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Authors	Maher, Gillian M.;Khashan, Ali S.;O'Byrne, Laura;Flanagan, Sinead;Mortimer, Roisin .M.;Kiely, Mairead E.;Hourihane, Jonathan O'B.;Kenny, Louise C.;Murray, Deirdre M.;McCarthy, Fergus P.
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Full length article

Periconceptual and prenatal alcohol consumption and neurodevelopment at age two and five years

Gillian M. Maher [a,b,*], Ali S. Khashan [a,b], Laura O'Byrne [a], Sinead Flanagan [a,b], Roisin M. Mortimer [a,c,d], Mairead Kiely [e], Jonathan O'B. Hourihane [a,f], Louise C. Kenny [g], Deirdre Murray [a,f], Fergus P. McCarthy [a,c]

[a] INFANT Research Centre, University College Cork, Cork, Ireland
[b] School of Public Health, University College Cork, Cork, Ireland
[c] Department of Obstetrics and Gynaecology, Cork University Maternity Hospital, Cork, Ireland
[d] Department of Obstetrics and Gynaecology, Brigham and Women's Hospital and Harvard Medical School, Boston, USA
[e] Department of Food Science and Nutrition, University College Cork, Cork, Ireland
[f] Department of Paediatrics and Child Health, University College Cork, Cork, Ireland
[g] Department of Women's and Children's Health, Institute of Translational Medicine, Faculty of Health and Life Sciences, University of Liverpool, Liverpool, UK

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ABSTRACT

Objective: Examine the association between alcohol consumption before and during pregnancy and neurodevelopmental outcomes in the offspring at two and five years.

Study design: Retrospective analysis of a prospective longitudinal cohort; SCOPE-BASELINE. Data on preconception and prenatal alcohol consumption were obtained at 15 weeks' gestation and categorised as abstinent, occasional-low (1-7units/week) and moderate-heavy (≥8units/week). Binge drinking was defined as ≥6 units/session. Outcome measures (Child Behaviour Checklist and Kaufman Brief Intelligence Test) were obtained at two and five years. Linear regression examined an alcohol consumption and Child Behaviour Checklist and Kaufman Brief Intelligence Test relationship, adjusting for several potential confounders.

Results: Data on alcohol consumption was available for 1,507 women. Adjusted linear regression suggested few associations: pre-pregnancy occasional-low alcohol consumption was associated with lower log externalizing Child Behaviour Checklist scores (-0.264, 95% CI: −0.009, −0.520), while pre-pregnancy moderate-high levels of alcohol consumption was associated with lower Kaufman Brief Intelligence Test verbal standard scores (-0.034, 95% CI: −0.001, −0.068) and composite IQ scores (-0.028, 95% CI: −0.056, −0.0004) at five-years. In the first trimester, moderate-high levels of alcohol consumption was associated with lower internalizing Child Behaviour Checklist scores at two-years (-0.252, 95% CI: −0.074, −0.430). No significant associations were observed between number of binge episodes pre-pregnancy or binge drinking in the first trimester and Child Behaviour Checklist or Kaufman Brief Intelligence Test.

Conclusions: We did not find strong evidence of associations between pre-pregnancy and early pregnancy maternal alcohol consumption and adverse neurodevelopmental outcomes at age two and five years overall. Further research examining alcohol consumption (including binge drinking) beyond 15 weeks' gestation and subsequent neurodevelopmental outcomes is needed to examine the potential effect of alcohol consumption in later pregnancy.

Introduction

Childhood neurodevelopmental disorders are a source of growing public health concern affecting 10–20% of adolescents [1]. They typically emerge in early childhood and may manifest as behavioural ('externalising' disorders), emotional ('internalising' disorders) or

Abbreviations: SCOPE, Screening of Pregnancy Endpoints; BASELINE, Babies After; SCOPE, Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints; CBCL, Child Behaviour Checklist; Kaufman BIT, Kaufman Brief Intelligence Test.

* Corresponding author at: INFANT Research Centre, University College Cork, Cork, Ireland.
E-mail address: gillian.maher@ucc.ie (G.M. Maher).

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intellectual issues such as specific learning difficulties or disabilities. There is an increasing recognition that prenatal risk factors may play a role in their development, and periconceptual alcohol consumption has been highlighted as a possible modifiable risk factor [2].

It is widely recognised that alcohol use during pregnancy is a risk factor for miscarriage, stillbirth, intrauterine growth restriction, preterm delivery and low birthweight infants [3,4]. However, it has also been linked to adverse neurodevelopmental outcomes, and while the most well-known of these is fetal alcohol syndrome disorder, it is also associated with attention deficit hyperactivity disorder, cerebral palsy and poorer educational attainment [5–8]. Despite these known risks, and the recommendations from bodies such as the Royal College of Obstetricians and Gynaecologists that abstinence from alcohol during pregnancy is the safest option, prevalence of alcohol use during pregnancy remains high. Globally, 10% women use alcohol during pregnancy, with the highest prevalence estimates reported in the World Health Organisation European region [9]. Evidence from routinely collected data and representative cohort studies show a wide variation in prevalence estimates of alcohol use during pregnancy, with an estimated prevalence of 7.3% in the United States, 75% in the United Kingdom (UK) and between 20% and 82% in Ireland [10,11]. These statistics come despite many advisory bodies recommending alcohol avoidance in pregnancy [12].

Binge drinking (both during the pre-conception and prenatal period) may be particularly harmful and has been shown to be associated with reduced IQ scores and child behavioural outcomes, although light-moderate drinking may also have adverse effects on neurodevelopment [13–20]. However, results are conflicting, particularly regarding lower levels of alcohol consumption, potentially as a result of inconsistencies in the methodologies used to examine the association. Furthermore, a key limitation of many studies has included lack of adjustment for socioeconomic indicators such as income or maternal education, while timing of alcohol exposure should also be considered when examining a maternal alcohol consumption-neurodevelopmental outcome relationship [18].

This study aimed to examine the association between maternal alcohol consumption (before and during pregnancy) and neurodevelopmental outcomes at age two and five using the Child Behaviour Checklist and Kaufman Brief Intelligence test, while adjusting for several potential confounding factors. We also aimed to examine the effects of varying degrees of alcohol consumption before and during pregnancy, including binge drinking and timing of binge alcohol exposure.

Materials and methods

Study population

Mother and child pairs were identified from a prospective longitudinal cohort; SCOPE (Screening of Pregnancy Endpoints) and BASELINE (Babies After SCOPE: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints).

SCOPE: SCOPE is a prospective, multicentre cohort study. Its main objective is to develop a screening test to predict preeclampsia, spontaneous preterm birth and infants born small for gestational age (SGA). Inclusion criteria included healthy nulliparous women with singleton pregnancies, with recruitment taking place between November 2004 and January 2011 in Auckland, New Zealand, Cork, Ireland, Adelaide, Australia, and London, Leeds and Manchester, United Kingdom. Each woman was interviewed at 15 ± 1 weeks' gestation through hospital antenatal clinics, general practitioners, obstetricians, community midwives, and self-referral in response to advertisements or recommendations of friends, as previously described [21,22]. Women were excluded from the study if they were considered to be at high risk of preeclampsia, spontaneous preterm birth or delivery of an SGA infant because of a previous medical condition, gynaecological history, ≥3 previous miscarriages, ≥3 terminations of pregnancy, or had received interventions, (for example, aspirin), that may modify the pregnancy outcome.

SCOPE participants were interviewed and examined by SCOPE research midwives at 15 ± 1 weeks' gestation and all pregnancy information and pregnancy outcome data were collected prospectively. Data were entered on a secure internet accessed central database with a complete audit trail (MedSciNet) at the time of interview. All data entries were individually checked for errors (including data entry errors in the lifestyle questionnaire) and a customised software program to detect any systematic data entry errors was used.

BASELINE: BASELINE is the first longitudinal birth cohort study in Ireland. All women who participated in the Cork cohort of the SCOPE study were informed about the BASELINE birth cohort and were invited to enrol their infants in the study. Written informed consent was requested at 20 weeks' gestation and infants were registered to the Cork BASELINE birth cohort if consent was provided [23]. Fig. A1 in the Appendix shows the flow of mother-infant pairs through the SCOPE and BASELINE studies.

Exposure

Alcohol consumption

Data on alcohol consumption were obtained from the Irish SCOPE study. Alcohol consumption was reported as units consumed per week. During the 15 weeks' gestation interview, women were asked "were you drinking alcohol prior to pregnancy?", "were you drinking alcohol earlier in the pregnancy?" and finally "are you still drinking alcohol?" If the women answered yes to any of the above, then the amount of alcohol was quantified. Women who confirmed that they had consumed alcohol during pregnancy, were asked when they stopped drinking.

One unit of alcohol was defined as 8 g or 10 ml (1 dl) of pure alcohol. The number of units was calculated by multiplying the volume drunk (mls) × % of alcohol (by volume) and dividing by 1000. One unit of alcohol was equivalent to one glass of wine (approximately 125 ml); a single nip/shot of spirits (approximately 35 ml); one small glass of sherry or half a pint of regular strength lager. A can or small bottle of regular strength beer (300–330 ml, 4–5% alcohol) was equivalent to 1.5 units of alcohol and a bottle of alcohol pop was equivalent to 2 units of alcohol.

Binge alcohol consumption was defined as ≥ 6 units of alcohol per drinking session. Examples of how alcohol consumption was estimated are; if the participant had only 1 drink per month, then 0.25 units per week was recorded, 2 drinks per month was recorded as 0.5 units per week. If the patient had 1 binge drinking session (≥6 units)/month and no other drinking during the month then 6 units/4 weeks = 1.5 units per week was recorded. If the participant had a regular alcohol intake of 4 units per week plus 1 episode of binge drinking per month the total number of units per month was divided by 4 i.e. (16 + 6)/4 = 5.5 units per week. The timing of cessation of alcohol consumption was also recorded. Alcohol intake was classified as follows for the purpose of this study: occasional (1–2 units/week), low (3–7 units/week), moderate (8–14 units/week) and heavy (>14 units/week). In addition, information about the number of binges before pregnancy and prior to 15 weeks' gestation was collected and recorded separately.

Outcomes

Neurodevelopmental outcomes

Data on neurodevelopmental outcomes were obtained from BASELINE. At two years and five years of age all children were invited to be screened using the Child Behaviour Checklist 1.5–5. The Child Behaviour Checklist is part of the Achenbach System of Empirically Based Assessment. Its aim is to detect emotional and behavioural problems in children [24], while its reliability and validity have been objectively demonstrated [25]. Moreover, it has been used in a previous epidemiological study investigating the association between prenatal alcohol exposure and child neurodevelopment [26]. There are seven syndrome scales: Emotionally Reactive; Anxious/Depressed; Somatic Complaints;

Withdrawn; Attention Problems; Aggressive Behaviour, and Sleep Problems. These scales group into either internalizing (formed by combining Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn) or externalizing traits (formed by combining Attention Problems and Aggressive Behaviour). Sleep Problems is treated as a separate syndrome, while a scaled composite score (derived from the seven syndromes) is used to give each infant an overall 'total' score with lower scores indicating more positive outcomes [24]. The infant's primary caregiver completed the questionnaire.

At five years of age the children were also assessed using the Kaufman Brief Intelligence test, a screener for intellectual abilities which is administered by trained professionals. This test has high correlations with other widely used measures of intelligence including the Wechsler Intelligence Scales [27,28]. It consists of three subtests: expressive vocabulary, verbal knowledge and matrices. These raw scores are then converted to a verbal standard score and a non-verbal standard score, each with a mean of 100, standard deviation of 15 and range from 40 to 160 with higher scores indicating more positive outcomes. The verbal and non-verbal standard scores are also converted to a composite IQ score.

Covariates

Only covariates which we believed to be associated with the exposure and outcome were included in our model. We excluded any variables that might be potential mediators of the association. Therefore, we controlled for the following potential confounding factors: maternal age, maternal education, marital status, family income, maternal body mass index (BMI), maternal smoking status at 15 weeks gestation, and infant sex. Where a variable had missing data, the data were added as a separate category using the missing data indicator method [29].

Statistical analysis

Data were analysed using Stata/MP 14.2. Mother and child characteristics relating to maternal alcohol consumption in the first trimester and neurodevelopmental outcomes were reported. In all the statistical tests, the reference group were women with either no alcohol intake prior to or during pregnancy or women with no binge drinking prior to or during pregnancy. The distribution of outcome variables was assessed using histograms and as a result, outcomes were log transformed using the natural log in order to approximate a normal distribution. Crude and adjusted linear regression were used to analyse the association between maternal alcohol consumption and continuous outcome measures among those who completed neurodevelopmental assessment at two years, five years, or both. Adjusted models controlled for maternal age, maternal education, marital status, family income, maternal body mass index (BMI), maternal smoking status at 15 weeks gestation, and infant sex.

Maternal alcohol consumption before and during pregnancy: First, we examined the association between maternal alcohol consumption during the three months prior to conception and neurodevelopmental outcomes at 2 and 5 years. A three-category variable was created: 1) abstinent (reference group); 2) occasional-low (1–7 units/week); and moderate-heavy (≥8 units/week). Second, we examined the effect of maternal alcohol consumption in the first trimester. Alcohol consumption in the first trimester was represented as a three-category variable: 1) abstinent (reference group); 2) occasional-low (1–7 units/week); and 3) moderate-heavy (≥8 units/week).

Binge alcohol consumption before and during pregnancy: First, we examined the effect of binge drinking in the three months prior to conception using a three category variable: 1) no binge drinking (reference group); 2) 1–3 episodes binge drinking; and 3) ≥ 4 episodes binge drinking. Second, we examined the effect of binge drinking during pregnancy (before 15 weeks' gestation) by generating a binary variable; 1) women with no history of binging during pregnancy (reference group); and 2) binge drinking in pregnancy but quit before 15 weeks' gestation. Due to small numbers, we could not examine the effect of continuing to binge at 15 weeks' gestation on neurodevelopmental outcomes.

Sensitivity analyses: We examined the association of maternal alcohol consumption status at 15 weeks' gestation by generating a three-category variable; 1) abstinent (reference group); 2) quit before 15 weeks' gestation; and 3) continued at 15 weeks' gestation. Additionally, we examined the effect of total units of alcohol consumed in the first 15 weeks' gestation on neurodevelopmental outcomes at 2 and 5 years. Finally, we compared maternal and child characteristics between those who completed neurodevelopmental assessments at two and five years compared to those who did not.

Results

A total of 1537 mothers were recruited to the BASELINE study from SCOPE (eFig. 1), of which 1507 had data on maternal alcohol consumption. Mother and child characteristics are outlined in Table 1 according to maternal alcohol consumption in the first trimester. Abstaining from alcohol in the first trimester was reported among 19.17% (n = 289) of women, while 59% (n = 884) reported occasional-low alcohol consumption and 22% (n = 334) moderate-heavy alcohol consumption. Overall, 14.27% (n = 215) of women reported 1–3 episodes of binge alcohol consumption in the three months pre-pregnancy, and 44.53% (n = 671) reported ≥ 4 binge episodes in the three months pre-pregnancy, while 44.86% (n = 676) reported binge episodes in pregnancy but quit before 15 weeks' gestation.

Alcohol consumption before pregnancy

Child Behaviour Checklist: At age two years, adjusted results suggested no significant difference in the internalizing, externalizing or total Child Behaviour Checklist scores of children, regardless of maternal pre-pregnancy alcohol consumption (Table 2). At age five years, children of mothers who reported occasional-low alcohol consumption per week pre-pregnancy had a significant reduction in log externalizing (i.e. Attention Problems and Aggressive Behaviour) Child Behaviour Checklist score only (-0.26, 95% CI: −0.01, −0.52) compared to children of mothers who reported abstaining from alcohol.

Kaufman Brief Intelligence Test: Children whose mothers reported moderate-high levels of alcohol consumption per week pre-pregnancy had a significant reduction in log verbal standard score (-0.03, 95% CI: −0.001, −0.06) and composite IQ score (-0.02, 95% CI: −0.05, −0.0004) at age five years, while no significant association was observed for non-verbal standard score (Table 2).

Alcohol consumption during pregnancy

Child Behaviour Checklist: At age two years, children whose mothers reported moderate-high levels of alcohol consumption per week in the first trimester had a significantly lower log internalizing (i.e. formed by combining Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn) score (-0.25, 95% CI: 0.07, −0.43). However, no significant difference in log externalizing or total scores were observed, in comparison to children of mothers who reported abstaining from alcohol. Similarly, no significant differences were observed at age five years.

Kaufman Brief Intelligence Test: Adjusted results suggested no significant association between occasional-low or moderate-heavy alcohol consumption per week in the first trimester and log verbal standard, non-verbal standard and composite IQ scores at age five years (Table 3).

Binge alcohol consumption before pregnancy

Child Behaviour Checklist: At age two and five years, no significant

Table 1
Mother and child characteristics relating to maternal alcohol consumption in the first trimester and neurodevelopmental outcomes among SCOPE-BASELINE participants.

	Abstinent N = 289	Occasional-Low Alcohol Consumption (1–7 units/week) N = 884	Moderate-Heavy Alcohol Consumption (≥8 units/week) N = 334
Maternal age (years) n (%)			
18–24	28 (9.8)	79 (9.0)	53 (16.1)
25–29	94 (33.0)	263 (29.8)	104 (31.5)
30–34	125 (43.9)	420 (47.6)	137 (41.5)
35–45	38 (13.3)	120 (13.6)	36 (10.9)
Maternal education n (%)			
>12 years	276 (95.5)	866 (97.9)	319 (95.5)
<12 years	13 (4.5)	18 (2.1)	15 (4.5)
Marital status n (%)			
Married/stable relationship	250 (86.5)	777 (87.9)	266 (79.6)
Single/separated/ divorced	10 (3.5)	29 (3.3)	33 (9.9)
Missing	29 (10.0)	78 (8.8)	35 (10.5)
Family income n (%)			
<€25,000	17 (5.9)	61 (6.9)	47 (14.2)
€25-€74,999	133 (46.3)	308 (34.8)	127 (38.5)
€75-124,999	112 (39.1)	404 (45.7)	122 (37.0)
>€125,000	25 (8.7)	111 (12.6)	34 (10.3)
Maternal body mass index n (%)			
Underweight/ normal weight	176 (60.90)	548 (62.0)	180 (53.9)
Overweight	71 (24.5)	240 (27.1)	107 (32.0)
Obese	42 (14.5)	96 (10.9)	47 (14.1)
Maternal Smoking Status n (%)			
Non-smoker	257 (89.0)	690 (78.1)	170 (50.9)
Quit during pregnancy	16 (5.5)	130 (14.7)	103 (30.8)
Smoked in first trimester	16 (5.5)	64 (7.2)	61 (18.2)
Infant Sex n (%)			
Male	134 (46.3)	447 (50.5)	177 (52.9)
Female	155 (53.7)	437 (49.5)	157 (47.1)
Small for gestational age n (%)			
Yes	24 (8.3)	76 (8.6)	42 (12.6)
CBCL at 2 years (n = 941)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Internalizing score	4 (6)	4 (5)	3 (5)
Externalizing score	8 (7)	8 (8)	8 (8)
Total score	21 (21)	20 (18)	18 (18)
CBCL at 5 years (n = 737)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Internalizing score	4 (5.5)	5 (7)	4 (8)
Externalizing score	5 (8)	6 (8)	5 (8)
Total score	16 (18)	18 (19)	16 (22)
Kaufman BIT at 5 years (n = 734)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Verbal standard score	109 (13)	109 (13)	107 (14)
Non-verbal standard score	97 (10)	100 (10)	98 (10)
Composite IQ score	104 (12)	104 (11)	104 (11)

If missing data > 5%, number (%) of missing data reported.
Abbreviations: CBCL, Child Behaviour Checklist. Kaufman BIT, Kaufman Brief Intelligence test. IQR, interquartile range.

associations were observed between number of binge episodes in the three months pre-pregnancy and internalizing, externalizing or total Child Behaviour Checklist scores of children.

Kaufman Brief Intelligence Test: Similar to above, there was no significant associations between number of binge episodes in the three months pre-pregnancy and verbal standard, non-verbal standard and composite IQ scores of children at age five years (Table 4).

Table 2
The association between pre-pregnancy maternal alcohol consumption (units of alcohol consumed per week in the 3 months pre-pregnancy) and neurodevelopmental outcomes at 2 and 5 years among SCOPE-BASELINE participants.

	Abstinent	Occasional-Low Alcohol Consumption (1–7 units/week)		Moderate-Heavy Alcohol Consumption (≥8 units/week)	
Log transformed outcomes		Crude Estimate (95% CI)	Adjusted Estimate[1] (95% CI)	Crude Estimate (95% CI)	Adjusted Estimate[1] (95% CI)
CBCL at 2 years	N = 86	N = 739		N = 116	
Internalizing score	Ref	−0.13 (-0.32, 0.04)	−0.09 (-0.27, 0.09)	−0.01 (-0.25, 0.21)	−0.07 (-0.31, 0.16)
Externalizing score	Ref	−0.07 (-0.25, 0.10)	−0.07 (-0.25, 0.10)	0.03 (-0.18, 0.26)	−0.06 (-0.30, 0.17)
Total score	Ref	−0.14 (-0.32, 0.03)	−0.12 (-0.30, 0.05)	0.02 (-0.19, 0.25)	−0.04 (-0.27, 0.19)
CBCL at 5 years	N = 61	N = 589		N = 87	
Internalizing score	Ref	0.02 (-0.22, 0.26)	0.01 (-0.23, 0.25)	0.05 (-0.24, 0.34)	−0.06 (-0.37, 0.23)
Externalizing score	Ref	**−0.28 (-0.03, −0.53)**	**−0.26 (-0.01, −0.52)**	−0.20 (-0.51, 0.10)	−0.27 (-0.59, 0.04)
Total score	Ref	−0.17 (-0.42, 0.06)	−0.16 (-0.40, 0.08)	−0.05 (-0.35, 0.24)	−0.13 (-0.44, 0.17)
Kaufman BIT at 5 years	N = 60	N = 587		N = 87	
Verbal standard score	Ref	−0.001 (-0.02, 0.02)	−0.001 (-0.02, 0.02)	**−0.03 (-0.01, −0.07)**	**−0.03 (-0.001, −0.06)**
Non-verbal standard score	Ref	−0.007 (-0.03, 0.01)	−0.007 (-0.03, 0.01)	−0.01 (-0.04, 0.01)	−0.01 (-0.04, 0.01)
Composite IQ score	Ref	−0.002 (-0.02, 0.01)	−0.002 (-0.02, 0.02)	**−0.03 (-0.01, −0.05)**	**−0.02 (-0.05, −0.0004)**

Abbreviations: CBCL, Child Behaviour Checklist. Kaufman BIT, Kaufman Brief Intelligence test.
[1] Adjusted for maternal age, maternal education, marital status, family income, maternal body mass index (BMI), maternal smoking status at 15 weeks gestation, and infant sex.

Binge alcohol consumption during pregnancy

Child Behaviour Checklist: At age two and five years, there were no significant differences in Child Behaviour Checklist scores of children of women who reported binge drinking during the first trimester of pregnancy but quit before 15 weeks' gestation compared to those who did not binge alcohol during pregnancy.

Kaufman Brief Intelligence Test: Similar to above, there were no significant differences in Kaufman Brief Intelligence Test scores of children of women who reported binge drinking during the first trimester of pregnancy but quit before 15 weeks' gestation (Table 5).

Sensitivity analysis

There was no significant difference observed between Child Behaviour Checklist scores or Kaufman Brief Intelligence Test scores of either the children of women who quit drinking before 15 weeks' gestation or the children of women who continued to drink at 15 weeks' gestation when compared to those who abstained from alcohol in pregnancy (Table A1 in the Appendix). Similarly, there was no significant association between total units of alcohol consumed in first 15 weeks' gestation and Child Behaviour Checklist scores or Kaufman Brief Intelligence

Table 3
The association between maternal alcohol consumption (units of alcohol consumed per week in the first trimester) and neurodevelopmental outcomes at 2 and 5 years among SCOPE-BASELINE participants.

Log transformed outcomes	Abstinent	Occasional-Low Alcohol Consumption (1–7 units/week)		Moderate-Heavy Alcohol Consumption (≥8 units/week)	
		Crude Estimate (95% CI)	Adjusted Estimate[1] (95% CI)	Crude Estimate (95% CI)	Adjusted Estimate[1] (95% CI)
CBCL at 2 years	N = 173	N = 574		N = 194	
Internalizing score	Ref	−0.03 (-0.17, 0.10)	−0.01 (-0.16, 0.12)	**−0.17 (-0.006, −0.35)**	**−0.25 (-0.07, −0.43)**
Externalizing score	Ref	−0.04 (-0.18, 0.09)	−0.05 (-0.19, 0.08)	−0.001 (-0.17, 0.16)	−0.06 (-0.24, 0.11)
Total score	Ref	−0.05 (-0.18, 0.08)	−0.05 (-0.18, 0.08)	−0.13 (-0.30, 0.02)	−0.21 (-0.04, −0.38)
CBCL at 5 years	N = 132	N = 443		N = 162	
Internalizing score	Ref	0.01 (-0.15, 0.19)	0.004 (-0.16, 0.17)	−0.0002 (-0.20, 0.20)	−0.11 (-0.33, 0.10)
Externalizing score	Ref	−0.03 (-0.21, 0.15)	−0.03 (-0.21, 0.14)	0.04 (-0.17, 0.26)	−0.005 (-0.22, 0.21)
Total score	Ref	−0.01 (-0.19, 0.16)	−0.02 (-0.20, 0.14)	−0.06 (-0.27, 0.14)	−0.14 (-0.36, 0.06)
Kaufman BIT at 5 years	N = 131	N = 442		N = 161	
Verbal standard score	Ref	−0.004 (-0.02, 0.01)	−0.001 (-0.02, 0.01)	**−0.02 (-0.002, −0.04)**	−0.01 (-0.04, 0.004)
Non-verbal standard score	Ref	0.002 (-0.01, 0.01)	0.003 (-0.01, 0.02)	−0.01 (-0.03, 0.008)	−0.01 (-0.03, 0.007)
Composite IQ score	Ref	0.00004 (-0.01, 0.01)	0.002 (-0.01, 0.01)	−0.01 (-0.03, 0.001)	−0.01 (-0.03, 0.006)

Abbreviations: CBCL, Child Behaviour Checklist. Kaufman BIT, Kaufman Brief Intelligence test.
[1] Adjusted for maternal age, maternal education, marital status, family income, maternal body mass index (BMI), maternal smoking status at 15 weeks gestation, and infant sex.

Table 4
The association between pre-pregnancy maternal binge alcohol consumption (number of times binging occurred in the 3 months pre-pregnancy) and neurodevelopmental outcomes at 2 and 5 years among SCOPE-BASELINE participants.

Log transformed outcomes	No binge alcohol consumption	1–3 episodes binge drinking		≥4 episodes binge drinking	
		Crude Estimate (95% CI)	Adjusted Estimate[1] (95% CI)	Crude Estimate (95% CI)	Adjusted Estimate[1] (95% CI)
CBCL at 2 years	N = 402	N = 143		N = 396	
Internalizing score	Ref	−0.01 (-0.17, 0.14)	0.02 (-0.13, 0.18)	−0.06 (-0.18, 0.05)	−0.10 (-0.22, 0.01)
Externalizing score	Ref	−0.12 (-0.27, 0.03)	−0.10 (-0.25, 0.04)	−0.04 (-0.15, 0.07)	−0.10 (-0.22, 0.01)
Total score	Ref	0.02 (-0.12, 0.18)	0.05 (-0.09, 0.21)	−0.03 (-0.14, 0.08)	−0.08 (-0.20, 0.03)
CBCL at 5 years	N = 295	N = 116		N = 326	
Internalizing score	Ref	0.14 (-0.04, 0.33)	0.16 (-0.02, 0.35)	0.08 (-0.05, 0.22)	0.007 (-0.13, 0.15)
Externalizing score	Ref	−0.03 (-0.23, 0.16)	0.02 (-0.17, 0.22)	0.03 (-0.10, 0.18)	−0.01 (-0.16, 0.14)
Total score	Ref	0.08 (-0.10, 0.27)	0.12 (-0.06, 0.31)	0.04 (-0.09, 0.18)	−0.001 (-0.14, 0.14)
Kaufman BIT at 5 years	N = 294	N = 115		N = 325	
Verbal standard score	Ref	0.008 (-0.01, 0.02)	0.006 (-0.01, 0.02)	−0.01 (-0.02, 0.004)	−0.005 (-0.02, 0.01)
Non-verbal standard score	Ref	−0.003 (-0.02, 0.01)	−0.003 (-0.02, 0.01)	−0.01 (-0.02, 0.002)	−0.01 (-0.02, 0.003)
Composite IQ score	Ref	0.002 (-0.01, 0.01)	0.001 (-0.01, 0.01)	−0.01 (-0.02, −0.001)	−0.01 (-0.02, 0.002)

Abbreviations: CBCL, Child Behaviour Checklist. Kaufman BIT, Kaufman Brief Intelligence test.
[1] Adjusted for maternal age, maternal education, marital status, family income, maternal body mass index (BMI), maternal smoking status at 15 weeks gestation, and infant sex.

Test scores (Table A2 in the Appendix). Finally, there were no significant differences in alcohol consumption between those who completed neurodevelopmental assessments at both timepoints compared to those who did not. Additionally, distributions of maternal and child characteristics were broadly similar with some minor differences for socioeconomic position indicators which were slightly higher among those who completed neurodevelopmental assessments at age two and five years (Table A3 in the Appendix).

Discussion

This study has examined the association between maternal alcohol consumption before and during pregnancy on neurodevelopmental outcomes at age two and five years (using the Child Behaviour Checklist and Kaufman Brief Intelligence Test) as well as examining the effects of binge drinking and timing of binge alcohol exposure.

We did not find strong evidence of associations between maternal alcohol consumption and adverse neurodevelopmental outcomes overall. Although few associations were observed, the direction of effect was often inconsistent, and it is likely that these associations may have occurred due to chance as a result of multiple testing. For example, pre-pregnancy occasional-low alcohol consumption per week showed a protective association in externalizing Child Behaviour Checklist score, while conversely moderate-high levels of alcohol consumption per week showed a significant reduction in Kaufman Brief Intelligence Test verbal standard score and composite IQ score at age five years. Additionally, in the first trimester, moderate-high levels of alcohol consumption showed a protective effect in internalizing Child Behaviour Checklist score at age two years. With regards to pre-pregnancy binge alcohol consumption, no significant associations were observed between number of binge episodes in the three months prior to conception and Child Behaviour Checklist or Kaufman Brief Intelligence Test scores. Similarly, binge drinking during the first trimester of pregnancy but quit before 15 weeks' gestation was not significantly associated with Child Behaviour Checklist or Kaufman Brief Intelligence Test scores.

These inconsistent results are reflected in much of the available literature on alcohol consumption in pregnancy and neurodevelopmental outcomes. While some studies have shown an association between light-moderate alcohol consumption and adverse childhood neurodevelopmental outcomes [30], others did not demonstrate an association [8,16,31], or indeed have demonstrated a protective association [18,32]. There is more consistency in previous literature on the association between moderate-high levels of alcohol consumption and adverse outcomes in children, which somewhat agrees with our finding that children's IQ scores decrease modestly in those whose mothers who

Table 5
The association between maternal binge alcohol consumption before 15 weeks' gestation and neurodevelopmental outcomes at 2 and 5 years among SCOPE-BASELINE participants.

Log transformed outcomes	No binge alcohol consumption in pregnancy	Binged in pregnancy but quit before 15 weeks' gestation	
		Crude Estimate (95% CI)	Adjusted Estimate[1] (95% CI)
CBCL at 2 years	N = 543	N = 396	
Internalizing score	Ref	−0.03 (-0.13, 0.07)	−0.08 (-0.19, 0.03)
Externalizing score	Ref	0.005 (-0.10, 0.11)	−0.04 (-0.16, 0.06)
Total score	Ref	−0.001 (-0.10, 0.10)	−0.06 (-0.16, 0.04)
CBCL at 5 years	N = 413	N = 323	
Internalizing score	Ref	0.05 (-0.07, 0.18)	−0.01 (-0.15, 0.11)
Externalizing score	Ref	0.02 (-0.10, 0.16)	−0.06 (-0.16, 0.04)
Total score	Ref	0.008 (-0.12, 0.14)	−0.04 (-0.18, 0.08)
Kaufman BIT at 5 years	N = 412	N = 321	
Verbal standard score	Ref	−0.008 (-0.02, 0.005)	−0.003 (-0.01, 0.01)
Non-verbal standard score	Ref	−0.01 (-0.02, 0.002)	−0.01 (-0.02, 0.001)
Composite IQ score	Ref	−0.009 (-0.02, 0.002)	−0.005 (-0.01, 0.006)

Abbreviations: CBCL, Child Behaviour Checklist. Kaufman BIT, Kaufman Brief Intelligence test.

[1] Adjusted for maternal age, maternal education, marital status, family income, maternal body mass index (BMI), maternal smoking status at 15 weeks gestation, and infant sex.

reported moderate-high levels of alcohol consumption per week [33–36].

With regard to binge drinking, this study did not demonstrate any significant association between binge drinking pre-pregnancy or during early pregnancy, on childhood neurodevelopmental outcomes. This is in contrast to other studies which have investigated the effect of binge drinking in pregnancy [18,37]. These conflicting results are possibly due to differences in timing of alcohol consumption as binge drinking in the second and third trimesters has been shown to increase the risk of child mental health issues [18,37].

Furthermore, different measures of neurodevelopmental outcomes, varying degrees of adjustment for potential confounding factors and ranges in follow-up, and different reporting methods may have contributed to the inconsistent findings examining a maternal alcohol consumption-neurodevelopmental outcome relationship [18,38–40].

Strengths and limitations

This study had several strengths. First, detailed information about the timing and degree of alcohol consumption was recorded using a standardised approach to measure alcohol intake [41]. Second, data on neurodevelopmental outcomes were collected prospectively; therefore, recall bias was less likely to influence results. Third, the Child Behaviour Checklist and the Kaufman Brief Intelligence Test are reliable and valid tests which are recognised as appropriate screeners for neurodevelopmental difficulties and constitute a broad assessment of a child's neurodevelopmental functioning [27,42]. Finally, a limitation of many studies examining a prenatal alcohol exposure-neurodevelopmental relationship was the lack of adjustment for socioeconomic status (e.g. income or education) [18]. We had access to a wide range of potential confounding factors allowing us to adjust for several covariates including maternal age, maternal education, marital status, family income, maternal BMI, maternal smoking status at 15 weeks' gestation, and infant sex.

Several limitations should also be noted. First, as with all observational research, residual confounding cannot be ruled out. Potential confounders that we did not have access to included parental IQ, familial environment and drug use, all of which have been shown to be important predictors of childhood cognition [19]. Second, recall bias may have led to under reporting the amount of alcohol consumed as no objective test or measure exists to record alcohol exposure over a long period of time. Furthermore, social stigma against drinking during pregnancy may contribute to misclassification of the exposure, which could potentially bias results towards the null [18,43]. However, all data were collected in a standardised manner by trained research midwives in an effort to limit this potential bias. Third, our study specifically examines alcohol consumption prior to conception and in early pregnancy and does not provide habitual drinking data throughout the whole of pregnancy. While the first trimester is a crucial time for brain development, and usually the most susceptible period to teratogenesis, further research using larger sample sizes should be conducted to examine the effect of alcohol consumption (including binge drinking) after 15 weeks' gestation [44]. Fourth, loss to follow up in this study may have led to selection bias as some minor differences for socioeconomic position indicators were observed between those who participated in the study at age two and five years and those who did not. For example, children with neurodevelopmental outcome data at both time points were more likely to be born to older, married women with a higher family income than those who did not participate in the study at both timepoints. However, the distribution of variables for alcohol consumption were broadly similar between the groups suggesting a lower likelihood of selection due to missing data. Nonetheless, this may have biased our results towards the null as previous evidence suggests that children with behavioural disorders are more prone to loss to follow-up [45].

Conclusion

We did not find strong evidence of associations between pre-pregnancy and early pregnancy maternal alcohol consumption and adverse neurodevelopmental outcomes at age two and five years overall. While few associations were observed, it is likely that many of these occurred as a result of chance given the large number of tests conducted. Although strong associations were not observed in this study, abstinence from alcohol during pregnancy is still considered the safest option considering its effects on other adverse outcomes. As this study was restricted to examining the effects of alcohol consumption before 15 weeks' gestation, further research examining alcohol consumption (including binge drinking) beyond 15 weeks' gestation and neurodevelopmental outcomes is needed to examine the potential effect of alcohol consumption in later pregnancy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author Agreement

All authors agreed with the content and gave explicit consent to submit manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2022.05.034.

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