INVESTIGATING THE EFFECTS OF LOW TO MODERATE LEVELS OF PRENATAL ALCOHOL EXPOSURE ON CHILD BEHAVIOUR: A CRITICAL REVIEW

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ABSTRACT

Conflicting findings exist regarding the risks of low to moderate levels of alcohol use during pregnancy. A recent study from Australia has suggested that mild gestational drinking is not associated with adverse fetal effects, and may even be associated with favorable outcomes as compared to "no drinking".The study may lead women to continue consuming alcohol throughout pregnancy, despite methodological limitations that render its conclusions uncertain. This review discusses the challenges of assessing long-term effects of moderate drinking during pregnancy. Recommendations are provided for researchers investigating the effects of prenatal alcohol consumption on subsequent developmental outcomes in children.

For years, researchers have shown that alcohol consumption during pregnancy can have a teratogenic effect on the fetus, resulting in facial dismorphology, growth deficiency, and damage to the central nervous system.[1-3] The adverse effects of prenatal alcohol exposure on child development have been well-documented by experts in the field.[4-10]

Currently, however, the evidence is equivocal regarding the effects of low to moderate levels of prenatal alcohol exposure. Some research suggests that alcohol exposure has a dose-response mechanism during gestation, such that even low to moderate levels of drinking during pregnancy have been associated with significantly higher rates of externalizing and aggressive behaviour[11], learning and behaviour difficulties[12], and mental health problems in offspring.[13] Researchers have also found a relationship between moderate prenatal alcohol exposure (an average of 0.3 to 1.7 oz of absolute alcohol per day) and deficits in attention, behavior and working memory in childhood.[14-15] Conversely, other researchers have found no association between gestational exposure to low or moderate levels of alcohol and adverse behavioral or cognitive outcomes[16-18], and even imply that light drinking during pregnancy may have a protective effect on subsequent child behaviour.[16,17] These conflicting findings regarding the risks of low level alcohol use during pregnancy are likely a result of the numerous methodological limitations inherent in this line of research.

For example, women may under-report their alcohol intake due to retrospective recall bias and prevailing social stigmas regarding alcohol use during pregnancy.[19] Reliance on self-report measures makes it difficult to obtain accurate information regarding the quantity, timing, frequency, and pattern of maternal alcohol intake.[20] It is also difficult to identify, measure, and accurately adjust for the large number of potentially confounding variables that influence child development. These include maternal psychopathology, socioeconomic factors, maternal nutrition, parenting styles, and maternal and fetal genetics.[19-20] Prospective longitudinal studies are often plagued by attrition.[19] The generalizability of findings from studies from different countries may be limited due to dissimilarities in the nature and characteristics of the sample populations, such as socioeconomic factors, genetics, and the social acceptability of alcohol consumption.[19-20] To date, many studies have failed to utilize comprehensive batteries of well validated, reliable standardized measures that assess multiple

domains of functioning (e.g., neurodevelopmental, cognitive, behavioral, and emotional functioning). Furthermore, some researchers have had a tendency to favour less labour intensive assessment methods over the direct testing of children, perhaps due to considerations regarding feasibility. Data from behavioural questionnaires using maternal informants may be inherently biased.

The critical evaluation of the methodology of studies investigating low to moderate alcohol exposure during gestation and it effect on subsequent child development is essential for a number of reason. Firstly, up to half of all pregnancies are unplanned.[21-22] Moreover, in North America, "light drinking" in women of childbearing age is common and generally considered socially acceptable.[23-24] Consequently, a large proportion of fetuses may be routinely exposed to low levels of alcohol, especially during the first trimester when pregnancy is often undetected. Exposing one's own child, albeit unintentionally, to a teratogenic substance can cause severe guilt and anxiety in the mother. Evidence-based information regarding the actual magnitude of the risk of low level alcohol exposure during gestation is necessary in order that women can be counselled accurately and sensitively, and to avoid potentially harmful feeling of guilt and stress in the mother, which in some instances may lead to the unwarranted termination of pregnancies. On the other hand, misinformation derived from inadequately designed studies that minimizes the risk of low level exposure can also be extremely counterproductive because mothers may be encouraged to continue drinking throughout their pregnancy, potentially causing harm to the fetus. Scientific findings often receive immediate and widespread publicity, particularly when results appear controversial.[25-26] For example, following the online publication of the study conducted by Kelly, et al.[16] that reported a J-shaped relationship between drinking during pregnancy and adverse outcomes in offspring, Fox News reported that "light drinking during pregnancy may benefit baby".[25] More recently, in response to the Robinson, et al.[17] study, McLean's opined that "One or two drinks a week don't seem to harm the child".[27] Close scrutiny of studies investigating the effects of gestational exposure to low levels of alcohol is essential in order that health care professions and the general public can be accurately informed about the associated risks.

We have recently published a brief critique of the methodology used in the prospective cohort study conducted by Robinson and colleagues[17], investigating the effects of low to moderate drinking during pregnancy.[28] Herein we provide an in depth description of the key methodological concerns touched upon in this brief Letter to the Editor.

Robinson, et al.[17] found that children prenatally exposed to low levels of alcohol within the first three months of pregnancy had significantly lower total and internalizing CBCL scores, indicating more positive behaviour, when compared to children of mothers who abstained for the first 3 months of pregnancy. Furthermore, they reported that children of light to moderate drinkers at 18 weeks were at a significantly lower risk of total, internalizing and externalizing behavioural problems at the clinical level, when compared to the offspring of mothers who abstained.

The study conducted by Robinson and colleauges[17] has a number of strengths, and does add to the small body of literature suggesting that prenatal alcohol exposure at low levels is not linked to subsequent adverse behavioural outcomes in offspring.[28] This study utilized a prospective pregnancy cohort, thus obviating retrospective recall bias of alcohol consumption during pregnancy. The longitudinal nature of the study allowed for assessment of child behaviours at multiple stages of development. The large sample size (n=1860) resulted in ample statistical power for detecting differences among groups. The researchers measured and statistically adjusted for a number of potential confounding variables, which could theoretically affect behavioural outcomes in children. And lastly, the outcome measure utilized by the researchers (Child Behavioural Checklist)[29] is a widely used, well validated measure of behavioural and emotional problems in children and adolescents, with strong psychometric properties.[17] Although this study has notable strengths, it also has significant methodological limitations that compromise the generalizability of its findings.

One such limitation is the selective attrition of research participants. Approximately one third

of mothers were lost to follow-up, and these mothers had a more disadvantaged socioeconomic profile compared to the mothers who ended up participating in the study.[28] A significantly larger proportion of mothers who were lost to follow-up were under the age of 20, single parents, had not completed high school, and had an annual income of less that 24 thousand dollars.[17] Although the sociodemographic profile of participants who stayed in the study was similar to that of the general Western Australian population[17], those lost to attrition differed markedly from the mothers who remained in the study.

Prenatal alcohol exposure may be associated with higher risks of adverse outcomes in offspring of socially and financially underprivileged mothers, due to factors such as poorer maternal nutrition and increased stress. An interaction effect may exist between SES and prenatal alcohol exposure.[28] Bingol, et al.[30] investigated the effect of SES on the prevalence of Fetal Alcohol Syndrome (FAS) and Alcohol Related Effects (ARE) in the offspring of two populations of alcoholic mothers: (1) alcoholic mothers who were classified as having an upper or upper middle socioeconomic status, and (2) alcoholic mothers who were classified as having a lower socioeconomic status. All participants had previously given birth to a child and had a proven history of chronic alcoholism, with no significant difference in the reported absolute alcohol intake between groups. FAS and ARE were identified in 4.6 % of children born to upper class alcoholic mothers, compared with 71% of children born to alcoholic mothers with a lower socioeconomic status. Furthermore, attention deficit disorder was present in 21.1% of children in the upper SES group, and 71.8% of children in the lower SES group. This study suggests that the difference in the prevalence of FASD–related disorders between these two groups of alcoholic mothers is a result of an interaction between a number of genetic factors and environmental factors related to SES.[30] Higher SES appeared to buffer or counteract the adverse effects of alcohol on the fetus.

The effect of the selective attrition of participants in the Robinson et al. study is equivalent to removing the lower third of the data from a scatter plot. As a result of the missing data, the strength of a genuine relationship may be obscured. If an interaction effect between alcohol exposure and SES does exist, one would hypothesize that alcohol exposed children born to low SES mothers would have higher rates of behavioural problems than non-exposed children born to low SES mothers and than exposed children of higher SES mothers. Thus, had the lower SES group of mothers been included in the follow-up cohort, the overall strength of the relationship might have looked different. The conclusion that low to moderate drinking during pregnancy does not lead to adverse long-term behavioural affects in offspring may not be directly generalizable to women and children from more socially disadvantaged backgrounds.

Another major concern is Robinson, et al.'s failure to control for maternal psychopathology.[28] As they themselves acknowledged, some research has suggested that individuals who choose to drink in moderation tend to have better mental health than individuals who choose not to consume alcohol.[31] A number of studies have found either a J-shaped or U-shaped association between alcohol use and rates of psychological distress[32-33], or levels of depression and anxiety.[34-36] In fact, two population-based Australian studies found that individuals who abstained from alcohol displayed significantly more anxious and depressive symptoms[35], as well as higher rates of affective and anxiety disorders[34], compared to a reference group of low to moderate consumers. Therefore, it may be the case that the group of abstainers in the Robinson, et al. study had higher rates of depression and anxiety than the groups of light and moderate drinkers, thus producing a between-groups difference in children's mean CBCL scores. Maternal psychopathology has been found to be a strong predictor of behavioural problems in children and adolescents. In one study designed to assess the effects of prenatal alcohol exposure on child behaviour, Sood, et al.[11] found that maternal psychopathology was the strongest predictor of child behavioural outcomes, accounting for between 13 and 29 % of variance in the overall symptom scores. Furthermore, a retrospective chart review of a clinically referred population of children and adolescents found that children with evidence of parental psychiatric disorders had significant poorer scores on the anxious/depressed, social problems, and attention problem subscales of the CBCL, when compared

to children without a history of parental psychopathology.[37]

More specifically, numerous studies have found that depression itself adversely impacts child behaviour and mental health.[38,39] The offspring of parents afflicted by depression have a significantly higher risk for experiencing psychopathology[40,41], and are significantly more likely to exhibit various behavioral problems, compared to children born to mentally healthy parents.[38,39,42] If this J-shape relationship between mental health and alcohol consumption did exist in Robinson, et al.'s participants, then the increased rates of psychological distress, depression and anxiety in the group of abstainers could have contributed to the significantly higher behavioural problems found in their children, compared to the children of mentally healthier, light to moderate drinkers.

It is also important to consider the impact that national attitudes on alcohol consumption have on the likelihood of finding this J or U-shaped relationship between poorer mental health and alcohol intake. This relationship may be more prevalent in populations where low to moderate alcohol consumption or "social drinking" is the prevailing societal norm, because in these cohorts abstinence would be regarded as abnormal, and may be associated with social exclusion or isolation.[36] The fact that a large proportion of women in this cohort continued to consume alcohol throughout pregnancy speaks to the social attitudes on alcohol use in pregnancy in Australia during this time period. Compared to the United States and Canada, historically there has been a more liberal policy on alcohol consumption during pregnancy in the medical community in Australia, as well as an overall lack of recognition of FASD.[43] For example, the Australian National Health and Medical Research Council (2001)[44] policy statement advised that "Women who are pregnant or might soon become pregnant may choose not to drink alcohol; most importantly should never become intoxicated; if they choose to drink, over a week, should have less than 7 standard drinks and, on any one day, no more than 2 standard drinks (spread over at least 2 hours)…" (pg.16). Because alcohol consumption during pregnancy was not deemed dangerous or socially unacceptable during the recruitment period for the study, it can be assumed that the women who reported no alcohol use in the first 18 weeks of pregnancy were likely "true" abstainers, as opposed to social drinkers who stopped using alcohol solely due to their intention of becoming pregnant. Moreover, women were included in the abstinence control group at 18 weeks, only if they reported no alcohol consumption throughout the first 18 weeks of gestation. Pregnancy is often unknown or unconfirmed during the first few weeks of gestation - thus reports of alcohol consumption during this time-period are likely to reflect the women's usual drinking patterns, rather than deliberate abstinence due to pregnancy.[17]

The potential difference in mental heath status between abstainers and light-moderate drinkers could directly contribute to improved behavioural outcomes in the children of light-moderate drinkers via environmental and genetic mechanisms. For example, women who are mentally healthier (i.e., low-moderate drinkers) may have the ability to provide more effective parenting, or model more adaptive behavioural and emotional regulation. Furthermore, offspring of women who are at higher risk for depression and anxiety (i.e., abstainers) may share their mother's genetic predisposition or vulnerability to mental heath problems.

Of equal importance, ratings on the CBCL can also be affected by reporting biases linked to the responders' level of emotional impairment.[28] Najman, et al.[45] investigated symptoms of anxiety and depression as potential sources of bias in child outcome measures from the CBCL. Mothers with clinically significant symptoms of anxiety and depression tended to over-report the rate of child behavioural problems, endorsing more behavioural problems on the CBCL than did their children themselves. Interestingly, unimpaired mothers showed the opposite pattern, endorsing fewer behavioural problems compared to their children's own reports on the Youth-Self Report form.[45] It is therefore possible that the potentially higher rates of depression and anxiety hypothesised to exist in the group of abstainers may have directly biased their perceptions and reports of their children's behavioural problems on the CBCL. Furthermore, alcohol using mother's responses on the CBCL could have also been biased by their conscious awareness of the objective of the study they were participating in. Women gave informed consent to participate in

this study[17], and thus would have been cognizant of the researchers' intentions to evaluate the link between alcohol use in pregnancy and subsequent child behaviour. Perhaps mothers who drank during pregnancy, consciously or subconsciously downplayed any behavioural concerns regarding their children, in an effort to reduce any guilt stemming from the scientific inquiry into the effects of their drinking behaviours during pregnancy. Maternal guilt could potentially bias mothers' reports of child functioning, and thus it is recommended that future researchers include reports from multiple informants.

CONCLUSIONS

The objective of this article is not to discredit the findings of the low-level drinking studies that have found no effect on child behaviour, but to encourage a higher standard for the evaluation of the validity and generalizability of *all* observational epidemiological studies investigating the long-term developmental effects following *any* level of prenatal alcohol exposure. Overall, the study published by Robinson, et al.[17] highlights the need for future research with demographically diverse samples, utilizing observational data from multiple sources including parents, teachers and the child themselves, as well as direct testing of children and adolescents. Furthermore, when assessing behavioural teratogens such as alcohol, researchers should employ a test battery that assesses functioning across multiple domains of development, in order to obtain a complete and comprehensive picture of adaptation.[46] Fetal alcohol spectrum disorder and heavy prenatal exposure to alcohol is associated with a wide range of impairments across a variety of neuropsychological domains.[47-51] In order to accurately evaluate the neurodevelopmental effects of exposure to low–moderate levels of alcohol during pregnancy, researchers must employ dependent measures that address behavioural, emotional, social, adaptive, and executive functioning, as well as memory, attention, language skills, visual-spatial abilities, processing speed and motor skills. Moreover, an effort to control for the various confounding factors that are known to impact child development such as SES, parental psychopathology, maltreatment/abuse, family environment, and parenting styles, is essential in order to establish the true effect or non-effect of low-moderate alcohol exposure on child development.

Researchers in this area of inquiry must be extremely careful when publishing the results of a study with known limitations because of the risks that the data can easily be misinterpreted and sensationalized by the media. The shock and awe approach the media tend to adopt when reporting the results of controversial scientific studies, combined with the general public's willingness to accept "scientifically proven" results, without critically analyzing the study's design or limitations, creates an extremely dangerous environment. Sensationalized media reports of the "positive effects" found in recent low-level drinking studies[16,17] may encourage alcohol consumption during pregnancy, especially in high-risk populations with less education. For instance, the findings from the Robinson, et al. study that consuming 2 to 10 drinks per week during pregnancy is associated with more positive behaviours in children[17], could easily be misconstrued by the general public. Naive pregnant women may receive this information, and erroneously conclude that the an occasional binge drinking episode is perfectly safe for their baby, as long as it means drinking fewer that 10 drinks per week.

As scientists, our allegiance lies with the truth, however we also have an ethical obligation to be mindful of how the general public might interpret our findings, as well as the implications on public health and policy development. In the knowledge translation stage, cautionary steps must be taken to ensure that research findings are not misunderstood. This is especially important when dealing with the historically socially sensitive topic of drinking during pregnancy. Overall, we as scientists and clinicians must be held responsible for the impact the dissemination of our findings has on society, particularly when those findings may undermine the current promotion of positive health practices, such as abstinence during pregnancy. The small body of literature suggesting that alcohol consumption at low levels during pregnancy is not associated with adverse behavioural and cognitive outcomes, has inherent methodological limitations that

compromise the generalizability of results, and thus by no means, should be translated into a public message that drinking during pregnancy at "low levels" is "safe".[25-26] Furthermore, the message that low level drinking is beneficial during pregnancy is extremely hazardous, especially when received by women in high-risk populations.[52] Presently, no clear threshold limit can be established, and thus the only socially responsible message to deliver regarding alcohol use during pregnancy is abstinence.

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