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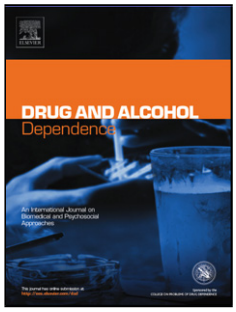

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Maternal and partner prenatal alcohol use and infant cognitive development*

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Highlights

- A large pregnancy cohort study assessed alcohol use by mothers and partners.
- No observable effects of prenatal alcohol exposure on infant cognition.
- Alcohol use by partners showed similar patterns of association.
- Findings were robust using multiple methods to control for confounding.
- Interaction between alcohol, social factors and infant development likely.

Abstract

Background: Teratogenicity of heavy prenatal alcohol exposure is established, but uncertainty remains regarding the impact of moderate alcohol exposure on cognitive deficits in infants. Separating in utero effects from environmental confounding is a challenge for observational studies; consideration of alcohol use by partners as well as mothers may help clarify this. This study examined associations between prenatal alcohol use by both mothers and their partners and infant cognitive developmental outcomes at 12-months.

Methods: Pregnant women (n=1331) and their partners (n=699) were recruited from antenatal clinics of three metropolitan public hospitals in Australia, and completed detailed interviews about alcohol consumptions throughout pregnancy. Infants were assessed with the Bayley Scales of Infant Development - Third edition (Bayley) at 12-months of age.

Results: Alcohol use during pregnancy was reported by 65.7% of mothers and 84.1% of partners. Using multiple methods to adjust for confounding factors, no evidence for impaired

cognitive ability associated with alcohol use by mothers or their partners was observed. Children born to women who drank low-levels of alcohol had slightly higher Bayley cognitive scores than those born to abstaining women. There was some evidence for an interaction between sociodemographic factors and prenatal alcohol exposure on infant cognitive outcomes.

Conclusion: This finding corroborates existing evidence to suggest there are no detrimental effects to infant cognitive development at 12-months of age following low-level prenatal alcohol exposure. Future prospective studies involving families of a broad range of backgrounds would be informative to clarify interaction between alcohol exposure and environmental factors on developmental outcomes.

Keywords: alcohol; pregnancy; infant development; cognition; prenatal alcohol exposure; fetal alcohol syndrome

1. Introduction

Alcohol has been established as a teratogen and may produce central nervous system deficits at high levels of exposure, yet uncertainty remains regarding the association between low-level prenatal alcohol exposure and impaired cognitive development. Most large-scale studies fail to detect any observable effect (Alati et al., 2008; Forrest et al., 1991; Kelly et al., 2009; Kesmodel et al., 2012; O'Callaghan et al., 2007; Williams Brown et al., 2010). A recent meta-analysis found evidence for lower IQ scores among children exposed to binge-level alcohol exposure, yet this effect was no longer statistically significant when only studies considered 'high-quality' were included (Flak et al., 2014). The same meta-analysis found a small but significant counterintuitive effect in with low-level exposure was associated with higher IQ

scores in childhood (Flak et al., 2014). No association was found between binge or moderate exposure and impairment in other cognitive domains including attention, verbal ability, mathematical ability at school, language development, or visuo-spatial ability (Flak et al., 2014 supplement). Some studies, however, have shown the apparent 'positive' effect of low-level alcohol exposure on IQ is mitigated with appropriate adjustment for confounders such as maternal socioeconomic status and education (Brown et al., 2010; Jacobson et al., 1993; Kelly et al., 2009).

A major challenge facing research in this area is that systematic differences exist between women who drink alcohol during pregnancy and women who are non-drinkers on factors that are independently associated with child developmental outcomes. Furthermore, comparison of two systematic reviews reveals divergent sets of characteristics between those whose children have a diagnosis of FASD compared with those who tend to drink alcohol in pregnancy – an "epidemiological puzzle" (Meurk et al., 2014). A systematic review found that apart from pre-pregnancy alcohol consumption, older age, higher educational attainment, higher parity, being employed, and higher income were consistent predictors of increased likelihood to drink (Skagerström, et al., 2013). Many of these factors describe a population of overall advantaged women whose offspring are likely to be raised in enriched environments. In contrast, a systematic review found that lower educational attainment, being single during pregnancy, unemployment, residing in a remote area, and lower income were all associated with having a child with FASD (Esper and Furtado, 2014). This is in line with the common finding that Fetal Alcohol Spectrum Disorders (FASD) are concentrated in disadvantaged, low SES populations (Abel, 1995; Abel and Hannigan, 1995; Burns et al., 2013; Chudley, 2008; Kvigne et al., 2003; Lange et al., 2013; May et al., 2000; May et al., 2004; May et al., 2009; Meurk et al., 2014).

Older maternal age, substance use, smoking, and experience of trauma or violence were common risk factors for both FASD (Esper and Furtado, 2014) and prenatal alcohol exposure (Skagerström et al., 2013). At an epidemiological level, these divergent sets of demographic predictors suggest some interaction between prenatal alcohol exposure and environmental factors in producing deficits. For this reason, it is critical that studies attempting to assess impacts of prenatal alcohol exposure collect comprehensive data on psychosocial and demographic factors and include these in models.

Random allocation to an alcohol exposure condition in pregnancy is impossible; therefore, confounding in observational studies is dealt with statistically by inclusion of covariates in regression models. Propensity Score Matching is an alternative technique, used when randomisation to conditions is not possible, which ensures baseline characteristics are consistent between groups and any differences between them attributable to 'treatment' or exposure effects (Austin, 2011; Rosenbaum and Rubin, 1985). The Millennium Cohort Study in the UK observed no difference in cognitive performance between children with low-level prenatal alcohol exposure and those not exposed, and this was regardless of whether ordinary least-squares regression or propensity score matching was used to account for bias (Kelly et al., 2013).

One method by which the impact of shared postnatal family environment can be disentangled from that of the intrauterine environment is to compare magnitude of associations between maternal alcohol use and offspring outcomes with that of alcohol use by partners (Alati et al., 2008; Smith, 2008). Some studies using animal models suggest paternal effects of pre-conception alcohol use on offspring, including lower birth weight (Abel, 2004; Meek et al., 2007), and some suggest cognitive deficits in early life (Abel, 2004). In human research, one

prospective cohort study found that while moderate alcohol use by mothers predicted poorer language ability in children, this effect was no greater in magnitude than the association with alcohol use by fathers (Alati et al., 2008). However, a subsequent follow-up of the same sample found a specific effect of frequent, heavy alcohol consumption by mothers and associated lower academic abilities in offspring (Alati et al., 2013). Few other prospective longitudinal studies have accounted for the effect of partner alcohol consumption when studying effects of prenatal alcohol exposure on child development.

The aims of this paper were to (1) examine the relationship between prenatal alcohol exposure across four time points during pregnancy on infant cognitive development at 12 months of age and (2) assess the relationship between alcohol consumption by partners and infant cognitive development.

2. Methods

2.1 Participants

Data were drawn from The Triple B Study (Bumps, Babies and Beyond), a prospective pregnancy cohort study. This study was approved by the Sydney Local Health District Research Ethics and Governance Office, and this was ratified by Ethics Committees at participating hospital and university sites. Pregnant women were recruited between 2008 and 2013 from waiting rooms of antenatal clinics at metropolitan public hospitals in New South Wales and Western Australia. All women in waiting rooms on designated recruitment days, with even coverage across different days of the week, were approached by researchers and screened for eligibility. Eligibility criteria included being at least 16 years of age, having no major known medical complications (mother or fetus), intention of mother or both parents to be the primary caregiver/s, intention to reside in Australia for at least the child's first year, and sufficient

literacy in English. Informed consent was obtained from women at the point of recruitment, and consent for infants' participation was obtained from parents at the first postpartum assessment.

Of 4293 eligible women, 1623 participated. Detailed description of the sample is published in a cohort profile paper separately (Hutchinson et al., in press), including comparisons with respect to Australian population demographics. The present study includes women (n=1331) whose infants completed the 12-month Bayley infant development assessment. Partners of 699 of these mothers participated and were also included. In all but 26 cases, including 18 who were female, partners were biologically related to the baby. For a portion of the sample, demographic data on partners who did not themselves participate was obtained indirectly from mothers. Partners who participated in the study were slightly younger with higher educational attainment than non-participating partners, but they did not differ in terms of employment status, same sex relationship status, or proportion of Aboriginal or Torres Strait Islander origin (see Hutchinson et al., in press, for more details). In the case of twins or triplets, only one child of each mother was randomly selected to be included in analyses.

2.2 Measures

2.2.1 Alcohol use. Maternal prenatal alcohol consumption was assessed at phone interviews during the first and second trimesters and retrospectively at 8-weeks postpartum to capture alcohol consumption across the entire third trimester. Interviewers possessed, at a minimum, an undergraduate degree in Psychology or a related discipline. Recruitment and training of examiners and interpretation of scores was carried out under the supervision of two clinical psychologists. All researchers were trained by senior investigators, and regular reliability checks ensured consistency in administration and recording of responses between team members. No researcher was involved in any way with the clinical care of participants, and this was

emphasized at study enrollment. Alcohol use in Trimester 1 was calculated separately for the first and second six weeks of the trimester as a proxy for consumption pre- and post-awareness of pregnancy. This was to account for previous observations from this sample that significant change to alcohol use occurred following recognition of pregnancy (McCormack et al., 2017a). Alcohol use by partners was recorded at baseline phone interviews during the third trimester, where past-month alcohol consumption was recorded. Partners were given the option of completing baseline interviews in self-complete format if they were unable to participate in a phone interview. Of 755 participating partners, 187 opted to complete the self-report version. All mothers provided alcohol use information via phone interview.

Participants were asked to indicate frequency and quantity of alcohol used on typical as well as on heaviest occasions, and this was converted into standard drinks (SDs) (10g alcohol=1 SD). Mothers were categorized into five different levels of alcohol consumption for each time period using a composite method, taking into account frequency and quantity of consumption (O'Leary et al., 2010). These categories were “abstinent” (no consumption), “low” (≤7 SDs per week, up to 2 SDs per occasion), “moderate” (≤7 SDs per week, >2 to ≤4 SDs per occasion), “binge” (≤7 SDs per week, >4 SDs per occasion), and “heavy” (>7 SDs per week; with a frequency of at least weekly or more often). The definition of “binge” was altered slightly from O’Leary et al.’s (2010) definition so as to be more consistent with the most recent Australian National Health and Medical Research Council guidelines around heavy episodic drinking. Definitions of ‘binge’ and ‘heavy’ alcohol use for partners were consistent with guidelines for non-pregnant adults: “binge” was defined as >4 SDs on one occasion with no more than 14 SDs per week and “heavy” as > 14 SDs per week with a frequency of at least weekly.

2.2.2 Tobacco and illicit substance use. At each interview, participants were asked whether they used tobacco in the preceding time period. This question was repeated for cannabis, heroin, cocaine, amphetamines, hallucinogens, club drugs, non-prescribed benzodiazepines, non-prescribed opioids, non-prescribed anti-depressants, and inhalants ("illicit substances").

2.2.3 Demographic factors. Demographic factors obtained at baseline interview for mothers and their partners included age, maternal education, parity, whether of Aboriginal or Torres Strait Islander origin, first language spoken, and country of birth. Pre-pregnancy weight and height were self-reported and used to calculate BMI. The Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) from the Socio-Economic Indexes for Areas (SEIFA) data package from the Australian Bureau of Statistics (ABS) was used to classify participants into SES categories based on residential postcode at recruitment (Australian Bureau of Statistics, 2011).

2.2.4 Verbal IQ. Given that parental IQ is one of the greatest predictors of offspring IQ, we obtained IQ estimates from mothers and their partners. Trained interviewers administered the Test of Premorbid Functioning (TOPF) from the Advanced Clinical Solutions of the Wechsler Adult Intelligence Scale-4th Edition (Holdnack et al., 2013) to mothers at 12-month follow up or at 3-year follow up (a pilot study with a subsample of the cohort).

2.2.5 Stress and anxiety. At Trimester 1, Trimester 2, and Trimester 3, mothers were administered the Anxiety and Stress subscales of the Depression Anxiety Stress Scale with items referring to the preceding four weeks. Scores on the Anxiety subscale in the moderate (10-14), severe (15-19), or extremely severe range (20+) at any time point were considered elevated. Participants with a score on the Stress subscale in moderate (19-25), severe (26-33), or extremely severe (34+) ranges at any time point were coded as having elevated stress.

2.2.6 Depression. The Edinburgh Depression Scale (Cox et al., 1987) was administered in Trimester 1, Trimester 2 and baseline (Trimester 3). This variable was binary-coded to indicate the presence or absence of elevated depression (scores >9) at any time point.

2.2.7 Spousal abuse. The self-complete Index of Spousal Abuse was administered at the baseline (Trimester 3) interview (Hudson and McIntosh, 1981). Scores above threshold on the physical or non-physical subscale were binary-coded to indicate presence of any abuse. Mothers and partners were provided with separate envelopes to seal their responses in and return separately so as to ensure confidentiality within couples.

2.2.8 Child factors. Infants' birth outcome measures included gestational age, sex, birth weight, head circumference, length at birth, and 5-minute Apgar score taken from obstetricians or GPs measurements at birth.

2.2.9 Infant cognitive development. The Bayley Scales of Infant Development – Third Edition (Bayley, 2006) was administered to children as close to their first birthday as possible (mean age = 12.05 months, range = 11 to 16 months) by qualified examiners in participants' homes. Composite scores on the Cognitive scale were used, adjusted for child age and prematurity. Drawing on an eclectic theoretical foundation, the Cognitive scale of the Bayley consists of such activities as play, novelty preference, habituation, and number ordering. The Bayley cognitive scale has good test-retest reliability and high correlation with the Wechsler Preschool and Primary Scale of Intelligence – Third edition (Albers and Grieve, 2007).

2.3 Statistical analyses

2.3.1 Maternal alcohol consumption and infant cognitive outcomes. Analyses were conducted in STATA 13 (StataCorp, 2013) and SPSS 20 (IBM Corp, 2013). To deal with bias due to attrition, missing data was accounted for using multiple imputation (Graham, 2009;

Rubin, 2004). This procedure was carried out twice: first 20 complete datasets were imputed based on the full sample of women, and then this was repeated for women who had partners participating in the study and their partners. Continuous variables were Box-Cox transformed prior to imputation. Nominal variables were dummy coded, and all binary and ordinal variables were log transformed before imputation. Data were imputed under a multivariate normal model in which all variables that were to be used in analysis were incorporated in the model. Variables were subsequently back-transformed (with adaptive rounding) after imputation. Nominal variables were back-transformed using the rounding method reported by Allison (Allison, 2001). Descriptive results are based on raw non-imputed data whilst all inferential analyses are based on pooled estimates combined using Rubin's rules (Bayley, 2006).

First, an unadjusted comparison of Bayley cognitive composite scores at 12-months across alcohol use categories was made for each trimester of pregnancy. The second model included all demographic factors as covariates: household SES, maternal age, maternal education level, whether of Aboriginal or Torres Strait Islander origin, country of birth, whether single parent household, and first language. The third model included the above factors with the addition of maternal factors that were independent predictors of alcohol use: tobacco and illicit substance use, anxiety, IQ, parity, and BMI. The final model additionally included child-related variables that were independently associated with alcohol use; gestational age at birth was the only additional factor at this level.

2.3.2 Partner alcohol use and infant cognitive outcomes. The first regression model compared infant cognitive scores across partner alcohol use categories without adjustment. The second model adjusted for partner and demographic factors including household SES, age, BMI, level of education, estimated IQ, country of birth, first language, past month tobacco and illicit

substance use, experience of depression, anxiety, or stress, and experience of spousal abuse. The third model additionally adjusted for mother alcohol use (in the first six weeks of Trimester 1, chosen to capture the highest level of alcohol use) and child-related factors as described above. The fourth model again adjusted for all demographic, partner, and child related factors, in addition to maternal factors described above.

2.3.3 Propensity score matching. A score was calculated that reflects the propensity of a woman to consume alcohol at low-levels during Trimester 2, the time point at which low-level prenatal alcohol exposure was most prevalent. This score was used to pair each participant in the drinking group with a close match in the abstaining group. Variables used to define the propensity score were selected from the logistic regression described above. Matching was done without replacement, and priority was given to exact matches. Match tolerance was conservatively set at 0.1 to minimize mean squared error (Austin, 2008). First, whole matched samples of women who drank at low-levels in Trimester 2 and abstainers were directly compared using independent samples T-tests. Then, to examine whether the effect of prenatal alcohol exposure may differ according to an individual's risk of being exposed to alcohol based on their baseline characteristics, samples were stratified into two separate groups indicating higher or lower risk of alcohol exposure based on their calculated propensity score. T-tests were again conducted comparing abstainers to drinkers separately for groups of higher or lower risk.

3. Results

3.1 Patterns of maternal and partner alcohol consumption

3.1.1 Prevalence of alcohol consumption by mothers and partners. Alcohol use at any time during pregnancy was reported by the majority (65.7%) of women (Table 1). In the first 6 weeks of Trimester 1, consumption at binge and heavy levels was the most common pattern,

with 27.3% and 23.1% of drinkers (16.5% and 14.0% of total sample) falling into these categories, respectively. Alcohol consumption was markedly less common and occurred at lower levels in the latter half of Trimester 1, with 72.3% of women abstaining from alcohol completely and the majority of women who did drink doing so only at low levels. This pattern remained consistent across Trimester 2 and Trimester 3, with 68.8% and 69.3% of women abstaining from alcohol at these stages, respectively (Table 1). Analysis of factors associated with change to alcohol use following pregnancy recognition in this sample is given in McCormack et al. (2017).

Alcohol use was reported by the majority (84.1%) of partners (Table 1), with binge consumption being the most commonly reported pattern (31.4%). Low level drinking was reported by 21.7% of partners, 15.6% reported moderate levels, and 14.6% were considered heavy drinkers (Table 2). There was high concordance between maternal and partner alcohol use; most women who drank above low-levels also had a partner who drank above low-levels. It was uncommon for women with partners who abstained from alcohol to drink (Supplementary Table 1[1]).

3.1.2 Predictors of alcohol use by mothers. Women who drank alcohol were less likely to be of low or moderate SES than they were to be high SES, were more likely to be normal weight than obese, more likely to have an unplanned pregnancy, more likely to have completed university than to have discontinued education before year 12, more likely to have been born in Australia or another primarily English-speaking country than to be of non-English speaking background, more likely to have spoken English as their first language, more likely to use

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:...

tobacco and illicit substances, and less likely to have experienced elevated anxiety (Table 2). More detailed description of prevalence and predictors of prenatal alcohol use in this cohort is published elsewhere (McCormack et al., 2017).

3.1.3 Use of illicit substances. Use of an illicit substance at least once during pregnancy was reported by 5.3% (n=70) of mothers. The most common substance used was cannabis, which was used by 70% (n=49) of mothers who reported illicit substance use. Cannabis use was most common prior to pregnancy recognition; only 19 women reported use in Trimester 2 and 13 reported use in Trimester 3. There was no difference in offspring 12-month Bayley cognitive score between those who used cannabis at any point during pregnancy (M= 105.0, SD=10.80) and those who did not (M=106.8, SD=11.66; t=1.082, p=0.280). Nevertheless, illicit substance use by mothers was included as a covariate in 2nd and 3rd level of adjustment in analyses assessing alcohol exposure and infant Bayley outcomes.

3.1.4 Predictors of alcohol use by partners. Partners who drank alcohol, relative to abstainers, were more likely to be aged 30-35 than to be aged over 36 years, more likely to be born in a primarily English-speaking country outside Australia than a non-primarily English-speaking country, their first language was more likely to be English than another language, and they were more likely to have stress levels within the normal range than to have elevated stress (Table 3).

3.2 Prenatal alcohol exposure and 12-month infant cognitive outcomes

Alcohol exposure at any level in the first 6 weeks of Trimester 1 was not associated with any difference in Bayley cognitive score in unadjusted analyses nor following any level of statistical adjustment (Table 4). For the second 6 weeks of Trimester 1, and for Trimester 2 and Trimester 3, only the low-level alcohol exposure group was compared to the abstinent group

because of small group sizes at heavier exposure levels. No difference between the abstinent group and the low-level exposure group in the second 6 weeks of Trimester 1 was found in either unadjusted or adjusted analyses.

A small but significant difference was seen between the low-level exposure and abstinent groups in Trimester 2 in unadjusted comparisons (β=2.82, S.E=0.76, p<0.001); low-prenatal alcohol exposure infants had higher cognitive scores than those not exposed. This remained significant following the first level of adjustment for demographic confounders (β=2.06, S.E=0.75, p<0.01), the third level of adjustment additionally including all maternal factors (β=2.24, S.E=0.76, p<0.01), and the final model, which incorporated child birth outcomes (β=2.11, S.E=0.77, p<0.01).

The same pattern of results was observed in Trimester 3 in unadjusted analyses (β=1.52, S.E=0.75, p<0.05), with low-level prenatal alcohol exposure infants having higher cognitive scores than those not exposed. This effect remained following first (β=1.79, S.E=0.76, p<0.05), second (β=1.73, S.E=0.77, p<0.05), and third (β=1.60, S.E=0.77, p<0.05) levels of adjustment (Table 4).

3.2.1 Alcohol consumption by partners and infant cognitive outcomes. Unadjusted analyses showed significantly higher Bayley cognitive scores in children born to mothers whose partners drank at low (β=3.67, S.E=1.39 p<0.01), binge (β=3.81, S.E=1.31 p<0.01), or heavy (β=3.21, S.E=1.57 p<0.05) levels compared with those born to women whose partners abstained (Table 5).

The second regression model controlled for demographic and partner-related factors. This analysis showed an attenuated yet still significant main effect associated with low (β=3.05,

S.E=1.44, $p<0.05$) and binge (β=2.91, S.E=1.41 $p<0.05$) drinking, but not heavy drinking, by partners (Table 5).

The third analysis additionally adjusted for child-related factors. Higher Bayley cognitive scores were again seen in children born to mothers whose partners drank at low levels (β=2.95, S.E=1.44, $p<0.05$), but there was no association at binge or heavy levels.

The final model additionally included maternal alcohol use (in the first six weeks of Trimester 1, in order to capture the highest level of alcohol exposure) as well as maternal factors as described above. No difference in Bayley cognitive scores was seen between children born to mothers whose partners drank at any level and those who abstained in this final model.

3.2.2 Analyses using propensity score matching: low-level exposure vs. no exposure. Using the propensity score matching technique described in the Methods, 374 low-level drinkers in Trimester 2 were matched to 337 abstinent mothers. In these matched samples, children born to drinkers had higher cognitive scores (M=108.83, SD=11.06) than those born to abstainers (M=106.59, SD=11.06; t=-2.585, p=0.01).

This sample was then stratified using propensity scores into two levels of risk, as described in the Methods. As per predictors of alcohol use described above, "highest risk" of alcohol exposure refers to factors including higher SES, higher education, older age, being of English speaking origin, tobacco use, and unplanned pregnancy. In the lowest risk subgroup, there were 152 abstinent women matched to 152 drinkers. In the highest risk subgroup, 158 abstainers were matched to 160 drinkers. Only in the highest risk subgroup were significant differences observed between drinkers and abstainers (t=-3.15, p=0.002), with children born to low-level drinkers having higher cognitive scores (M=111.06, SD=10.32) than those born to abstainers (M=107.25, SD=11.28). (Figure 1)

3.2.3 Heavy exposure vs. low exposure. This was repeated comparing women who drank at heavy levels in the first 6 weeks of Trimester 1 to those who abstained (Figure 2). This was a post-hoc analysis, conducted because of the unexpected finding from regression analyses that cognitive outcomes were no different among children born to heavy drinkers during this time. Using the same propensity score matching method as described above, 213 heavy drinkers were matched to 172 abstainers. No difference between heavy drinkers and abstainers was observed (t=-0.018, p=0.986). Using the same stratification method as above, there were no differences in cognitive outcomes between children born to abstinent women and those born to heavy drinkers among the lowest risk 50% subgroup (t=0.169, p=0.866) or the highest risk 50% subgroup (t=0.007, p=0.994).

4. Discussion

Infants born to women who drank at low levels during Trimester 2 had higher cognitive ability at 12-months of age than those born to abstainers; this finding was robust and significant, even in samples matched on all baseline characteristics distinguishing drinkers from abstainers via propensity score matching. This is not the first study to report this finding; the meta-analysis by Flak et al. (2014) made the same finding when pooling results of high-quality studies. In a systematic review by Henderson et al. (2007), a small but significant protective effect of low-level prenatal alcohol exposure on physical birth outcomes was found which was not attributable to confounding by extraneous factors (Henderson et al., 2007).

Despite this apparent robust positive association between low-level alcohol exposure and infant cognition, our interpretation is not that this represents a “protective” effect of occasional drinking. Because there are known significant differences between drinkers and abstainers that are difficult to extricate, even with the most complete adjustment for confounders, it is always

possible these differences may be driving any apparent effect of alcohol use. Those who continued to drink were from higher SES backgrounds, affording the potential for improved nutrition and a more enriched environment generally.

The finding that heavy alcohol exposure during the first 6 weeks of Trimester 1 was not associated with impaired cognitive ability was somewhat inconsistent with existing knowledge in this area (Korkman et al., 2003; Mattson et al., 2010; McGee et al., 2008; Vaurio et al., 2011). It is possible that for many women in this group categorized as heavy drinkers (>7 standard drinks per week) the level of alcohol consumed may not be as high as in previous studies linking heavy prenatal alcohol exposure with impaired cognitive outcomes. For example, some previous studies defined heavy alcohol use as women who met criteria for alcohol abuse or dependence (McGee et al., 2008) or consumption of at least 10 standard drinks per week or higher (Korkman et al., 2003; Mattson et al., 2010; Vaurio et al., 2011). In addition, this is not considered the most critical period of gestation in terms of brain development; it is exposure during the third trimester that has demonstrated the strongest observable effects in cognitive outcomes in animal models (Popović et al., 2006; Schneider et al., 2011). This is difficult to determine in humans, as women who drank in Trimester 2 and in Trimester 3 also consume alcohol in Trimester 1 and prior to pregnancy in most cases, including the present sample.

We also have provided evidence to suggest possible interaction between alcohol exposure and other demographic and maternal risk factors in their relation to cognitive outcomes for children, in line with data from epidemiological studies. When the sample was stratified by propensity score, the relationship between alcohol exposure and cognitive outcome was different for groups of women with different patterns of baseline characteristics. In samples including

more women of low SES and high-risk backgrounds, this potential interaction effect could be further explored using this technique.

We did not find evidence of any negative association between alcohol use by partners and infant cognitive outcomes; indeed, the same apparent positive association between partners alcohol use and infant cognitive development was noted. However, following adjustment for sociodemographic factors, this effect was no longer apparent. This was true despite noting that sociodemographic and psychological factors were only moderately related to partner likelihood to drink, as opposed to the strong associations seen with alcohol use by mothers. However, the direction of associations was the same, overall describing a subset of relatively socially advantaged people. Noting similar associations between alcohol use by partners and that of mothers in infant outcomes at 12-months offers additional evidence that these associations are not simply attributed to intrauterine mechanisms.

4.1 Limitations

The most significant limitations relate to characteristics of the sample. Despite recruiting participants from multiple hospital antenatal clinics across diverse regions, women from low SES backgrounds were underrepresented in the sample, and those who were included tended to be abstainers rather than drinkers. This pattern was not unexpected, considering that lower SES has been associated with abstinence from alcohol in previous Australian surveys (Jonas et al., 2000). However, in this way, the present sample has not captured the group of children who appear to be most susceptible to harmful effects of prenatal alcohol exposure. FASD is consistently found to be concentrated among low-SES, marginalised populations (Abel, 1995; Esper and Furtado, 2014). Results are interpreted with the caveat that associations between alcohol use and cognitive outcomes may show a different pattern among lower-SES populations.

The present study has also only focused on one developmental outcome assessed at one time point. Deleterious effects of alcohol exposure have been observed in other domains of central nervous system functioning as well as other organ systems, and some effects may not be detectable until later in childhood.

Other methodological issues may have affected information about alcohol use. Despite assurances of confidentiality and the separation between researchers from any clinical care of participants, some women may have chosen not to disclose or minimise alcohol use to researchers. Alcohol use by partners was only measured at one time point, in the third trimester, and it is possible that consumption may have been different at earlier points during their partners' pregnancy which would not be captured. With less frequent contact between partners and the research team, rapport may also not have been as strong as it was for mothers, which may have influenced willingness to disclose alcohol use; however, the level of alcohol use reported by partners was still high. Since data about third trimester alcohol use was obtained at 8-weeks postpartum, some recall bias may have affected reporting of alcohol use during this time period. However, it is noted that consumption was broadly consistent with that reported for Trimester 2 as expected. Another limitation of study design is that examiners were not blinded to alcohol use status of participants.

4.2 Conclusions

We found no evidence to suggest prenatal exposure to low-levels of alcohol, nor alcohol use by partners, is associated with impaired cognitive outcomes at 12-months of age. This result remained following adjustment for confounding factors using a variety of methods and corroborates existing evidence to suggest there are no detectable harms to infant cognitive ability at 12-months of age associated with low-level prenatal alcohol exposure. These findings should

be interpreted with the caveat that this was generally a high functioning, high SES sample of women. It is possible that harms may be associated with similar levels of alcohol exposure among populations where the presence of other social and health-related risk factors is higher.

Author Disclosures

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Contributors

CM conceived the study, collected data, conducted analyses and wrote the manuscript under supervision of DH, RM and LB. DH, RM, LB, EE, CO, JN, SA, SJ conceived the parent study, obtained funding, oversaw research and provided critical review of the manuscript and approved the final manuscript. GY and JW assisted with data analyses and drafts of the manuscript, provided critical review and approved the final manuscript.

LR collected data, provided critical review and approved the final manuscript. All authors have contributed to and approved the final article.

Conflict of Interest

No conflict declared.

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Figure Legends

Figure 1: Bayley cognitive score in low prenatal alcohol exposure vs. abstinent groups, stratified by propensity score. *p<0.001

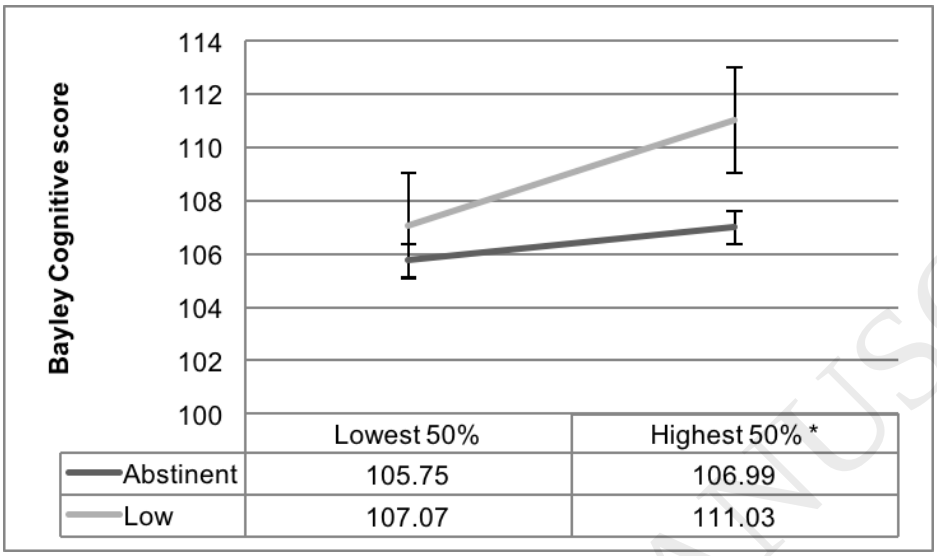

Figure 2: Bayley cognitive score in heavy prenatal alcohol exposure vs. abstinent groups, stratified by propensity score

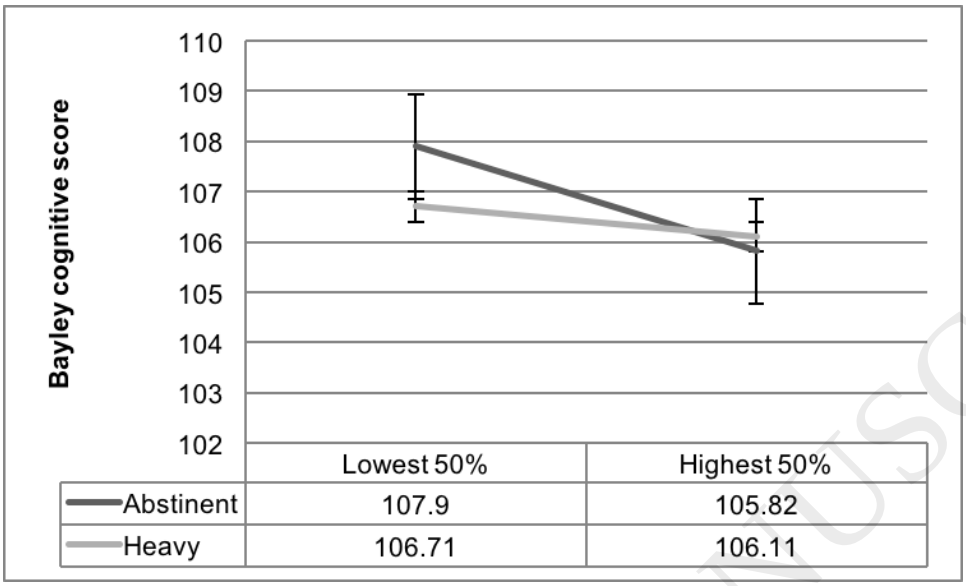

Table 1: *Patterns of alcohol use by mothers and partners*

	Alcohol use category				
	Abstinent	**Low**	**Moderate**	**Binge**	**Heavy**
Mothers					
Trimester 1 – Weeks 1-6					
n (%)	525 (39.4)	302 (22.7)	55 (4.1)	220 (16.5)	186 (14.0)
Trimester 1 – Weeks 7-12					
n (%)	962 (72.3)	235 (17.7)	29 (2.2)	42 (3.2)	24 (1.8)
Trimester 2					
n (%)	916 (68.8)	345 (25.9)	39 (2.9)	14 (1.1)	14 (1.1)
Trimester 3					
n (%)	922 (69.3)	347 (26.1)	31 (2.3)	10 (0.7)	13 (1.0)
Partners					
Trimester 3					
n (%)	111 (15.9)	158 (22.6)	111 (15.9)	216 (31.0)	103 (14.7)

Table 2: Factors associated with alcohol use by mothers

		Abstainers (n%)	**Drinkers (n%)**	**Drinkers vs. abstainers - Unadjusted OR (95% CI)**
Household SES				
	Low	39 (8.5)	22 (2.5)	0.223 (0.130-0.384)***
	Moderate	172 (37.6)	230 (26.3)	0.529 (0.413-0.677)***
	High	246 (53.8)	622 (71.2)	1
Age				
	≤ 24	38 (8.3)	38 (4.3)	0.474 (0.288-0.779)**
	25-29	110 (24.1)	162 (18.5)	0.698 (0.506-962)**
	30-35	183 (40.0)	408 (46.7)	1.056 (0.803-1.390)
	≥ 36	126 (27.6)	266 (30.4)	1
Aboriginal or Torres Strait Islander				
	Yes	10 (2.2)	11 (1.3)	1.759 (0.741-4.173)
	No	445 (97.8)	861 (98.7)	1
Body Mass Index				

	Underweight	37 (8.4)	34 (4.1)	0.677 (0.387-1.184)
	Normal weight	239 (54.6)	555 (66.3)	1.711 (1.213-2.414)**
	Overweight	92 (21.0)	153 (18.3)	1.225(0.819-1.833)
	Obese	70 (16.0)	95 (11.4)	1
Parity				
	0	245 (53.6)	514 (58.9)	1.526 (0.883-2.638)
	1-2	188 (41.1)	325 (37.3)	1.257 (0.721-2.191)
	3+	24 (5.3)	33 (3.8)	1
Pregnancy planning				
	Unplanned	91 (19.9)	201 (23.0)	1.203 (0.911-1.589)
	Planned	366 (80.1)	672 (77.0)	1
Level of education				
	Some school	43 (9.5)	33 (3.8)	0.380 (0.237-0.608)***
	Year 12	47 (10.3)	98 (11.2)	1.031 (0.713-1.492)
	Certificate / Diploma	68 (14.9)	126 (14.4)	0.969 (0.716-1.311)
	Bachelor or higher	299 (65.4)	616 (70.6)	1

Single parent household			
Yes	40 (8.8)	47 (5.4)	0.592 (0.382-

			0.918)*
No	417 (91.2)	827 (94.6)	1
First language			
English	185 (64.0)	454 (81.2)	2.431 (1.764-3.349)***
Other	104 (36.0)	105 (18.8)	1
Estimated IQ			
≤ 84	66 (22.6)	44 (7.8)	0.248 (0.149-0.414) ***
85-99	108 (37.0)	194 (34.4)	0.668 (0.441-1.012)
100-114	73 (25.0)	205 (36.3)	1.044 (0.677-1.612)
≥ 115	45 (15.4)	121 (21.5)	1
Tobacco in pregnancy			
No	408 (89.3)	728 (83.3)	0.599 (0.424-0.846)**
Yes	49 (10.7)	146 (16.7)	1

Illicit substances ever in pregnancy				
	No	441 (96.5)	820 (93.8)	0.551 (0.312-0.974)**
	Yes	16 (3.5)	54 (6.2)	1
Anxiety				
	Normal	304 (71.9)	626 (78.5)	1.433 (1.093-1.879)**
	Elevated	119 (28.1)	171 (21.5)	1
Stress				
	Normal	343 (83.1)	646 (81.5)	0.897 (0.656-1.227)
	Elevated	70 (16.9)	147 (18.5)	1
Depression				
	Normal	301 (70.7)	583 (71.5)	1.044 (0.806-1.351)
	Elevated	125 (29.3)	232 (28.5)	1
Victim of spousal abuse				
	No	371 (95.4)	708 (96.3)	1.272

				(0.692-2.340)
	Yes	18 (4.6)	27 (3.7)	1

*p<0.05; **p<0.01, ***p<0.001

Table 3: Factors associated with alcohol use by partners

	Abstainers n (%)	**Drinkers n (%)**	**Drinkers vs. Abstainers OR (95% CI)**
Partner Characteristics – n (%)			
Household SES			
Low	10 (9.0)	17 (2.9)	0.241 (0.105-0.551)***
Moderate	42 (37.8)	155 (26.4)	0.523 (0.338-0.810)**
High	59 (53.2)	416 (70.7)	1
Age			
≤ 24	4 (36)	13 (2.2)	0.696 (0.219-2.218)
25-29	19 (17.1)	73 (12.5)	0.823 (0.459-1.477)
30-35	34 (30.6)	246 (42.1)	1.550 (0.975-2.465)*
≥ 36	54 (48.6)	252 (43.2)	1
Aboriginal or Torres strait islander			
Yes	4 (3.1)	10 (1.6)	1.775 (0.473-6.661)

	No	123 (96.9)	620 (98.4)	1
BMI				
	Underweight	0	1 (0.2)	n/a
	Normal weight	37 (34.6)	196 (39.3)	1.625 (0847-3.116)
	Overweight	42 (42.1)	225 (45.1)	1.253 (0.674-2.326)
	Obese	25 (23.4)	77 (15.4)	1
Level of education				
	Some school	4 (6.6)	16 (4.7)	0.708 (0.224-2.237)
	Year 12	7 (11.5)	39 (11.5)	0.986 (0.410-2.371)
	Certificate / Diploma	13 (21.3)	75 (22.1)	1.021 (0.515-2.026)
	Bachelor or higher	37 (60.7)	209 (61.7)	1
First language				
	English	32 (50.8)	279 (83.8)	5.005 (2.821-8.881)***
	Other	31 (49.2)	54 (16.2)	1
Estimated IQ				
	≤ 84	12 (19.0)	27 (7.9)	0.175 (0.065-0.470)***
	85-99	21 (33.3)	107 (31.2)	0.396 (0.168-0.933)*
	100-114	22 (34.9)	106 (30.9)	.374 (0.159-0.879)*
	≥ 115	8 (12.7)	103 (30.0	1

Tobacco use in Trimester 3			
No	91 (82.0)	480 (81.6)	0.977 (0.577-1.655)
Yes	20 (18.0)	108 (18.4)	1
Illicit substance use in Trimester 3			
No	106 (95.5)	550 (93.5)	0.683 (0.263-1.775)
Yes	5 (4.5)	38 (6.5)	1

*p<0.05; **p<0.01, ***p<0.001

Table 3 (cont.)

		Abstainers n (%)	**Drinkers n (%)**	**Unadjusted OR - Drinkers VS Abstainers (95% CI)**
Anxiety				
	Normal	94 (95.9)	500 (93.8)	0.645 (0.223-1.862)
	Elevated	4 (4.1)	33 (6.2)	1
Stress				
	Normal	76 (89.4)	440 (92.1)	1.371 (0.637-2.950)
	Elevated	9 (10.6)	38 (7.9)	1
Depression				
	Normal	70 (85.4)	375 (90.1)	1.568 (0.785-3.132)
	Elevated	12 (14.6)	41 (9.9)	1
Victim of spousal abuse				
	No	89 (93.7)	484 (92.5)	0.837 (0.344-2.035)
	Yes	6 (6.3)	39 (7.5)	1

*p<0.05; **p<0.01, ***p<0.001. N.A.=small cell size

Table 4: Maternal alcohol use and infant cognitive outcomes

	Unadjusted mean (SE)	**Unadjusted comparison**		**Adjusted for demographic factors[1]**		**Adjusted for maternal factors[2]**		**Adjusted for maternal and child factors[3]**	
		β (S.E)	*p*	*β* (S.E)	*p*	*β* (S.E)	*p*	*β* (S.E)	*p*
T1 - first 6									
Abstinent	106.72	Reference		Referen		Referen		Referen	
Low	107.28	0.55	0.51	-.022	0.79	-0.39	0.65	-0.45	0.60
Moderate	107.95	1.22	0.45	0.38	0.81	0.29	0.86	1.35	0.93
Binge	106.69	-0.04	0.96	-0.91	0.33	-0.88	0.36	-0.90	0.35
Heavy	107.32	0.60	0.54	-0.29	0.77	0.01	0.99	-0.13	0.90
T1 - second 6									
Abstinent	106.81	Reference		Referen		Referen		Referen	
Low	107.93	1.12	0.19	0.56	0.51	0.59	0.50	0.54	0.53
Trimester 2									
Abstinent	106.12	Reference		Referen		Referen		Referen	
Low	108.93	2.82	<0.001	2.06	<0.0	2.21	<0.0	2.11	<0.0
Trimester 3									
Abstinent	106.31	Reference		Referen		Referen		Referen	
Low	108.49	2.18	<0.01*	1.52	<0.0	1.73	<0.0	1.60	<0.0

T1=Trimester 1, T2= Trimester 2, T3=Trimester 3

[1]First level adjustment: SEIFA category, maternal age, BMI, whether of Aboriginal or Torres Strait Islander origin, single parent household, education, country of origin, native language

[2]Second level adjustment: All first level factors, plus smoking, illicit substance use, anxiety, IQ, parity, and BMI

[3]Third level adjustment: All first and second level factors plus child gestational age at birth

*$p<0.05$

Table 5: *Alcohol use by partners and infant cognitive outcomes*

	Unadjusted mean (SE)	**Unadjusted comparison**		**Adjusted for partner factors₁**		**Adjusted for partner and child factors₂**		**Adjusted for partner, child, and maternal factors₃**	
		β (S.E)	*p*	*β* (S.E)	*p*	*β* (S.E)	*p*	*β* (S.E)	*p*
Abstinent	104.60 (1.06)	Reference		Reference		Reference		Reference	
Low	108.28 (0.90)	3.67 (1.39)	<0.01**	3.05 (1.44)	<0.05*	2.95 (1.44)	<0.05*	2.42 (1.55)	0.12
Moderate	106.84 (1.09)	2.23 (1.53)	0.15	1.11 (1.65)	0.50	1.28 (1.67)	0.45	0.67 (1.81)	0.71
Binge	108.41 (0.77)	3.81 (1.31)	<0.01**	2.91 (1.41)	<0.05*	2.76 (1.41)	0.05	2.00 (1.58)	0.21
Heavy	107.82 (1.14)	3.21(1.57)	<0.05*	1.58 (1.69)	0.35	1.43 (1.70)	0.40	2.19 (1.98)	0.27

₁ First level adjustment: SEIFA category, partner age, BMI, whether Aboriginal or Torres Strait Islander origin, education, country of origin, native language, IQ, smoking, illicit use, elevated stress, elevated anxiety, elevated depression, experience of abuse

₂ Second level adjustment: All first level factors, child's sex, 5 minute APGAR score, gestational age, birth head circumference, birth weight

₃ Third level adjustment: All first and second level factors plus following maternal factors: alcohol use, age, BMI, IQ, whether Aboriginal or Torres Strait Islander origin, education, native

language, country of origin, parity, smoking, illicit substance use, elevated stress, elevated anxiety, elevated depression, experience of abuse

* $p<0.05$

** $p<0.01$