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Different perspectives on the methodology of studying the potential effects of different alcohol drinking patterns in early pregnancy on neuropsychological development of young children

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First, we agree that the null results from our studies must be interpreted with caution. The published results were limited to the measurement of three neuropsychological effects in children aged five, and did not include other ages or other health outcomes. While these studies suggest that there are no serious effects on these three functions with low to moderate levels of alcohol consumption, they cannot rule out other harmful effects or negative health outcomes in older children.

We agree that reliable measurement of alcohol consumption, particularly alcohol consumption by pregnant women, is very difficult in both clinical and research settings. It is generally acknowledged that pregnant women are likely to underreport their alcohol consumption, irrespective of the actual level of consumption. This problem has been extensively assessed in the literature and many improvements in questions and manner of questioning have been developed that increase the reliability of the information. Those improved techniques were applied in the DNBC and some relevant references are provided in the papers. Based on post-partum meconium analysis, Garcia-Algar et al suggest pregnant women do not underreport but misreport; therefore self-reports are unreliable and that no conclusion can be drawn. Although self-report may be flawed, we believe it still yields important and useful information. At the time of data collection on alcohol exposure through the DNBC, procedures for obtaining exposure information represented a significant step forward. Questions were asked during pregnancy rather than years later after a child was found to have problems. We agree that as bio-measures may be developed and refined, future studies may be able to hone in on more precise aspects of exposure.

Interestingly, in their own recent paper (1), the authors state that “mothers from Mediterranean countries tend to underreport their drinking…., probably due to social pressure and guilt feeling.” This may be correct, and stresses the importance of underreporting. This may also explain why Astley et al. describe that a small proportion of mothers with children who have FAS reported low to moderate weekly intake of alcohol. To our knowledge, in the scientific literature, FAS is generally described for much higher levels of prenatal exposure. As mentioned in our papers, one of the important methodological aspects of the collection of exposure data relates to the fact that in Denmark, many pregnant women, doctors and midwives consider low to moderate alcohol consumption (such as the levels investigated in this study) to be acceptable (2,3,4). Therefore, as opposed to many other countries, self-reports by women in Denmark are likely to be less biased and the

results therefore more reliable. As mentioned in some of the articles, this was one reason the study was specifically conducted in Denmark.

While we agree that objective measures of alcohol intake would be ideal, such markers do not appear to exist for low intake levels or for measurement in early pregnancy. The original cut offs for meconium analyses were based on comparison with self-reports (5) and comparison of women with no alcohol intake, social drinkers (levels not specified) and heavy drinkers (5). Essentially no differences were detected in levels of biomarkers between self-reported non-drinkers and social drinkers. This suggests that even if meconium analyses may distinguish between heavy drinkers and social drinkers/non-drinkers, they cannot be used at this time to measure low weekly alcohol intake in early pregnancy, and they have not been shown to reliably reflect a few binge drinking episodes in early pregnancy, the focus of our study.

When the Lifestyle During Pregnancy Study was planned, we were well aware of the difficulties in assessing executive functioning, particularly in preschool children. We also were aware that executive functions are not fully developed in 5-year old children, and this was one of the reasons we decided to use a parent and teacher rating scale like the BRIEF rather than a child administered test. However, given the literature on prenatal alcohol exposure (at higher levels) and executive dysfunction, we thought it was important to include at least some measure of these skills. In the paper we point out that it is possible that the BRIEF is not sensitive enough to detect small effects of maternal alcohol consumption. However, when evaluating the results for the BRIEF and executive functions, the results for attention and general intelligence also should be considered. These outcomes were assessed with child administered tests, and the results corroborate the findings for BRIEF. Finally, time constraints and testing fatigue of the child needed to be considered since the IQ and attention measures required child administration. As stated in the articles, we hope future research will build upon our findings as they consider potential measures of all areas neurodevelopment.

In the Discussion section of the paper, we mention the age of the child at assessment as one important limitation of the study. We acknowledge that brain and human cognition is not fully developed at age five, and consequently it is possible that some long term effects of prenatal alcohol exposure on cognition can be detected only later in life. Further, we understand that the concern about age of assessment may be most relevant for complex executive functions. While we recognize the problems related to age of assessment, we believe these problems should be seen in a balanced perspective that distinguishes between the assessment of individual children and the assessment of groups of children exposed to different levels of maternal alcohol consumption. For example, it is well known that development of intelligence during childhood may be relatively unstable in the individual child, but also that intelligence is relatively stable from age 4–5 years on a group level (6). However, we note that at least one study suggests that early effects of prenatal alcohol exposure may be diluted in later childhood and adolescence rather than becoming more pronounced (7). We hope we conveyed that we see this study as an initial effort to measure these domains of neurodevelopment using these particular measures and believe additional

future studies will assess children at older ages perhaps using different, newer assessment measures.

Dr. Parker et al suggest that “the data challenge such a large body of extant evidence.” Generally, our results seem to be well in line with previous findings (8,9).

Finally, a few general comments are made by the authors: Firstly, Dr. Garcia-Algar et al. state “there is clear evidence from animal studies and from human clinical observation that prenatal exposure to alcohol has deleterious effects…” We agree and mention in the papers that there is evidence that daily intake of alcohol may be potentially damaging to the developing fetus. This is well documented in the literature. Our aim was to shed light on the potential effects of low, weekly average intake of alcohol and binge drinking independently of high daily consumption. We have done so in a follow-up design, which has the status of evidence level 2b. Some animal studies and clinical observation are evidence level 5 (10).

Secondly, Dr. Powell suggests that our study is irresponsible. Considering that alcohol is a known teratogen, the large number of women who drink small amounts of alcohol during pregnancy and the large number of women who admit to binge drinking in early pregnancy, we believe it to be reasonable to investigate to what extent this may influence the developing fetus and the child in later life. We consider publication of our findings to be the responsible and ethical course. Again, our intent is that future studies be conducted on this topic, building upon our methods and results.

In conclusion, we think the Lifestyle During Pregnancy Study contributes important methodological and statistical approaches to the literature and that these findings should be considered and incorporated in future studies of low-moderate alcohol consumption and binge drinking during pregnancy. We recognize that this is a single study in one specific population that used a very particular set of exposure and outcome measures, and by no means answers all questions regarding this topic. We reiterate our conclusion from each of the articles that for pregnant women small amounts consumed occasionally may not present serious concern. However, prenatal alcohol exposure is known to cause adverse reproductive outcomes, birth defects and developmental disability. Thus we believe that the most conservative advice for women is not to drink alcohol during pregnancy.

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