants that have been shown to attenuate ethanol-induced harm in animal models of FASD(Brocardo et al. 2011; Joya et al. 2015; Cohen-kerem & Koren 2003). Results from in animal models have reported inhibition in ROS production(Peng et al. 2005), protection of hippocampal cells (Nash et al. 2007), normalised fetal development (Wentzel et al. 2006), decreases in DNA

damage (Shirpoor et al. 2009) and diminished mortality and growth retardation (Satiroglu-Tufan & Tufan 2004) from treatment of antioxidants in the presence of ethanol exposure.

A diet low in antioxidant-rich foods may therefore induce a state of OS in the context of maternal alcohol consumption during pregnancy, potentially causing growth restriction in the developing fetus. However, studies investigating such a modifying effect of maternal diet in human participants are lacking.

The aim of this study was to investigate the association between maternal heavy episodic alcohol consumption 'binge drinking' during pregnancy and risk of SGA birth, and to determine whether or not this association is modified by maternal intakes of vitamin C, vitamin E and carotenoids.

## **Materials and Methods**

### *Design and participants*

We conducted a secondary analysis of data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based cohort study of pregnant women and their children living in the West of England. ALSPAC recruitment methods have previously been described in detail (Boyd et al. 2013; Fraser et al. 2013). Women were eligible for inclusion in ALSPAC if they resided in a pre-defined area within the former county of Avon and their estimated delivery date was between 1 April 1991 and 31 December 1992. The present analysis includes all women who gave birth to a singleton baby, alive at 1 year (n=13,616). The study website contains details of data available through a searchable data dictionary <http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>.

### *Outcome measures*

The primary outcome measure was SGA birth, defined as a birth weight <10<sup>th</sup> percentile. Customised birth weight centiles were used to assess fetal growth (Gardosi et al. 1992) using software developed by the Gestation Network (Gardosi & Francis 2016). These adjust for associated physiological factors (Gardosi 2006) (maternal

ethnicity, parity, height and pre-pregnancy weight, infant sex and gestational age at delivery). Maternal ethnicity, parity, height and pre-pregnancy weight were self-reported at either 12 or 18 weeks' gestation. Infant sex, birth weight and gestational age at delivery were obtained from hospital obstetric records. Gestational age at delivery was estimated using two sources from hospital obstetric records: from the last menstrual period (LMP) and a clinical estimate based on the LMP and ultrasound results. If there was a discrepancy between these two dates, an experienced obstetrician was consulted(Whincup et al. 1999).

If any maternal and infant characteristics required for the calculation of customised birth centiles were missing, notwithstanding birth weight and gestational age at delivery, default values were imputed as follows: parity (0), ethnicity (white European), maternal height (162.3cm) and weight (64.3kg), and infant sex (neutral: average between male [1] and female [0] coefficients).

#### *Alcohol consumption*

Alcohol consumption was gathered using a self-reported questionnaire at 18 weeks' gestation. Women reported the number of days during the past month when they had consumed approximately four or more UK units of alcohol ('binge drinking'), equivalent to 32 grams of ethanol. Available responses were 'None', '1–2 days', '3–4 days', '5–10 days', '>10 days' and 'Every day'. Due to the low numbers of women who reported more than 1–2 days of binge drinking during the past month, this variable was dichotomized into 'binge drinkers', defined as  $\geq 4$  units on at least one occasion during the past month, and 'non-binge drinkers'. Whilst binge drinking is typically defined in the UK as the consumption of  $\geq 6$  units/occasion(HSCIC 2014), during pregnancy we refer to an intake of  $\geq 4$  units/occasion as 'binge drinking' as it reflects an episodic pattern of alcohol consumption in contrast to the average quantity of units consumed per week, and is consistent with other analyses of ALSPAC data(Alati et al. 2013).

#### *Dietary data*

Women completed a 44-item food frequency questionnaire (FFQ) at approximately 32 weeks' gestation. Each food and drink item was allocated a standard portion size using a UK reference guide(Agency 1988). Women

reported the frequency with which they consumed each item as 'Never/Rarely', 'Once in 2 weeks', '1–3 per week', '4–7 per week' and 'More than once a day'. Women also reported how many slices of bread, cups of tea and coffee, teaspoons of sugar, and portions of fat spread they consumed on a daily basis.

Weekly nutrient intakes were calculated using the method described By Rogers and Emmett(Rogers et al. 1998a). Estimates of daily intakes of vitamin C, vitamin E and carotenoids (sum of  $\alpha$ -carotene,  $\beta$ -carotene, lutein, lycopene and  $\beta$ -cryptoxanthin) were calculated by multiplying weekly portion sizes by nutrient concentrations from UK dietary composition tables(McCance & Widdowson 2002). Because of the positive association between nutrient intakes and energy, dietary antioxidants were adjusted for energy intake using the method of residuals(Willett et al. 1997). An FFQ provides a crude measure of nutrient intake and is most useful for calculating relative, rather than absolute estimates of intake(Willett 2013). We therefore categorised intakes of vitamin C, vitamin E and carotenoids into quartiles for the analysis.

#### *Covariates*

At approximately 8 and 18 weeks' gestation, women completed a postal questionnaire and self-reported the following socio-demographic and lifestyle characteristics: maternal age ('<20 years', '20–24 years', '25–29 years', '≥30 years'); parity ('0' or '≥1'); Education ('<Secondary', 'Lower secondary', 'Upper secondary' or 'Tertiary'); single parent household ('yes' or 'no'); housing tenure ('owner-occupied', 'council/housing association rented' or 'privately rented'); and house crowding index (HCI), a ratio of household rooms (excluding the kitchen and bathrooms) to number of people per household(Melki et al. 2004) ('<0.50', '≥0.50–0.75', '>0.75–1.00' or '>1.00'). Due to low numbers in categories of non-white ethnic origin, ethnicity was dichotomised ('white' or 'non-white'). Women reported how many cigarettes they were currently smoking at 8 weeks' gestation and due to low numbers of smokers reporting more than 10 per day once stratified by binge drinking and diet, smoking was also dichotomised ('smoker' or 'non-smoker'). Women also reported whether they had taken any vitamin supplements this pregnancy or within the past three months when they were 18 and 32 weeks pregnant, respectively ('yes' or 'no').

#### *Missing data*

A total of 29% of data were missing in the complete case analysis (CCA). For all variables of interest, we explored the missing data mechanism by creating dummy variables (missing/not missing) and using logistic regression models. Missing observations for all variables of interest were imputed using chained equations under the assumption of missing at random (MAR). The substantive model compatible-fully conditional specification (SMC-FCS) approach, developed by Bartlett & Morris (2015), was used as it is a powerful technique when running imputation models with interaction terms (Bartlett et al. 2015). Data were imputed using 20 datasets which were combined according to Rubin's rules (Rubin 1987). The imputation model included all variables in the model of interest, interaction terms and auxiliary variables (variables that are not included in the analysis but are associated with missing variables of interest), which can improve the prediction of missing values when included in the imputation model (Hardt et al. 2012). Variables were imputed using the following models: maternal age, education, housing tenure, HCl, vitamin C, vitamin E and carotenoids using an ordinal logistic regression model; and SGA, binge drinking, smoking, parity, ethnicity, child gender and breastfeeding (auxiliary variable), using binary logistic regression models. We conducted a sensitivity analysis to test the MAR assumption (Héraud-Bousquet et al. 2012) by exploring the extreme effect estimates compatible with the observed data (Leacy et al. 2017). We hypothesised that, due to social desirability bias, pregnant women who do binge drink are less likely to report this (Wild et al. 2001; Meiklejohn et al. 2012). Firstly, we assumed that women with missing binge-drinking data were all binge drinking (worst-case scenario) and secondly, we assumed that women with missing binge-drinking data were not binge drinking (best-case scenario). The model of interest was then fitted and the results combined according to Rubin's rules (Rubin 1987). The results from the sensitivity analysis were not consistent, suggesting that data was missing not at random (MNAR). Therefore, we have presented results from the CCA in the results, but included the results from the MNAR and MAR MI models as supplementary data (Table S1).

#### *Statistical analysis*

SGA births, intakes of dietary antioxidants, socio-economic and lifestyle characteristics of participants were summarised as frequencies and percentages or means and standard deviations (SD), and stratified by maternal binge drinking. Bivariate analyses were conducted using chi-squared tests for categorical variables and t-tests

for continuous variables. Because nutrients tend to be consumed in combination rather than in isolation, intakes are often highly correlated (Willett et al. 1997). The Variance Inflation Factor (VIF) was therefore calculated to investigate multicollinearity between nutrient intake variables. In this case, VIF values were all <1.3, indicating a low level of collinearity. Logistic regression models were used to determine associations between intakes of vitamin C, vitamin E and carotenoids and binge drinking.

The association between maternal binge drinking and risk of SGA was first determined using simple logistic regression (Model 1). Antioxidant intake variables were then added as covariates (Model 2), followed by all other covariates as potential sources of confounding (with the exception of those already adjusted for in the customised birth centiles) (Model 3). To test the modifying effect of dietary antioxidants on the alcohol consumption–SGA birth relationship, interaction terms for maternal binge drinking and intakes of vitamin C, vitamin E and carotenoids were added to the models. Likelihood ratio tests were used to compare the fit of the models, both with and without the interaction terms. Non-significant interaction terms ( $p < 0.05$ ) were removed from the final regression model. Linear trend tests for vitamin C, vitamin E and carotenoids were also conducted by including each categorical variable as continuous.

Because women did not report the duration, dose or type of vitamin supplement they had taken during pregnancy, it was not possible to estimate vitamin E, C or carotenoid intake from this source. Therefore we conducted a sensitivity analysis to assess the effect of vitamin supplement use on the relationship between binge drinking, dietary antioxidants and SGA births. Women who reported taking vitamin supplements at any point during their pregnancy were excluded from the sample and the analysis was repeated. All statistical analyses were conducted using Stata 14 (StataCorp, Texas, USA).

## Results

Of the total number of women in the sample ( $n=13,616$ ), 9,699 (71%) women had complete data available for all variables of interest. Missing data ranged from 0% for age to 17% for maternal pre-pregnancy weight. Approximately 7% of binge drinking data, 14% of dietary data and 1% of SGA data were missing. Missing SGA data was not associated with any exposure variables or potentially confounding variables. However, women



with missing binge drinking data were more likely to have a SGA birth, smoke, not breastfeed their child, live in social housing, live in crowded conditions and report lower intakes of vitamin E and vitamin C.

Socio-demographic and lifestyle characteristics are presented in **Table 1**. The majority of women (58%) were aged 20–29 years. The vast majority were of white ethnic origin (97%), living with their partner (94%), living in a home they either owned outright or mortgaged (73%), and non-smokers (79%).

A total of 1,002 (8%) women reported at least one episode of binge drinking during the past month. Women who reported binge drinking were more likely to be parous, living in a single parent household, living in social housing, and smokers compared to women who did not report binge drinking during the same period. Women with relatively high intakes (Q4) of vitamin C (OR=0.55, 95% CI [0.45, 0.68]  $p<0.0001$ ) and vitamin E (OR=0.66, 95%CI [0.55, 0.81]  $p<0.0001$ ) were less likely to binge drink compared to women with low intakes (Q1). No association was observed between binge drinking and carotenoid intake (**Table 2**).

A total of 1,291 SGA births (11.3%) occurred in the sample population. Of the women who reported no binge drinking, 9% had a SGA birth, compared to 13% in women reporting  $\geq 1$  episode of binge drinking (**Table 3**). Women in the lowest quartile for vitamin C, vitamin E and carotenoid intakes had the highest rates of SGA birth compared to women in all other quartiles (**Table 3**).

There was no evidence of dietary antioxidant intakes modifying the relationship between binge drinking and SGA birth. Likelihood ratio tests indicated that interaction terms for the models did not provide a better fit compared to the more restrictive model (without interaction terms): vitamin C ( $p=0.116$ ); vitamin E ( $p=0.059$ ); and carotenoids ( $p=0.174$ ).

Binge drinking was associated with increased odds of SGA birth compared to women who did not binge drink (OR=1.52 [1.25, 1.85]  $p<0.0001$ ), and this association remained significant with the inclusion of vitamin C, vitamin E and carotenoid intakes (OR=1.38 [1.10, 1.72]  $p=0.005$  (**Table 4**). Higher vitamin C (Q4 vs. Q1: OR=0.73 [0.59, 0.90]  $p=0.003$ ) and vitamin E (Q4 vs. Q1: OR=0.70 [0.58, 0.85]  $p<0.0001$ ) intakes were associated with lower risk of SGA birth, although no such relationship was observed for carotenoid intake. The trend tests

indicated that as intakes of vitamin C (OR=0.90, 95% CI [0.84, 0.96] p=0.002) and vitamin E (OR=0.90, 95% CI [0.84, 0.95] p<0.0001) increased, the odds of having a SGA birth decreased. (**Table 4**, Model 2).

In the fully adjusted model, relationships between SGA births, maternal binge drinking and dietary antioxidant intakes during pregnancy were attenuated (**Table 4**, Model 3). A small, but non-significant, increase in odds of having a SGA birth from binge drinking persisted (aOR 1.12 [0.86, 1.46] p=0.391). The tests for trends indicated there was no evidence of relationships between dietary antioxidants and SGA births.

We conducted a sensitivity analysis to explore the effect of vitamin supplement use on the odds of SGA births. However, after excluding women who reported vitamin supplements at some point during their pregnancy (18%), there was no substantive change in the results from the univariable and multivariable logistic regression models (results not presented).

## **Discussion**

We found little evidence that maternal intakes of vitamin C, vitamin E and carotenoids modified the relationship between binge drinking during pregnancy and the odds of having a SGA birth in the ALSPAC cohort. After adjusting for potential confounders, the relationships between maternal binge drinking, dietary antioxidants and odds of SGA birth were attenuated.

To our knowledge, this is the first study to explore whether maternal dietary antioxidants modify the relationship between alcohol consumption and fetal growth. Whilst we found no evidence of an interaction between binge drinking and the dietary antioxidants studied, a study conducted in the US reported that multivitamin use during pregnancy appeared to mitigate the risk of SGA birth associated with alcohol consumption (Avalos et al. 2011). However, the sample size was small (n=800), with only 227 women reporting no multivitamin use, and the analysis was not adjusted for smoking, which is a strong predictor of SGA birth (Van den Berg et al. 2013). In addition to this, multivitamins contain concentrated amounts of a number of different vitamins, whereas we looked at dietary intakes only. Therefore, it is possible that the mitigating effects reported by Avalos et al. are

due to residual confounding, other compounds or the synergistic effects of a particular combination of compounds.

Whilst there is evidence from experimental studies to suggest antioxidants modify the relationship between alcohol and fetal growth(Wentzel et al. 2006; Heaton et al. 2000; Mitchell et al. 1999; Peng et al. 2005), there are a number of plausible reasons that we have not observed a similar relationship within this study. Firstly, the quantity and frequency of alcohol consumption may be too low within this study population to observe an effect on fetal growth. The dose of ethanol and antioxidants administered within experimental studies are usually large compared to the size of the organism under investigation, and may not reflect average intakes within pregnant human populations(McGonigle & Ruggeri 2014). The average consumption of ethanol in rat models is between 10-14g/kg/d with 35% of calories derived from ethanol, with rats typically achieving a BAC of more than 100mg/dl during peak feeding times(Driscoll et al. 1990). A study conducted by Thomas and colleagues developed a rat model of FASD and report BACs of more than 300mg/dl(Thomas et al. 2010). A BAC of more than 100mg/dl could be achieved if women were consuming many units in a short space of time(May et al. 2008). However, it is not possible to determine the BAC on women in this sample and is likely peak BAC of women in the binge-drinking category varied substantially.

Secondly, the timing and duration of exposure differed, which has been shown to be an important predictor of fetal growth(Feldman et al. 2012; Gundogan et al. 2015). In a study conducted in Sweden, pregnant rats were exposed to heavy doses of ethanol and vitamin E throughout the entire gestational period(Wentzel et al. 2006). Within this study, women were classified as binge drinkers if they had consumed  $\geq 4$  units on at least one day over the past month, which does not capture total fetal exposure to ethanol, only exposure to high peak concentrations during the second trimester. Additionally, there are physiological differences and animal models are conducted in controlled environments which do not reflect the complexities of the human behaviour(McGonigle & Ruggeri 2014).

Finally, dietary intake was estimated using an FFQ; therefore, relative estimates of antioxidant intake were explored, making it difficult to know how the range of nutrient intakes varied between quartiles. In animal models exploring nutrient and ethanol interactions, nutrient intakes are often not comparable with average

dietary intake levels observed in human populations(Wentzel et al. 2006) or the control group receive are exposed to a very nutrient restricted diet(Gutierrez et al. 2007). Therefore it is possible that if women are exposed to higher doses of ethanol and dietary antioxidants, over longer periods of time and observed repeatedly during pregnancy, an interaction may be detected.

Results from other studies exploring the relationship between binge drinking and fetal growth have reported similar findings. A systematic review found that inappropriate adjustment for confounding and variation in the definition of 'binge drinking' contributed to uncertainty surrounding the risks of this pattern of consumption(Henderson et al. 2007). Subsequent research has reported conflicting findings. A multicentre, observational cohort study(McCarthy et al. 2013) and studies conducted in Australia(Leary et al. 2009) and Switzerland(Meyer-Leu, Lemola, J. B. Daeppen, et al. 2011) reported no relationship between binge drinking and SGA births. However, studies conducted in the UK(Cooper et al. 2013) and Italy(Chiaffarino et al. 2006) reported significantly increased risks of having a SGA birth in women who reported binge drinking during pregnancy. The disparities between study findings are likely to be a result of the different definitions of binge drinking (ranging from  $\geq 3$  units per occasion(Meyer-Leu, Lemola, J.-B. Daeppen, et al. 2011) to  $\geq 3$  units per day(Chiaffarino et al. 2006)), timing of exposure, confounding and study sample sizes.

Few studies have explored associations between maternal dietary intake of antioxidants and fetal growth, instead looking at dietary supplements or biomarkers of oxidative stress(Scholl et al. 2006; Alice Rumbold et al. 2015; Rumbold et al. 2005). A recent systematic review and meta-analysis(Cohen et al. 2015) determined associations between maternal antioxidant levels (vitamin C, vitamin A/retinol, vitamin E [ $\alpha$ -tocopherol, total tocopherol, or unspecified] and carotenoid biomarkers) during pregnancy and the risk of SGA ( $n=9$ ), and the authors concluded there was no consistent evidence to support a relationship between plasma levels and fetal growth. Interestingly, a Cochrane review of randomised controlled trials evaluating vitamin C and pregnancy outcomes found that vitamin C supplementation, either alone or in combination with vitamin E, was associated with a small increase in risk of SGA births(Alice Rumbold et al. 2015; A Rumbold et al. 2015).

The proportion of births identified as SGA were similar to national estimates (for England and Wales) in 2007 reported by the Office for National Statistics (ONS) (Office for National Statistics 2010). However, the

proportion of births that were preterm were lower than nationally reported figures for England and Wales in 2005 (gestational age was not routinely collected until 2005) (Moser et al. 2008). However, this difference may reflect older women having more babies and advances in technology which have enabled more women to have babies used assisted fertility treatment, which result in more multiple pregnancies, increasing the risk of preterm births (March of Dimes, PMNCH, Save the Children & WHO 2012). In this study still and multiple births were excluded, which is likely to reduce the number of preterm births reported.

### *Strengths and limitations*

The main strengths of this analysis are the large sample size and longitudinal study design, enabling us to investigate exposures measured prospectively during pregnancy and subsequent SGA births. Another strength was that birth weights and gestational ages were attained using hospital obstetric records, which are typically more reliable than self-reported estimates (Adegboye & Heitmann 2008), particularly for second or third time mothers (Catov et al. 2018). This also means there were fewer missing data for SGA birth, enabling our analysis to explore missing data mechanisms of exposure variables and confounding variables in relation to the study outcome.

However, there are a number of limitations that must be considered when interpreting these findings. A major limitation is the self-reported data on alcohol and dietary exposures, both of which are prone to reporting biases, including recall bias and social-desirability bias (Gmel & Daeppen 2007; Wild et al. 2001; Meiklejohn et al. 2012). Whilst nutritional biomarker data has limitations, the addition of this data source would have provided an extra estimate that is not vulnerable to reporting biases (Hedrick et al. 2012). Moreover, the FFQ was not validated before use, although it was adapted from an existing dietary questionnaire (Yarnell et al. 1983) and has since been shown to estimate mean nutrient intakes similar (Rogers et al. 1998b) to those from a national dietary survey from the same time period (Gregory et al. 1990). Alcohol and dietary data were not measured contemporaneously. However, whilst alcohol consumption is known to change over the course of pregnancy (O'Keeffe et al. 2015), dietary intake appears to be relatively consistent throughout pregnancy (Crozier et al. 2006). Finally, women did not report type, dose or duration of vitamin supplement use, which may have been an important source of antioxidants for some women.

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## **Conclusions**

This study has found little evidence that vitamin C, vitamin E and carotenoids, when consumed at levels commensurate with a typical UK diet, modify the relationship between maternal binge drinking and fetal growth. Future research in this area may benefit from exploring diet–alcohol interactions in a more contemporary population, using a combination of robust assessment methods to capture dietary intake, biomarkers and supplement use data.

## **Acknowledgements**

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. We also wish to thank Dr Ron Gray from the NPEU, Oxford, for his input with this study.

## **Contribution of authorship**

VC conducted the analysis and prepared the manuscript. LS & SW contributed to the conception and design of the work. HI contributed to the statistical analysis plan. LS, SW, HI and KN provided feedback on drafts of the manuscript. All authors reviewed and approved the final version of the manuscript.

## **Conflicts of interest**

None

## **Details of ethics approval**

412 Ethical approval was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics  
413 Committee.  
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## Table Legends

**Table 1.** Socio-demographic and lifestyle characteristics of ALSPAC sample population, by maternal binge drinking (n=12,629)

**Table 2.** Maternal intakes of dietary antioxidants, by maternal binge drinking

**Table 3.** Maternal binge drinking and dietary antioxidant intakes, by SGA birth

**Table 4.** Associations between maternal binge drinking, dietary antioxidant intakes and SGA birth<sup>s</sup> (CCA)

**Table S1.** OR and 95% CI for associations between maternal binge drinking, dietary antioxidant intakes and SGA (<10<sup>th</sup> percentile) from CCA, MAR and MNAR



## Tables

**Table 1. Socio-demographic and lifestyle characteristics of ALSPAC sample population, by maternal binge drinking (n=12,629)**

		Total n (%)	No binge (n=11,627)	Binge (n=1,002)	p-value <sup>^</sup>	Missing n (%)
Age (years)						
	<20	542 (5)	499 (4)	43 (4)	0.660	0 (0)
	20–29	7266 (58)	6,699 (58)	567 (56)		
	30–39	4668 (36)	4,292 (37)	376 (38)		
	40+	153 (1)	137 (1)	16 (2)		
Parity					<0.0001	1,017 (7)
	0	5578 (45)	5,197 (45)	381 (39)		
	≥1	6834 (55)	6,233 (55)	601 (61)		
Ethnicity					0.459	1,603 (12)
	White	11,335 (97)	10,453 (98)	882 (98)		
	Non-white	274 (3)	256 (2)	18 (2)		
Single parent household					<0.0001	1,246 (9)
	No	11164 (94)	10,342 (94)	822 (91)		
	Yes	705 (6)	621 (6)	84 (9)		
Housing					<0.0001	914 (7)
	Own/mortgaged	9027 (73)	8,412 (75)	617 (64)		
	Council renting	1849 (16)	1,645 (15)	204 (21)		
	Private renting	1294 (11)	1,155 (10)	139 (15)		
HCI					<0.0001	1,133 (8)
	≤ 0.50	5,055 (42)	4,736 (43)	319 (34)		
	>0.50–0.75	3,771 (31)	3,481 (32)	290 (31)		
	>0.75–1.00	2,369 (20)	2,129 (19)	240 (26)		
	> 1.00	779 (7)	691 (6)	88 (9)		
Smoking					<0.0001	1,718 (13)
	Non-smoker	9,088 (79)	8,551 (81)	537 (62)		
	Smoker	2,280 (21)	1,957 (19)	323 (38)		
Maternal height (cm), mean (sd)		164.0 (6.7)	164.0 (6.7)	163.8 (6.9)	0.443	1,702 (13)
Maternal weight (kg), mean (sd)		61.7 (10.0)	61.7 (11.1)	62.2 (10.3)	0.228	2,255 (17)
Small for gestational age					<0.0001	171 (1)
	No	11346 (90)	10,484 (92)	862 (89)		
	Yes	1,126 (10)	1,001 (8)	125 (11)		
Birthweight (g), mean (sd)		3415 (541)	3424 (535)	3403 (564)	0.230	171 (1)
Gestational age (weeks), mean (sd)		39.5 (1.9)	39.5 (1.8)	39.6 (1.8)	0.208	0 (0)
Preterm birth (<37 weeks)						0 (0)
	No	12,002 (95)	11,044 (95)	958 (96)	0.384	
	Yes	627 (5)	583 (5)	44 (4)		

<sup>^</sup> Chi<sup>2</sup> and t-tests conducted

**Table 2. Maternal intakes of dietary antioxidants, by maternal binge drinking**

	No binge (n=10,540)	Binge (n=869)	OR (95% CI)	p-value
Vitamin C (mg/d)				
Q1	2,538 (90)	284 (10)	1.00	
Q2	2,633 (93)	212 (7)	0.72 (0.60, 0.87)	0.001
Q3	2,662 (93)	205 (7)	0.69 (0.57, 0.83)	<0.0001
Q4	2,707 (94)	168 (6)	0.55 (0.45, 0.68)	<0.0001
Vitamin E (mg/d) <sup>°</sup>				
Q1	2,559 (91)	257 (9)	1.00	
Q2	2,622 (92)	225 (8)	0.85 (0.71, 1.03)	0.099
Q3	2,650 (93)	205 (7)	0.77 (0.64, 0.93)	0.008
Q4	2,709 (94)	182 (6)	0.66 (0.55, 0.81)	<0.0001
Carotenoids (mg/d) <sup>*</sup>				
Q1	2,624 (92)	230 (8)	1.00	
Q2	2,660 (93)	190 (7)	0.81 (0.67, 0.99)	0.044
Q3	2,617 (92)	235 (8)	1.02 (0.85, 1.24)	0.803
Q4	2,639 (93)	214 (8)	0.92 (0.76, 1.12)	0.431

[OR, Odds Ratio]

<sup>°</sup>  $\alpha$ -tocopherol equivalents<sup>\*</sup>  $\alpha$ -carotene,  $\beta$ -carotene, lutein, lycopene and  $\beta$ -cryptoxanthin

**Table 3. Maternal binge drinking and dietary antioxidant intakes, by SGA birth**

		SGA		Total n
		No (n=11,346) n (%)	Yes (n=1,126) n (%)	
Binge drinking				
	<i>No binge</i>	10,484 (92)	1,001 (9)	11,485
	<i>≥1 binge episode</i>	862 (87)	125 (13)	987
Vitamin C (mg/d)				
	<i>Q1</i>	2,584 (89)	322 (11)	2,906
	<i>Q2</i>	2,667 (91)	249 (9)	2,916
	<i>Q3</i>	2,690 (92)	220 (8)	2,910
	<i>Q4</i>	2,680 (92)	220 (8)	2,900
Vitamin E (mg/d) <sup>°</sup>				
	<i>Q1</i>	2,585 (89)	322 (11)	2,907
	<i>Q2</i>	2,667 (92)	246 (8)	2,913
	<i>Q3</i>	2,663 (92)	240 (8)	2,903
	<i>Q4</i>	2,706 (93)	203 (7)	2,909
Carotenoids (mg/d) <sup>°</sup>				
	<i>Q1</i>	2,617 (90)	282 (10)	2,899
	<i>Q2</i>	2,702 (93)	218 (7)	2,920
	<i>Q3</i>	2,639 (91)	261 (9)	2,900
	<i>Q4</i>	2,663 (91)	250 (9)	2,913

[SGA, Small for Gestational Age]

<sup>°</sup> α-tocopherol equivalents<sup>°</sup> α-carotene, β-carotene, lutein, lycopene and β-cryptoxanthin

**Table 4. Associations between maternal binge drinking, dietary antioxidant intakes and SGA birth<sup>s</sup> (CCA)**

	Model 1 (n=12,470)	p-value	Model 2 (n=11,271)	p-value	Model 3 <sup>b</sup> (n=9,699)	p-value
	OR (95% CI)		OR (95% CI)		aOR (95% CI)	
Binge drinking						
<i>None</i>	1.00		1.00		1.00	
<i>≥1 episode</i>	1.52 (1.25, 1.85)	<0.0001	1.38 (1.10, 1.72)	0.005	1.12 (0.86, 1.46)	0.385
Vitamin C (mg/d)						
<i>Q1</i>	-	-	1.00		1.00	
<i>Q2</i>	-	-	0.81 (0.68, 0.98)	0.028	0.86 (0.70, 1.07)	0.169
<i>Q3</i>	-	-	0.73 (0.60, 0.89)	0.002	0.83 (0.66, 1.04)	0.102
<i>Q4</i>	-	-	0.73 (0.59, 0.90)	0.003	0.83 (0.65, 1.06)	0.135
Vitamin E (mg/d) <sup>a</sup>						
<i>Q1</i>	-	-	1.00		1.00	
<i>Q2</i>	-	-	0.80 (0.67, 0.96)	0.019	0.91 (0.74, 1.13)	0.386
<i>Q3</i>	-	-	0.82 (0.68, 0.99)	0.041	0.99 (0.81, 1.24)	0.982
<i>Q4</i>	-	-	0.70 (0.58, 0.85)	<0.0001	0.84 (0.67, 1.05)	0.129
Carotenoids (mg/d) <sup>a</sup>						
<i>Q1</i>	-	-	1.00		1.00	
<i>Q2</i>	-	-	0.78 (0.64, 0.95)	0.011	0.81 (0.70, 1.06)	0.062
<i>Q3</i>	-	-	0.99 (0.82, 1.20)	0.939	1.01 (0.82, 1.25)	0.897
<i>Q4</i>	-	-	0.99 (0.81, 1.21)	0.913	1.07 (0.85, 1.32)	0.541

[SGA, Small for Gestational Age; CCA, Complete Case Analysis; OR, Odds Ratio; aOR, Adjusted Odds Ratio]

<sup>a</sup> SGA birth classified as <10<sup>th</sup> customised centile, which adjusts for maternal weight, height, ethnicity, and parity as well as infant sex and gestational age at birth

<sup>o</sup> α-tocopherol equivalents

<sup>\*</sup> α-carotene, β-carotene, lutein, lycopene and β-cryptoxanthin

Model 1: Maternal binge drinking

Model 2: Model 1 + vitamin C, vitamin E and carotenoids

Model 3: Model 2 + maternal age, education, smoking, housing, HCl, single parent household.

