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Comparison of maternal reports of alcohol use in pregnancy and the effect of low prenatal alcohol exposure on NEPSY executive function subtests in young children

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Master of Public Health

Epidemiology

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2008

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

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INTRODUCTION The objectives of this study were 1) to compare maternal reports of alcohol consumption during pregnancy collected within 48 hours of delivery and 4.5 years after the birth of the child and 2) to determine relationship between low to moderate prenatal alcohol exposure and child executive function at 4.5 years of age. METHODS Population based sample consisting of 454 participants of the Fetal Growth and Development Study (FGDS) and the Follow-Up of Development and Growth Experiences (FUDGE) Study. Retrospective reports of maternal alcohol consumption during pregnancy were compared and correlated using kappa statistics. Multiple linear regression analysis was used to correlate reported alcohol consumption and child executive functioning at 4.5 years, as measured by the NEPSY Visual Attention and Statue subtests. RESULTS The greatest reporting of alcohol consumption during pregnancy occurred postpartum, with poor to fair agreement between postpartum reports and reports 4.5 years later. Children exposed to alcohol during the 2nd or 3rd trimester had significantly lower scores on the Visual Attention subtest at 4.5 years, scoring 18% lower than children who were not exposed in the controlled model and 19% lower in an alternative model which also controlled for age at follow-up. There was no significant association between alcohol exposure in pregnancy and performance on the Statue Test at 4.5 years. CONCLUSION Executive function deficits are seen in preschool age children who were exposed to low to moderate amounts of alcohol prenatally.

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CHAPTER I: Literature Review

Definitions

Fetal Alcohol Spectrum Disorder (FASD) is the diagnosis used to describe the broad range of effects thought to result from prenatal alcohol exposure (PAE). There are four diagnostic schemas for FASD, which vary in specific requirements to make a diagnosis, but all identify four common features of FASDs: 1) Prenatal exposure to alcohol, 2) facial dysmorphology, 3) growth deficiency and 4) central nervous system (CNS) involvement.[1,2,3,4] Facial features include short palpebral fissures, thin vermillion border and smooth philtrum.

There are three generally accepted syndromes within the umbrella of FASD: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), and neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE; also known as alcohol-related neurodevelopmental disorder, ARND). FAS is considered the most severe FASD and represents 10-15% of children affected by prenatal exposure to alcohol.[5] Diagnosis of FAS requires the following three characteristics: facial features, growth deficiency and CNS involvement. The diagnosis of FAS can be made without confirmation of PAE as long as all three of the other features of FASD are present. PFAS requires confirmed prenatal alcohol exposure, at least two facial features, and evidence of either growth retardation or CNS involvement. A diagnosis of ND-PAE requires confirmed prenatal alcohol exposure and impaired neurocognitive function, self-regulation, or adaptive function of a severity in which functioning is impaired.[6]

Incidence and Prevalence

The Surgeon General advises women who are pregnant (or considering pregnancy) not to drink alcoholic beverages and to be aware of the alcoholic content of food and drugs.[7] However, the CDC estimates 51.5% of nonpregnant women of childbearing age have used alcohol in the last 30 days, and 15.0% binge drank. Of pregnant women, 7.6% reported drinking in the last 30 days and 1.4% reported binge drinking. Of those who reported binge drinking, the amount and frequency of binge drinking (three times per month and six drinks per occasion on average) did not differ by pregnancy status. The highest reported incidence of drinking during pregnancy was among women who were white, employed, college educated and/or aged 34 – 44 years.[7] A previously published report of the population used in this analysis found that 35% of women at a public, primarily African American and low SES hospital drank during the first trimester of pregnancy. Twenty-eight percent of women at a private, primarily white and upper middle class hospital reported drinking during the first trimester of pregnancy. Eighty-five percent of women at both hospitals abstained from drinking in the second trimester. At the public hospital 7.5% reported drinking in the third trimester, whereas 25% of delivering moms at the private hospital drank in the third trimester. Binge, moderate and heavy drinking during pregnancy was more common at the public hospital.[8]

FASD is the most common preventable cause of neurodevelopmental defects, including mental retardation.[9] One recent review estimated the prevalence of FASD is estimated to be 2 – 5% in the US and many Western European countries and the prevalence of the

most severe form, FAS, is estimated to be 2 – 7 per 1,000.[10] However, most estimates are lower: the prevalence of FAS being 0.2 – 2 per 1,000 and the prevalence of FASD 9.1 per 1,000.[11]

Structural Changes

Prenatal alcohol exposure has been shown to cause structural alternations to the shape, volume and surface area of the brain.[12] Animal studies show prenatal alcohol exposure damages the hippocampus.[13] Postmortem studies show microcephaly, hypogenesis of the corpus callosum and anterior commissure, structural abnormalities in the basal ganglia and hippocampus, and cerebellar hypotrophy/hypoplasia in people with FASD.[14] Abnormalities have also been seen in the brain stem, ventricles, pituitary gland and optic nerve, as well as errors in migration and CNS disorganization.

Magnetic resonance imaging (MRI) studies show reductions in brain volume; displacement of the corpus callosum; reduced frontal lobe volumes; structural abnormalities in the cerebellum, caudate, and hippocampus; and functional/perfusion abnormalities in the temporal lobes. Reductions in white matter and increase in gray matter density in corresponding areas has also been shown.[12] Diffusion tensor imaging has shown microstructural abnormalities in white matter bundles of the corpus callosum, cerebellum and corticospinal tracts, which correlate with the severity of FASD and neurocognitive deficits.[14]

Functional MRI (fMRI) studies have shown frontal-subcortical circuits to be vulnerable to prenatal alcohol exposure, particularly projections from the frontal lobes to the basal

ganglia and thalamic nuclei, which are important in executive function. In particular, fMRI studies show increased activation of the prefrontal cortex of FASD individuals during trials requiring inhibition, suggesting it takes greater cognitive resources to execute inhibition in FASD individuals.[13,15]

Timing and Amount of Exposure

The timing of alcohol exposures determines the type of damage done to the brain. Alcohol exposure before week 7 of pregnancy affects the survival and proliferation of progenitor cells, which could lead to microcephaly seen in FAS. Exposure during weeks 7 to 20 alters patters of neuronal migration and cell fate, resulting in fewer neuronal and glial cells in the neocortex, hippocampus and sensory nuclei. Exposure in the 3rd trimester can lead to apoptosis of cells throughout the cerebrum, as well as interfere with astrocyte and oligodendrocyte development, synaptogenesis and cerebellar development.[14]

The amount of alcohol consumed has been associated with the severity of the neurocognitive outcome. Furthermore, the pattern of exposure has also been shown to play a role, as binging results in more severe deficits than chronic exposure of a lower quantity.[13]

Neurocognitive Profile

Recent research has sought to develop a neurocognitive profile of children with FASD. To date, children with FASD have been characterized as having low-average IQ, with deficiencies in both verbal and nonverbal domains; slower information processing; impairment in executive functioning; and deficiencies in visual attention, motor function,

social skills, externalizing behaviors and adaptive function.[16,13] Lack of impairment has been shown in auditory attention, retention of verbal information, and basic language function. This profile was tested in a recent analysis which demonstrated its ability to distinguish heavily alcohol-exposed children from controls.[13]

Intellectual Function

The average IQ for those with FAS is 70, and 80 for those without dysmorphic features.[13] There seems to be an interaction between IQ and psychopathology in FASD; those with an IQ <50 have been found to have worse psychiatric outcome than those with higher IQs.[13] Furthermore, one study found a dose dependent relationship of a 5-point decrease in full-scale IQ for every ounce of absolute alcohol consumed per day of pregnancy.[17,16]

Impairment in cognitive tasks requiring visual motor integration, mental manipulation of numerical information, phonological working memory and social pragmatics have also been shown in children with prenatal alcohol exposure.[16]

Social Cognition

Deficiencies in social cognition are also apparent in the FASD population. Parent and teacher rated scales reveal deficits in social skills. Children with FASD have also been described as displaying socially inappropriate behavior and difficulty with peers that seems to stem from a deficit in self-regulation, but not in difficulty initiating social interactions or using nonverbal communication. Deficiencies in social problem solving

and maladaptive patterns in the generation and evaluation of social responses has also been shown, both pointing to disabilities in executive control.[16]

Attention and Information Processing

Attention and information processing has been shown as an area of deficiency in FASD. Children with FASD have difficulty holding information temporarily in memory while performing a mental operation, as well as shifting attention from one stimulus dimension to another in a flexible way. They have also been shown to have difficulty with tests of vigilance, investment, organization; maintenance of attention over time; and processing relatively complex information.[16]

Learning and Memory

Children with heavy prenatal alcohol exposure exhibit learning and memory deficits, especially in processes that involve conscious effort such as free recall and organization. Even when controlling for IQ, deficits in ability to hold and manipulate information were seen on the backwards conditions of the digit span subtest of the Wechsler Intelligence Scales for Children (WISC) and in computerized visual-spatial working memory tests. Working memory processes underlie executive function and attention skills, which are also impaired in children with FASD.[13,16]

Executive Function

Executive function is the ability to perform goal-directed behavior. It is thought to involve the following constructs: working memory, shifting attention/cognitive

flexibility, inhibitory control and initiating behavior.[18,19] It involves the integration of many processes simultaneously, including: attention, sensation, perception and motor activity.[13,16] Furthermore, there is thought to be both an affective, or "hot," aspect and a cognitive, or "cool," aspect of executive functioning.[18] The affective aspects are associated with the ventral and medial regions of the prefrontal cortex, while the cognitive aspects are associated with the dorsolateral prefrontal cortex.[18]

Impairments in executive functioning in PAE children include deficiencies in planning, conceptual set shifting, affective set shifting, verbal and nonverbal fluency, concept formation and error correction; and greater difficulty with executive control tasks requiring higher levels of manipulation and regulation.[16] Impairment in affective set shifting, as described by parent-rated behavior problems, have also been shown.[16]

In particular, children with prenatal alcohol exposure have demonstrated poorer executive functioning than controls, scoring >1.5 standard deviations from the population average on all subscales of the Behavior Rating Inventory of Executive Functioning (BRIEF), a parent report of executive function. These deficits were predicative of poorer social skills and greater problem behaviors.[13] In 2014, Gross et al. confirmed deficits on the BRIEF but failed to find significant correlations between the parent reports and objective measures of executive function, suggesting that objective measures may fail to fully capture children's daily executive functioning.[19]

Studies using the Wisconsin Card Sorting Test (WCST) and California Card Sorting Test of the Delis-Kaplan Executive Functioning System (D-KEFS) show impairment in forming and shifting concepts, thinking analytically, and fluency in children with prenatal alcohol exposure. The Stroop Test, Go/No-Go tasks and theory of mind measures show deficits in response inhibition in children with prenatal alcohol exposure.[13]

The Rey-Osterrieth Complex Figure (ROCF) is a widely used instrument for evaluating the relationship between executive function, memory and visual perception and construction. Children with FASD show difficulty with organization during the initial encoding of the figure and accuracy in recalling the structural components of the figure over time; they also consistently misplaced design elements.[20]

The Cambridge Neuropsychological Tests Automated Battery (CANTAB), a computerized battery testing executive functioning, shows deficits in performance on a number of tasks in attention, planning, strategy use and working memory in children with FASD. Most impairment was seen in spatial working memory and tasks using spatial working memory and strategy demonstrated the most sensitivity to deficits in cognitive flexibility of FASD children. There was no significant difference across diagnostic sub groups (FAS, pFAS and ARND).[5] In a subsequent study using more subtests of the CANTAB, it was confirmed that children with prenatal alcohol exposure scored lower than the control group on measures of executive functioning, working memory and attention, with particular impairment in spatial working memory. The measure of spatial working memory was able to differentiate between children with PAE who had an FASD

diagnosis and PAE children who did not. However, impairments were not found on measures involving planning, visual discrimination and shifting attention.[20]

The Developmental NEuroPSYchological Assessment (NEPSY) is a tool used to assess attention, executive functioning, language, visuospatial functions and learning and memory in children 5 to 12 years. Few studies have used the NEPSY to test children with PAE. One in 1998 found children with PAE were impaired relative to controls on subtests indexing inhibition.[21] A later study using the NEPSY, found that alcohol-exposed children had deficits on measures of attention, language, motor abilities, visuospatial functions, memory, and learning.[22]

The NEPSY-II added more executive functioning subtests as well as social perception subtests, which include affect recognition and theory of mind. In 2013, a case control study of children with and without FASD aged 6 to 16 years showed impairment on the following NEPSY-II subtests: animal sorting, response set, inhibition (naming and switching conditions), comprehension of instructions, speeded naming, and memory for names. These subtests measure executive functioning, language and memory.[23]

Neurocognitive impairment has been most widely studied in school-aged children exposed to alcohol prenatally, however impairments in executive function has also been shown in pre-school aged children. In 2003, Noland et al. found four-year-olds with FASD performed worse on a tapping inhibition task than children who were not exposed to alcohol prenatally.[24] In 2014, Fuglestad et al. found impairments in both “cool” and

"hot" aspects of executive functioning in children under the age of six, as measured by a scale of cognitive flexibility/set-shifting and a Delay of Gratification task measuring inhibitory capacity and impulse control.[25]

Moderate Alcohol Consumption

Studies of lower levels of alcohol exposure in pregnancy are less conclusive than studies of higher levels of exposure or in FASD populations.[13] A meta-analysis in 2003 found PAE of less than 1 drink per day to have a significant effect on the Mental Development Index of the Bayley Scales of Infant Development at 1 year of age.[26]

Early studies by Streissguth et al. found a 6.7 point decrease in full-scale IQ on the Wechsler Intelligence Scale for Children (WISC) in 7.5 year old children with exposure to 2 or more drinks per day prenatally. This association was exacerbated by low SES, as measured by low paternal education and more children in the household.[27] The same cohort was examined when the children were 4 and 14 years of age; at 4 years of age there was a 4-point decrease in IQ at an exposure level of three drinks per day or more, however at 14 years the effects on IQ were no longer present.[28]

In 2006, Willford, Leech and Day did a prospective study of prenatal substance abuse in 636 mother-child pairs of low SES in a large urban maternity hospital, where most of the mothers drank low to moderate amounts in pregnancy. Women's drinking was assessed during each trimester of pregnancy and the children's growth, development and neurocognitive functioning was assessed in infancy and 3, 6, and 10 years. Separate

analyses were run for blacks and whites and found significant effects of PAE on cognitive development, at 10 years only among the black children—IQ was decreased by 1.9 points when alcohol intake was increased from none to one drink per day, prenatally. Namely, lower values were seen on the composite score and abstract/visual reasoning, verbal reasoning, quantitative reasoning and short-term memory tasks for black children exposed to alcohol in the second trimester (which included many children exposed in the first trimester as well.) It was unclear why different results were found for blacks and whites, but was determined not to be due to differences in the rate of drinking, the proportion of binge drinking or measureable characteristics of socioeconomic status between the races.[29]

In 2012, Falgreen Eriksen et al. did a prospective follow-up study of 1628 women and their children, sampled in four Danish cities, looking at low to moderate prenatal alcohol exposure. They tested children at 5 years of age using the Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R) and found no difference in test performance between children whose mothers reported drinking low amounts of alcohol, one to four or five to eight drinks per week, at some point in pregnancy and children whose mothers abstained. The consumption of higher levels of alcohol, nine or more drinks per week, was associated with a decrease of six IQ points, or 0.5 standard deviations, although this decrease was not statistically significant. When IQ was analyzed as a dichotomous variable, significant below-average full-scale and verbal IQs were observed for higher alcohol exposure.[28]

Study Objectives

The objectives of this study were 1) to determine the reliability of maternal reports of alcohol consumption during pregnancy collected postnatally (within 48 hours of delivery) and 4.5 years after the birth of the child (follow-up) and 2) to determine relationship between low to moderate prenatal alcohol exposure and child executive function at 4.5 years of age, as measured by the NEPSY.

CHAPTER II: Manuscript

H. Title, Author(s), Abstract

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Heather L. Hoecker, BA and Carolyn D. Drews-Botsch, PhD, MPH

INTRODUCTION The objectives of this study were 1) to compare maternal reports of alcohol consumption during pregnancy collected within 48 hours of delivery and 4.5 years after the birth of the child and 2) to determine relationship between low to moderate prenatal alcohol exposure and child executive function at 4.5 years of age. METHODS Population based sample consisting of 454 participants of the Fetal Growth and Development Study (FGDS) and the Follow-Up of Development and Growth Experiences (FUDGE) Study. Retrospective reports of maternal alcohol consumption during pregnancy were compared and

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I. Introduction

The Surgeon General advises women who are pregnant (or considering pregnancy) abstain from drinking alcohol.[7] However, 7.6% of pregnant women report drinking during a pregnancy, and 1.4% report binge drinking.[7] A previously published report of the population used in this analysis found that 35% of women at a public, primarily African American and low SES hospital drank during the first trimester of pregnancy. Twenty-eight percent of women at a private, primarily white and upper middle class hospital reported drinking during the first trimester of pregnancy. Eighty-five percent of women at both hospitals

abstained from drinking in the second trimester. At the public hospital 7.5% reported drinking in the third trimester, whereas 25% of delivering moms at the private hospital drank in the third trimester. Binge, moderate and heavy drinking during pregnancy was more common at the public hospital.[8]

Fetal Alcohol Spectrum Disorder (FASD), the diagnosis used to describe the broad range of effects thought to result from prenatal alcohol exposure, is the most common preventable cause of neurodevelopmental defects, including mental retardation.[9] It is characterized by a combination of any of the following four criteria: 1) Prenatal exposure to alcohol, 2) facial dysmorphology, 3) growth deficiency and 4) central nervous system (CNS) involvement.[1,2,3,4] FASD is the most common preventable cause of neurodevelopmental defects, including mental retardation.[9] One recent review estimated the prevalence of FASD is estimated to be 2 – 5% in the US and many Western European countries and the prevalence of the most severe form, FAS, is estimated to be 2 – 7 per 1,000.[10] However, most estimates are lower: the prevalence of FAS being 0.2 – 2 per 1,000 and the prevalence of FASD 9.1 per 1,000.[11]

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have shown frontal-subcortical circuits, particularly important for executive function, to be vulnerable to prenatal alcohol exposure.[13,15]

The amount of alcohol consumed has been associated with the severity of the neurocognitive outcome. Furthermore, the pattern of exposure has also been shown to play a role, as binging results in more severe deficits than chronic exposure of lower quantities.[13]

To date, children with FASD have been characterized as having low-average IQ, with deficiencies in both verbal and nonverbal domains; slower information processing; impairment in executive functioning; and deficiencies in visual attention, motor function, social skills, externalizing behaviors and adaptive function.[16,13]

The Developmental NEuroPSYchological Assessment (NEPSY) is a tool used to assess attention, executive functioning, language, visuospatial functions and learning and memory in children 5 to 12 years. Few studies have used the NEPSY to test children with PAE. One in 1998 found children with PAE were impaired relative to controls on subtests indexing inhibition.[21] A later study using the NEPSY, found that alcohol-exposed children had deficits on measures of attention, language, motor abilities, visuospatial functions, memory, and learning.[22] The NEPSY-II added more executive functioning subtests as well as social perception subtests which include affect recognition and theory of mind. In 2013, a case control study of children with and without FASD aged 6 to 16 years showed impairment on the following NEPSY-II subtests corresponding to deficiencies in executive functioning, language and memory: animal sorting,

response set, inhibition (naming and switching conditions), comprehension of instructions, speeded naming, and memory for names.[23]

Neurocognitive impairment has also been shown in preschool aged children. In 2003, Noland et al. found four-year-olds with FASD performed worse on a tapping inhibition task than children who were not exposed to alcohol prenatally.[24] In 2014, Fuglestad et al. found impairments in both "cool" and "hot" aspects of executive functioning in children under the age of six, as measured by a scale of cognitive flexibility/set-shifting and a Delay of Gratification task measuring inhibitory capacity and impulse control.[25]

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low amounts of alcohol (one to four, or five to eight drinks per week at some point in pregnancy) and children whose mothers abstained.[28]

The objectives of this study were 1) to determine the reliability of maternal reports of alcohol consumption during pregnancy collected within 48 hours of delivery and 4.5 years after the birth of the child (follow-up) and 2) to determine relationship between low to moderate prenatal alcohol exposure and child executive function at 4.5 years of age, as measured by the NEPSY.

J. Methods

Sample

The sample consisted of 454 participants of the Fetal Growth and Development Study (FGDS) and the Follow-Up of Development and Growth Experiences (FUDGE) Study. Participants were African-American and White singleton infants born between 32 and 42 weeks gestation, at Northside Hospital, a private hospital in the northern Atlanta suburbs, and at Grady, a county teaching hospital in urban Atlanta, between February 1, 1993 and December 31, 1994. The following groups were excluded due to small numbers and lack of appropriate comparison groups: multiple births, infants who were neither black nor white, and infants with a gestational age less than 32 or greater than 42 weeks.

Study Design and Data Collection

The FGDS was a case-control study of small for gestational age (SGA) children. Hospitals were randomly chosen within blocks of four weeks such that

births were recruited during two of each four week period. During the data collection weeks at each hospital, data was collected for all deliveries from labor and delivery logs at the public hospital and from nursery logs at the private hospital. Study staff abstracted basic information (race, sex, gestational age, plurality, and birth weight) about all deliveries at the chosen hospital. All infants whose birth weight was $<10^{th}$ percentile for gestational age, race and sex were selected as SGA cases. A random 3% sample of all other, AGA, singleton infants were included as controls.

Gestational age was taken from the labor and delivery log, the nursery log or the medical record, based on the clinician's best estimate. Birth weights and gestational ages were validated against information recorded on prenatal records, birth certificates, and a Ballard examination conducted by a study nurse. SGA was defined as a birth weight less than the 10^{th} percentile for gestational age, using fetal growth curves for singleton infants delivered at sea level (Yip, CDC Internal Document). Sex and race-specific norms for birth weight for gestational age were based on a previous population-based analysis of the U.S. birth cohort (Yip, personal communication, 1992).

Written informed consent was obtained from mothers of infants selected for the study. A structured interviewed was conducted with mothers, collecting information about their use of alcohol, drugs and cigarettes during pregnancy, demographic, reproductive, behavioral and medical factors. 98% of interviews took place in the hospital and 95% within 48 hours of delivery.

When the infants were 4.5 years of age, a subset of 760 mothers were re-contacted about participating in a follow-up via mail. This subset included all mothers reporting any alcohol use during pregnancy, all mothers of infants with average birth weight for gestational age, and half (50%) of mothers of SGA infants whose mothers reported abstaining from alcohol use throughout pregnancy. If they agreed to participate a single data collection session was arranged at one of two local clinics. All testing was done in the mornings, but weekend appointments were provided. At this session, children were measured by a trained staff member and a study psychologist or psychology intern tested the child. The testing session included: an assessment of overall cognitive ability (the Differential Abilities Scales), mathematical reasoning (Test of Early Mathematical Ability), and the Developmental NEuroPSYchological Assessment (NEPSY) to assess attention, executive functioning, language, visuospatial functions and learning and memory. This staff member also conducted a Vineland Adaptive Behavior Scales to assess adaptive functioning. While the child was completing these assessments, a trained study interviewer completed a detailed interview with the mother and administered the Child Behavior Checklist to assess behavior problems.

Objective 1: Variables

The FGDS Maternal Questionnaire asked mothers how often they drank alcoholic beverages during the 1st, 2nd and 3rd trimesters of their pregnancy. Dichotomous variables were created to indicate consumption of any alcoholic

beverages at all in pregnancy, in each trimester, and/or in the 2nd or 3rd trimester. Additional dichotomous variables indicating drinking alcohol once per month in all trimesters and in the 2nd and 3rd trimesters only were created.

The FGDS Maternal Questionnaire also asked mothers the largest number of drinks they drank in one day during the 1st, 2nd and 3rd trimesters of their pregnancy, respectively (see appendix for list of questions asked). Dichotomous binge-drinking variables were created indicating respondents who said they binge drank (drank greater than or equal to five drinks) in one day during *any* trimester of their pregnancy; during a specific trimester of pregnancy (1st, 2nd or 3rd); and during late pregnancy (2nd or 3rd trimester). Mothers were then asked *how often* they binge drank in each trimester, from which dichotomous variables were created to indicate mothers who binge drank at least once per month in any trimester, and once per month in both the 2nd and 3rd trimesters.

The FUDGE Maternal Questionnaire asked mothers how often they drank beer, wine and liquor when they were pregnant, from which dichotomous variables indicating drinking any alcoholic beverage any time during pregnancy, and at least once per month, were created.

The FUDGE Maternal Questionnaire also asked mothers what the largest number of drinks and how often they drank five or more drinks of beer, wine and liquor in one day when they were pregnant. They were also asked how often they drank beer, wine and liquor when they were pregnant (Appendix). Dichotomous binge-drinking variables indicating drinking five or more drinks at any point and at least once per month during pregnancy were created.

Objective 1: Statistical Analysis

Frequencies and percentages of baseline and follow-up drinking and binge-drinking variables were calculated and compared using a simple kappa coefficient.

Objective 2: Variables

The primary outcomes were Z scores from the Visual Attention and Statue subtests of the NEPSY (Korkman, Kirk & Kemp, 1998), a standardized neuropsychological battery for children ages 3 – 16. The Visual Attention subtest is a sustained attention control task in which the child was instructed to select only the items that match the target stimuli on a page containing both targets and irrelevant stimuli. The Statue subtest is a measure of motor persistence in which the child was asked to maintain a fixed body position with eyes closed during a 75-second period in which the examiner made a series of distracting noises.

Exposures were drinking and binge-drinking during pregnancy. Dichotomous exposure variables collected at baseline (FGDS) included: consumption of any alcohol in the 2nd or 3rd trimester, drinking once per month in the 2nd and 3rd trimesters, drinking greater than or equal to five drinks in one day during the 2nd or 3rd trimesters, and binge drinking at least once per month in both the 2nd and 3rd trimesters. Dichotomous exposure variables collected at follow-up (FUDGE) included: drinking any alcoholic beverage any time during pregnancy, drinking at least once per month, drinking 5 or more drinks in one day, and binging at least once per month during pregnancy.

Covariates included: birth hospital (proxy for race and SES), gestational age, small for gestational age (SGA; <10th percentile for gestational age), gender, Differential Ability Scales General Cognitive Cluster Standard Score (proxy for IQ), maternal report of illicit drug use during pregnancy and maternal report of smoking during pregnancy. The sample was restricted to babies born between 37 and 42 weeks.

Objective 2: Statistical Analysis

Univariate analyses were performed for 8 demographic variables; mean and standard deviation were reported for continuous variables, and frequencies and percentages were reported for dichotomous variables. Statistics were reported for mothers who drank and binge drank in pregnancy, as reported at baseline and follow-up. Simple linear regression and Chi-Square tests were performed to compare the differences in demographics for mothers who reported drinking and those who did not. Statistical significance was determined for each comparison of demographic information between those who responded "yes" and "no" to each exposure variable.

Bivariate analyses were performed between the demographic characteristics and the maternal drinking exposure variables and the executive functioning outcome variables, respectively. Pooled t-tests were used to assess the relationship between the following covariates and the executive functioning Z scores: birth hospital, gender, SGA, drug use and smoking during pregnancy. Pooled t-test were also used to assess the relationship between IQ and the

drinking exposure variables. Pearson Correlation Coefficients were used to assess the relationship between IQ and the executive functioning Z scores. Chi-Square tests assessed the relationship between the following covariates and the drinking exposure variables: drug use during pregnancy, smoking during pregnancy, birth hospital, gender and SGA.

Multiple linear regression was used to assess the relationship between maternal drinking during pregnancy and executive functioning of the child at follow-up. Crude and controlled models were run. The following covariates were used in the controlled model: IQ, smoking during pregnancy, SGA, sex and birth hospital. Alternative models, which added the covariates drug use during pregnancy and age at follow-up, respectively, were fit. Birth hospital (Grady vs. Northside) was used as a proxy of socioeconomic status. General DAS score was used as a proxy for IQ because participants were too young to measure a true IQ. Confounders were chosen based on evidence from the literature of association with the exposure (maternal drinking) and outcome (executive functioning), not the bivariate analysis.

Difference in Least Squares Means (LSMeans) and beta estimates were used to assess the magnitude of the association between maternal drinking during pregnancy and executive functioning of the child. Adjusted R-square was used to assess model fit.

All analyses were performed using SAS Version 9.3 and an alpha level of 0.05 was used to determine statistical significance.

K. Results

Objective 1

Table 1 presents the frequency and percentage of mothers who drank and binge-drank alcohol during their pregnancy, reported at baseline and follow-up. Table 2 presents agreement between baseline and follow-up reports of drinking. In general, the greatest reporting of alcohol consumed occurred postpartum (earlier time point), with the exception of reporting binging at least once per month throughout pregnancy. Kappa coefficients comparing baseline to follow-up reports of alcohol use during pregnancy were 0.25 and 0.50 for binge drinking and any drinking, respectively. This suggests poor to fair agreement between post-partum reports and reports later in childhood. In general, agreement was lower for binge-drinking variables than for other consumption variables.

Objective 2

Table 3 presents the results of the univariate analysis. Birth Hospital, smoking during pregnancy, drug use during pregnancy, SGA and IQ differed significantly ($p<0.05$) by almost all drinking variables. Some of the drinking variables reported at follow-up had >10% data missing, which could introduce bias.

Tables 4 and 5 describe the bivariate associations between demographic characteristics (child IQ, smoking during pregnancy, drug use during pregnancy, SGA, gender and birth hospital) and alcohol exposure and executive functioning outcomes, respectively. Smoking and drug use during pregnancy were

significantly associated ($p<0.05$) with both maternal drinking (reported at both baseline and follow-up) and child executive functioning. Smoking and drug use during pregnancy, IQ, and being born at Grady Memorial Hospital were confounders of the association between *binge* drinking during pregnancy and child executive functioning.

Children exposed to alcohol during the 2nd or 3rd trimester in utero had significantly lower scores on the Visual Attention subtest at 4.5 years, scoring 18% lower than children who were not exposed in the controlled model (difference LSMeans = -0.177, 95% CI = -0.334, -0.020), and 19% lower in an alternative model which also controlled for age at follow-up (difference LSMeans = -0.186, 95% CI = -0.343, -0.029). Visual Attention was significantly lower in the crude models for the following alcohol exposure variables: baseline reported drinking monthly during 2nd and 3rd trimesters, follow-up reported monthly drinking during pregnancy, baseline reported binging at all and monthly during the 2nd and 3rd trimesters, and follow-up reported binging any time and monthly during pregnancy (Table 6). While Visual Attention scores were lower for children with these alcohol exposures, these associations were not statistically significant in the controlled models.

There was no significant association between alcohol exposure in pregnancy and performance on the Statue Test at 4.5 years (Table 7).

The models explained a relatively low percentage of variability in the controlled models for both the Visual Attention (adjusted $R^2 = 0.266 – 0.294$) and

Statue Test (adjusted $R^2 = 0.063 – 0.074$), with better model fit for the Visual Attention subtest.

L. Discussion

This study found the greatest reporting of alcohol consumed occurred postpartum (earlier time point). Kappa coefficients suggested poor to fair agreement between post-partum reports and reports 4.5 years later. This is the only analysis, to our knowledge, comparing two retrospective reports of maternal drinking during pregnancy and seems to suggest that the closer the report in time to the pregnancy the better. One study compared antenatal reports of drinking to retrospective reports 5 years later and found the reporting at the two timepoints to be correlated (r = 0.67), but that a large proportion of women had higher reported drinking during pregnancy when asked 5 years later, than when asked during pregnancy.[30] Similarly, a study comparing antenatal reports of drinking to reports 14 years later found significantly more reporting 14 years later.[31] One possible explanation for the discrepancy between these findings and ours is that alcohol consumption occurred after the antenatal reports, as there were still weeks of the pregnancy left. Alvik et al conducted a prospective, population-based questionnaire study of women's alcohol use during pregnancy. Women filled out surveys regarding their alcohol use at 17 and 30 weeks of pregnancy and 6 months after term. They found that retrospective reports of alcohol use during pregnancy were significantly higher than concurrent reports.[33].In this case the retrospective reports were closer in time to our postpartum reports, however since

they did not include a later time point it is hard to compare these results to our study. Another limitation of our comparison is that the questions were worded slightly differently at postpartum and 4.5 years later, which could account for the poor agreement between the reports and the discrepancy between our finding and the literature.

Toward the second objective, it was found that children exposed to alcohol during the 2nd or 3rd trimester in utero had significantly lower scores on the Visual Attention subtest at 4.5 years, scoring 18% lower than children who were not exposed in the controlled model and 19% lower in an alternative model which also controlled for age at follow-up. Visual Attention was significantly lower in the crude models of alcohol exposure, but these associations were not statistically significant in controlled models. There was no significant association between alcohol exposure in pregnancy and performance on the Statue Test at 4.5 years.

Limitations of this study were greater than10% missing data among some of the drinking variables reported at follow-up and an over-sampling of drinking women in the follow-up study, both potentially introducing bias into the analysis. The study was also lacking in statistical power due to small sample sizes of women who reported drinking, and especially drinking in higher amounts during pregnancy. While all drinking was associated with poorer executive functioning outcomes, the drinking variable with the largest sample size was the only significant association. Thus the higher exposures, such as binge drinking, were likely not significantly correlated to executive function due to lack of statistical power.

Strengths of the study include a population-based sample that covers a broad SES spectrum. This study adds to the literature of executive function deficits in preschool age children who were exposed to low to moderate amounts of alcohol prenatally. Deficits in executive function have direct impact on a child's future success in school and living independently. Identifying children affected by prenatal alcohol exposure at a younger age has implications for earlier and more effective interventions. Furthermore, evidence suggesting significant cognitive deficits resulting from low amounts of prenatal alcohol exposure late in pregnancy further strengthens the argument that there is no safe amount of alcohol and a greater public health effort to reduce prenatal alcohol exposure is needed.

M. Tables*

Table 1. Frequency and percentage of alcohol drank during pregnancy, reported at baseline (FGDS) and follow-up (FUDGE)

Reported at delivery (FGDS) n = 454		**Reported at follow-up (FUDGE)** n = 454	
	n (%)		**n (%)**
Binge drank during pregnancy	56 (11.2)	Binge drank during pregnancy	22 (4.8)
Binge drank during 2nd or 3rd trimester	29 (5.8)		
		Binge drank at least once per month in **any** trimester	17 (3.3)
Binge drank at least once per month in **2nd and 3rd trimester**	16 (3.2)		
Binge drank at least once per month in **every** trimester	13 (2.6)		
Drank alcohol during pregnancy	258 (51.6)	Drank alcohol during pregnancy	145 (31.2)
Drank alcohol during 2nd or 3rd trimester	125 (25.1)		
		Drank alcohol at least once per month during **any** trimester	58 (11.4)
Drank alcohol at least once per month **every** trimester	56 (11.0)		
Drank alcohol at least once per month in the **2nd and 3rd trimester**	61 (12.0)		

Table 2. Agreement of reports of drinking alcohol during pregnancy

Reported at delivery (FGDS) n = 454		**Reported at follow-up (FUDGE)** n = 454		
	n (%)		**n (%)**	**Kappa**
Binge drank during pregnancy	56 (11.2)	Binge drank during pregnancy	22 (4.8)	0.246
Drank alcohol during pregnancy	258 (51.6)	Drank alcohol during pregnancy	145 (31.2)	0.480

Table 3. Descriptive statistics of demographic, maternal and child characteristics

	Overall n = 454	**Drink any time during pregnancy** n = 258	**Drink during 2nd or 3rd trimester** n = 125	**Drink monthly in 2nd and 3rd trimesters** n = 61	**Binge any time during pregnancy** n = 56	**Binge during 2nd or 3rd trimester** n = 29	**Binge monthly in both 2nd and 3rd trimesters** n = 16
Demographic Characteristics				**n (%)**			
Private Hospital	236 (52.0)	128 (55.4)	66 (55.9)	17 (31.5)*	16 (33.3)*	1 (4.2)*	0 (0.0)*
Public Hospital	208 (45.8)	103 (44.6)	52 (44.1)	37 (68.5)*	32 (66.7)*	23 (95.8)*	12 (100.0)*
Maternal Characteristics							
Smoking during pregnancy	115 (25.3)	97 (42.2)*	63 (53.9)*	42 (77.8)*	38 (79.2)*	23 (95.8)*	11 (91.7)*
Drug use during pregnancy	55 (12.1)	45 (19.5)*	27 (22.9)*	27 (50.0)*	22 (45.8)*	18 (75.0)	11 (91.7)*
Child Characteristics							
Small for Gestational Age	287 (63.2)	169 (73.2)*	87 (73.7)*	44 (81.5)*	40 (83.3)*	23 (95.8)*	11 (91.7)
Male	231 (50.9)	123 (53.3)	61 (51.7)	25 (46.3)	28 (58.3)	18 (75.0)*	10 (83.3)*
				mean (sd)			
Differential Ability Scales General Cognitive Cluster Standard Score (proxy for IQ)	88.1 (18.4)	89.9 (18.6)*	89.8 (19.5)	82.0 (20.0)*	82.7 (19.0)*	72.4 (12.1)*	73.4 (12.4)*
Gestational Age (weeks)	39.0 (1.2)	39.0 (1.2)	39.1 (1.3)	39.1 (1.2)	39.0 (1.15)	38.5 (0.93)*	38.6 (0.90)

*p<.05; statistical significance was determined for each comparison of demographic information between those who responded "yes" and "no" to each exposure variable

[$]>10% data missing

Table 4. Bivariate analysis to identify confounders of the association between maternal drinking variables and executive functioning outcomes

	Baseline reported drinking				**Executive Functioning Outcomes**			
	during 2nd or 3rd trimester		**monthly in 2nd and 3rd trimesters**		**Visual Attention (Z-score)**		**Statue Test (Z-score)**	
Covariate	**test**	**p-value**	**test**	**p-value**	**test**	**p-value**	**test**	**p-value**
IQ[4]	-1.34[1]	0.182	2.48[1]	**0.014**	0.51[2]	**<.0001**	0.28[2]	**<.0001**
Smoking during pregnancy	64.02[3]	**<.0001**	85.62[3]	**<.0001**	2.9[1]	**0.004**	1.09[1]	0.275
Drug use during pregnancy	17.18[3]	**<.0001**	82.14[3]	**<.0001**	6.36[1]	**<.0001**	2.59[1]	**0.010**
Small for Gestational Age	5.91[3]	0.015	7.70[3]	**0.006**	1.96[1]	0.051	1.57[1]	0.118
Male	0.00[3]	0.955	0.08[3]	0.779	-4.21[1]	**<.0001**	-0.73[1]	0.469
Grady Memorial Hospital	0.46[3]	0.499	11.73[3]	**0.001**	7.81[1]	**<.0001**	2.94[1]	**0.004**

[1]Pooled t-tests
[2]Pearson Correlation Coefficients
[3]Chi-Square test
[4]Differential Ability Scales General Cognitive Cluster Standard Score, used as a proxy for IQ

Table 5. Bivariate analysis to identify confounders of the association between maternal binge drinking variables and executive functioning outcomes

	Baseline reported binging				**Executive Functioning Outcomes**			
	during 2nd or 3rd trimester		**monthly in both 2nd and 3rd trimesters**		**Visual Attention (Z-score)**		**Statue Test (Z-score)**	
Covariate	**test**	**p-value**	**test**	**p-value**	**test**	**p-value**	**test**	**p-value**
IQ[4]	4.12[1]	**<.0001**	2.68[1]	**0.008**	0.51[2]	**<.0001**	0.28[2]	**<.0001**
Smoking during pregnancy	64.26[3]	**<.0001**	27.88[3]	**<.0001**	2.90[1]	**0.004**	1.09[1]	0.275
Drug use during pregnancy	93.53[3]	**<.0001**	74.20[3]	**<.0001**	6.36[1]	**<.0001**	2.59[1]	**0.010**
Small for Gestational Age	10.85[3]	**0.001**	3.98[3]	**0.046**	1.96[1]	0.051	1.57[1]	0.118
Male	5.42[3]	**0.020**	4.84[3]	**0.028**	-4.21[1]	**<.0001**	-0.73[1]	0.469
Grady Memorial Hospital	24.58[3]	**<.0001**	14.13[3]	**0.000**	7.81[1]	**<.0001**	2.94[1]	**0.004**

[1]Pooled t-tests
[2]Pearson Correlation Coefficients
[3]Chi-Square test
[4]Differential Ability Scales General Cognitive Cluster Standard Score, used as a proxy for IQ

Table 6. Models to assess the association between prenatal alcohol exposure and Visual Attention subtest

	Drinking exposure	Model[1]	Difference Least Squares Means	95% CI		p-value
Baseline reported drinking	**during 2nd or 3rd trimester**	crude	-0.137	-0.303	0.029	0.106
		controlled	-0.177	-0.334	-0.020	**0.027**
		alternative 1	-0.150	-0.306	0.005	0.058
		alternative 2	-0.186	-0.343	-0.029	**0.045**
	monthly in 2nd and 3rd trimesters	crude	-0.360	-0.582	-0.137	0.002
		controlled	-0.204	-0.420	0.012	0.064
		alternative 1	-0.100	-0.325	0.125	0.382
		alternative 2	-0.208	-0.424	0.008	0.059
Baseline reported binging	**during 2nd or 3rd trimester**	crude	-0.518	-0.856	-0.180	0.003
		controlled	-0.075	-0.399	0.249	0.651
		alternative 1	0.099	-0.237	0.434	0.564
		alternative 2	-0.084	-0.408	0.240	0.610
	monthly in both 2nd and 3rd trimesters	crude	-0.727	-1.199	-0.254	0.003
		controlled	-0.275	-0.705	0.155	0.209
		alternative 1	-0.066	-0.509	0.377	0.770
		alternative 2	-0.266	-0.695	0.164	0.225

[1]controlled model: IQ, smoking during pregnancy, SGA, sex and birth hospital; alternative models: added drug use during pregnancy (1) and age at follow-up (2)

Table 7. Models to assess the association between prenatal alcohol exposure and Statue Test

	Drinking exposure	Model[1]	Difference Least Squares Means	95% CI		p-value
Baseline reported drinking	**during 2nd or 3rd trimester**	crude	0.038	-0.144	0.220	0.681
		controlled	0.025	-0.169	0.220	0.797
		alternative 1	0.040	-0.155	0.235	0.686
		alternative 2	0.012	-0.182	0.206	0.785
	monthly in 2nd and 3rd trimesters	crude	-0.062	0.619	-0.062	0.184
		controlled	0.044	**0.748**	**0.044**	0.311
		alternative 1	0.103	**0.467**	**0.103**	0.380
		alternative 2	0.040	**0.767**	**0.040**	0.306
Baseline reported binging	**during 2nd or 3rd trimester**	crude	-0.208	-0.581	0.165	0.273
		controlled	0.013	-0.387	0.412	0.951
		alternative 1	0.088	-0.325	0.500	0.676
		alternative 2	0.000	-0.398	0.398	1.000
	monthly in both 2nd and 3rd trimesters	crude	-0.220	-0.741	0.301	0.407
		controlled	-0.018	-0.547	0.511	0.947
		alternative 1	0.092	-0.459	0.643	0.743
		alternative 2	0.003	-0.525	0.530	0.993

[1]controlled model: IQ, smoking during pregnancy, SGA, sex and birth hospital; alternative models: added drug use during pregnancy (1) and age at follow-up (2)

N. Appendix

FGDS Maternal Questionnaire Questions

1. I would like you to think back to the [1st trimester]* of your pregnancy. In the [1st trimester] on an average how often did you drink alcoholic beverages? Was it
    a. Every day
    b. 3 or 4 times a week
    c. Once or twice a week
    d. 2 or 3 times a month
    e. About once a month
    f. Less than once a month
    g. Or did you not have even one drink in this period
2. In [1st trimester] when you did drink alcoholic beverages, what type of alcoholic beverages did you most often drink? Was it
    a. Beer
    b. Wine
    c. Or Liquor
    d. Beer and Wine
    e. Beer and Liquor
    f. Wine and Liquor
    g. Beer, Wine and Liquor
3. In [1st trimester] on days when you drank alcoholic beverages, how many drinks would you usually have in one day?
4. In [1st trimester] what was the largest number of drinks you ever drank in one day?
5. In [1st trimester] how often did you drink more than 5 drinks in one day? Was it
    a. Every day
    b. 3 or 4 times a week
    c. Once or twice a week
    d. 2 or 3 times a month
    e. About once a month
    f. Less than once a month

    *The same questions were asked separately for each trimester of pregnancy (1st, 2nd and 3rd)

FUDGE Maternal Questionnaire Questions

1. Now, I'd like you to think back to the time when you were pregnant with [*child*]. When you were pregnant with [*child*], how often did you drink beer? Did you drink beer…? [PROMPT: Beer includes beer and malt liquor.]
    a. Every day
    b. 5 or 6 times a week
    c. 3 or 4 times a week
    d. Once or twice a week

   e. 2 or 3 times a month
   f. About once a month
   g. Less than once a month or
   h. Not at all
2. When you were pregnant with [*child*], on days when you drank beer, how many beers would you usually have in one day? [PROMPT: A drink of beer means a can or bottle of beer]
3. When you were pregnant with [*child*], how often did you drink wine? Did you drink wine…? [PROMPT: Wine includes white, red or blush wine, champagne, wine coolers, sweet wines and fortified wines.]
   a. Every day
   b. 5 or 6 times a week
   c. 3 or 4 times a week
   d. Once or twice a week
   e. 2 or 3 times a month
   f. About once a month
   g. Less than once a month or
   h. Not at all
4. When you were pregnant with [*child*], on days when you drank wine, how many glasses of wine would you usually have in one day? [PROMPT: A drink of wine means a glass of wine]
5. When you were pregnant with [*child*], how often did you drink liquor? Did you drink liquor…? [PROMPT: Liquor includes whiskey, vodka, coctails, mixed drinks and liqueurs.]
   a. Every day
   b. 5 or 6 times a week
   c. 3 or 4 times a week
   d. Once or twice a week
   e. 2 or 3 times a month
   f. About once a month
   g. Less than once a month or
   h. Not at all
6. When you were pregnant with [*child*], on days when you drank liquor, how many glasses would you usually have in one day? [PROMPT: A drink of liquor means a shot]
7. When you were pregnant with [*child*], what is the largest number of drinks of beer, wine and liquor that you ever drank in one day?
8. When you were pregnant with [*child*], how often did you drink 5 or more drinks of beer, wine and liquor in one day?
   a. Every day
   b. 5 or 6 times a week
   c. 3 or 4 times a week
   d. Once or twice a week
   e. 2 or 3 times a month
   f. About once a month
   g. Less than once a month

O. The FUDGE Maternal Questionnaire asked mothers how often they drank beer, wine and liquor when they were pregnant, from which dichotomous variables indicating drinking any alcoholic beverage any time during pregnancy, and at least once per month, were created.
P. The FUDGE Maternal Questionnaire also asked mothers what the largest number of drinks and how often they drank five or more drinks of beer, wine and liquor in one day when they were pregnant. They were also asked how often they drank beer, wine and liquor when they were pregnant (Appendix).

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