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Breastfeeding and Neurodevelopment in infants exposed to alcohol during pregnancy

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in

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by

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The thesis of Kristen Schaffer is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
ADHD	Attention Deficit Hyperactivity Disorder
AFR	African Region
AMR	Region of the Americas
ARBD	Alcohol-Related Birth Defects
ARND	Alcohol-Related Neurodevelopmental Disorder
BSID	Bayley Scales of Infant Development
CDC	Centers for Disease Control and Prevention
CIFASD	Collaborative Initiative on Fetal Alcohol Spectrum Disorders
EMR	Eastern-Mediterranean Region
EUR	European Region
FASD	Fetal Alcohol Spectrum Disorder
FAS	Fetal Alcohol Syndrome
ICD-10	International Classification of Diseases, Version 10
IQ	Intelligence Quotient
IRB	Internal Review Board
MDI	Mental Developmental Index
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIH	National Institutes of Health
ozAA	Absolute Ounces of Alcohol
PAE	Prenatal Alcohol Exposure
PDI	Psychomotor Developmental Index

PFAS	Partial Fetal Alcohol Syndrome
SD	Standard Deviation
SEAR	South-East Asia Region
SES	Socioeconomic status
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WPR	Western Pacific Region

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ABSTRACT OF THE THESIS

Breastfeeding and Neurodevelopment in infants exposed to alcohol during pregnancy

by

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Few previous studies have evaluated the differential benefits of breastfeeding on infant neurodevelopment depending on the level of prenatal alcohol exposure (PAE). This study aims to identify if the association between breastfeeding and infant neurodevelopment is modified by pattern of PAE.

The study sample included 392 Ukrainian infants born to pregnant mothers prospectively enrolled in a cohort study who reported various levels of prenatal alcohol consumption. Infant neurodevelopment was assessed at 6- and 12-months using the Bayley Scales of Infant Development II (BSID-II) Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI). Linear regression modeling with interaction terms and stratification by PAE group was used to determine the relationship between breastfeeding and infant neurodevelopment.

When controlling for PAE and key covariates, breastfeeding had a positive significant association with the PDI and MDI at 6 months but not at 12 months. The interaction terms were significant at the 0.05 level for the MDI and PDI at 6- and 12-months, indicating a joint effect of PAE and breastfeeding on infant neurodevelopment that goes beyond the effects of PAE and breastfeeding alone. Infants exposed to high levels of PAE who were breastfed had the greatest mean increase in PDI and MDI scores at both 6- and 12-months compared to infants who were never breastfed.

There is a significant joint effect of PAE and breastfeeding on infant neurodevelopment at 6- and 12-months. Infants exposed to high levels of PAE may experience the greatest benefits from breastfeeding, especially for durations of four months or longer.

CHAPTER 1: INTRODUCTION

Fetal Alcohol Syndrome (FAS) was first recognized by Kenneth Jones in 1973 when he identified patterns of growth deficiency and developmental delay in infants of alcoholic mothers.[1] FAS is now considered the most severe form of fetal alcohol spectrum disorder (FASD), which encompasses the range of physical and neurodevelopmental deficits that can result from prenatal alcohol exposure (PAE). FASD is estimated to affect 7.7 per 1000 population throughout the world, though rates are disproportionately higher in countries and regions with increased drinking patterns.[2] For example, a meta-analysis that included studies from 187 countries found that South Africa had the highest prevalence of FASD by country at 111.1 per 1000 population.[3] The highest prevalence by region is the World Health Organization's European region (comprised of 53 countries) with a prevalence of 19.8 per 1000 population.[3,4]

Though facial and other physical features are the hallmark visible sign of FASD, the deficiencies in neurocognition and behavior are what define this disorder.[5-7] The neurocognitive and behavioral signs are difficult to identify, especially in more mild cases that lack the characteristic facial and physical features Jones identified in 1973.[1] In one cross-sectional study involving 1,842 children across four regions of the United States, researchers found identifiable behavioral and cognitive effects of PAE even in the absence of physical characteristics.[8]

The neurodevelopmental deficits that result from PAE occur in a wide range of severity, with the most detrimental deficits in infants exposed to heavy episodic or binge drinking in utero. The evidence is less clear when it comes to low and moderate alcohol consumption during pregnancy, but this may be due to imprecise methods of exposure classification.[5-7] Bandoli et al. aimed to address this gap by employing longitudinal trajectory modeling of maternal drinking

patterns to determine associations with infant growth and neurodevelopment deficits. This study found that, though high, sustained PAE posed the greatest risk for poor neurodevelopmental outcomes at 6- and 12- months of age, low-to-moderate PAE throughout gestation was also associated with reduced neurocognitive performance.[5]

The specific aspects of neurodevelopment that infants and children experience deficits in are cognition, memory, executive functioning, hearing, vision, motor skills, behavior, and social adaptation. These result from a variety of biological mechanisms, but all are critical functions across the life course.[2] This underscores the need to identify ways to prevent, treat, and manage potential consequences of alcohol consumption during pregnancy.

One potential mitigation strategy for reducing the impact of PAE is through breastfeeding; however, this has not been well studied. Scientific evidence on breastfeeding is promising when it comes to its benefits to infant neurodevelopment. Whereas PAE is associated with various harms to infant neurodevelopment, breastfeeding benefits cognitive development in infancy and throughout childhood.[9,10] A prospective cohort study conducted in Crete, Greece that included 540 mother-child pairs found a dose-response relationship with breastfeeding duration and cognitive, language, and motor development at 18 months of age. This association was independent from a wide range of infant and parental characteristics.[11] Belfort discusses similar findings: even when controlling for socioeconomic status, parental education, maternal Intelligence Quotient (IQ), and the home environment, breastfeeding for longer durations, especially when breastfeeding is exclusive, was associated with higher IQ in school age children.[12]

Scientific literature for FASD, breastfeeding, alcohol consumption during pregnancy, and, scarcely, alcohol consumption during breastfeeding can be found; however, there are

significant gaps in the research when it comes to how breastfeeding may specifically benefit infants exposed to alcohol in-utero, whether they have received an official FASD diagnosis or not. This research gap drives the current analysis. It is important to understand how breastfeeding may counteract or mitigate the neurodevelopmental harms caused by PAE.

CHAPTER 2: LITERATURE REVIEW

2.1 FASD

Fetal alcohol spectrum disorder (FASD) was first separately described by Lemoine et al. and Jones et al. in 1968 and 1973, respectively.[1,13,14] Lemoine's article, published in French and initially unseen by Jones, discussed a cohort of 69 families with 127 children born to alcoholic mothers.[13] Five years later, Jones described eight infants born to alcoholic mothers with the same pattern of craniofacial, limb, and cardiovascular defects associated with prenatal-onset growth deficiency and developmental delay resulting from prenatal alcohol exposure (PAE). Jones coined the term 'Fetal alcohol syndrome' (FAS) and concluded that, because the mothers of all eight infants drank excessively throughout gestation, the physical defects and intellectual, motor, and behavioral dysfunctions observed gave sufficient evidence that maternal alcoholism can cause serious abnormal fetal development.[1] One additional - and noteworthy – detail in Lemoine's paper was that five of the mothers in the cohort who previously had children with impairments from PAE stopped drinking and then gave birth to one or more healthy infants.[13,14]

FASD encompasses the full range of adverse effects associated with PAE, which include facial dysmorphology, severe growth delay, birth defects, neurological abnormalities, and cognitive and behavioral impairment.[2,15,16] Diagnosis of FASD is further classified into one of four distinct diagnostic categories - FAS, partial fetal alcohol syndrome (PFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD) – depending on level of PAE (if known and documented), impaired growth, facial dysmorphology, and neurodevelopmental abnormalities present.[2,6,8,15] Diagnosis of FAS and PFAS, according to the Hoyme et al., 2016 diagnostic criteria, both require the presence of at least two of the three cardinal facial dysmorphologies: short palpebral fissures, smooth philtrum, and thin vermillion

border of the upper lip.[2,15,17] In contrast to the PFAS and FAS diagnostic conditions, criteria required for both ARND and ARBD diagnoses do not include the characteristic facial features, which are the most recognized and observable visible effects of PAE.[6,8,15,18-20] Additionally, ARND and ARBD diagnoses both require confirmation of PAE. ARND is less likely to be diagnosed, and ARBD is rarely used as a diagnosis.[16,18-20]

Diagnosis of FASD involves a multidisciplinary team of clinicians, including a pediatrician or clinical dysmorphologist, and a comprehensive neuropsychological assessment.[15,18-20] The clinical team may also include psychiatrists, occupational therapists, speech therapists, audiologists, and/or ophthalmologists.[15,18] Though FASD is as common as autism spectrum disorder, it is highly underdiagnosed for a multitude of reasons.[2,16] As the multidisciplinary approach suggests, FASD is a complex diagnosis that cannot be detected with a single assessment. Not only are multiple assessments required, but most validated measures only have high sensitivities for certain age groups. The appropriate assessments change as an individual ages, but the ways in which neurobehavioral deficits manifest also change from infancy to childhood and onward. Some infants and children affected by PAE have subtle, less easily measured impairments that are not as likely to prompt clinical care.[2,16] Research has made clear that binge and high, sustained alcohol consumption are devastating to fetal development, but evidence is inconsistent when it comes to lower levels of PAE that likely result in the more subtle adverse effects.[16] Another barrier is that many clinicians still rely on facial dysmorphology for diagnosis even though the cardinal facial features are usually only present in severe cases.[2,18] Even if parents seek out medical attention, social stigma and reliance on self-reporting of PAE make it easier to deny or underreport prenatal alcohol use.[2,15,18] Finally, there is a strong overlap

of FASD with attention deficit hyperactivity disorder (ADHD), and many children with FASD also have comorbidities that complicate an accurate diagnosis.[2,3,21]

2.2 Global Prevalence of FASD & PAE

The estimated global prevalence of FASD is 7.7 per 1000 population, which equates to 1,700 infants born with FASD each day or 630,000 each year.[2,3,22] It is estimated that, on average, 9.8% of women worldwide consume alcohol during pregnancy. In areas of the world where this rate is higher, FASD prevalence rates increase, as well.[22] Unfortunately, estimating the prevalence of FASD accurately has proven difficult. The latest estimates are likely below true prevalence rates due to the difficulty in diagnosing FASD, the use of passive methods in prevalence studies, and the lack of agreement on methodology and diagnostic features.[2,15,18,19,22,23] To stay consistent with multiple systematic reviews related to the global prevalence of FASD and prenatal alcohol use, prevalence rates discussed below will be based on six regions defined by the World Health Organization (WHO).[3,22-24]

The WHO European region (EUR), which includes 53 member states, is estimated to have the highest prevalence of FASD of all the world regions at 19.8 per 1000 population.[3,22,25] It makes sense, then, that this region also has the highest prevalence of alcohol consumption during pregnancy at 25.2%.[22] Croatia, Ireland, and Italy are three countries that significantly contribute to this high regional prevalence of FASD, with estimated country-specific rates of 53.3 per 1000 population, 47.5 per 1000 population, and 45 per 1000 population, respectively.[3] A meta-analysis conducted in 2017 estimated that the prevalence of alcohol use during pregnancy in Ireland is 60.4%, which is more than double the overall rate in the WHO EUR region.[23]

With 35 members states, the WHO Region of the Americas (AMR) has an estimated FASD prevalence rate of 8.79 per 1000 population, and an estimated 11.2% of women drink during pregnancy.[3,22,23,25] The latest prevalence estimates in the United States, which were found using active case ascertainment, range from 11 to 50 per 1000 population.[19,26] In Latin America, rates of alcohol consumption during pregnancy vary significantly by country. Among the general population, the prevalence of alcohol consumption in pregnancy is 1.2% in Mexico and 15.2% in Brazil.[27]

The WHO African region (AFR) is comprised of 47 members states and has an estimated FASD prevalence rate of 7.83 per 1000 population.[3,22,25] Though an estimated 10% of women consume alcohol during pregnancy, this region has the highest prevalence of prenatal binge drinking among all WHO world regions.[22,23] An estimated 3.1% of women binge drink during pregnancy, which means they consume three to five or more drinks on a single occasion.[22,28] This type of heavy episodic drinking causes the most harm to a developing fetus, often resulting in the most severe FASD diagnosis of FAS.[2,7,15,16,23] Within this region, South Africa is estimated to have the world's highest country-specific prevalence of FASD, with estimates ranging from 111.1 to 207.5 per 1000 population.[3,16,29] Notably, the estimated prevalence of FASD is extremely high relative to the prevalence of prenatal alcohol use in South Africa, which is 13.2%.[23,24] This is likely because those who do drink during pregnancy often consume high volumes each drinking occasion, making the likelihood of adverse effects higher.[23]

The remaining WHO regions demonstrate that lower rates of prenatal alcohol consumption, especially binge drinking, are directly associated with lower prevalence rates of FASD. The estimated prevalence of FASD in the Western Pacific region (WPR), which has 27 members states, is 6.74 per 1000 population.[3,22,25] Though the prevalence of alcohol use during

pregnancy is 8.6%, only 1.8% of the general population binge drinks during pregnancy.[22,23] Finally, the WHO regions with the lowest prevalence of FASD are the South-East Asia region (SEAR) with 11 members states and the Eastern-Mediterranean region (EMR) with 21 members states.[3,22,25] The prevalence of FASD in the respective regions are 1.41 per 1000 population (SEAR) and 0.13 per 1000 population (EMR).[3,22] These rates correspond to the low prevalence of alcohol use during pregnancy – 1.8% in SEAR and 0.2% in EMR.[22,23] A systematic review and meta-analysis conducted in 2017 predicted that Oman, United Arab Emirates, Saudi Arabia, Qatar, and Kuwait, all in the EMR, all have approximately 0% estimated prevalence rates of drinking during pregnancy. The cultural standards found in these regions likely play a large role, as there are expectations of abstinence from all alcohol. In EMR, Islam is the predominant religion practiced, and followers of this faith are very likely to completely abstain from alcohol.[23]

2.3 PAE's Adverse Effects

PAE results from any maternal alcohol consumption during the nine months of gestation.[30] Alcohol is a known teratogen that freely crosses the placenta, harming not only the developing fetus but also the placenta and umbilical cord.[1,2,21,31,32] These organs play critical roles in fetal development, but alcohol impairs their functioning and ability to provide adequate oxygen and essential nutrients to the fetus.[31] PAE interrupts fetal development through distinct epigenetic, molecular, cellular, and physiological mechanisms, including oxidative injury, hypoxia, apoptosis, modulation of gene expression, and disruption of neuronal migration and axon pathfinding. These modifications permanently affect the fetus and persist into infancy, childhood, and beyond.[2,21,32] The adverse effects of alcohol are most clearly demonstrated by altered structure and function of most areas of the brain.[2,6,15,32] Neuroimaging has revealed

abnormal brain structure and functional connectivity, along with decreased overall brain volume, in those affected by PAE. Combined with other central nervous system damage, these abnormalities modify developmental trajectories and likely contribute to global cognitive, executive functioning, memory, vision, hearing, motor skills, behavior, and social adaptation deficits.[2,6,32]

Of particular interest in this analysis are the neurodevelopmental effects of PAE. The overall evidence suggests that PAE contributes to lower scores on the Bayley Scales of Infant Development (BSID) Psychosocial Developmental Index (PDI) and/or the Motor Developmental Index (MDI), as well as other assessments of infant neurodevelopment.[16,33-38] One cohort study assessed mental development in 392 infants born in South Africa, a region with a high prevalence of FASD. Investigators found that infants diagnosed with FASD had lower overall development scores and noticeable motor delays compared to infants without FASD. Additionally, the developmental gap between infants with and without FASD grew wider as infants entered early childhood.[34] Some studies have failed to identify an effect of PAE on neurodevelopmental assessments, but this may be partially due to study methods or imprecise classification of the gestational timing, frequency, and dose of PAE.[5,39,40] Part of the problem with neurodevelopmental deficits is that they are difficult to identify when infants lack the typical physical effects of PAE, which often spur clinical evaluation.[2,7,8,15,20] Though research confirms that binge and high levels of PAE lead to cognitive and behavioral deficits, the evidence on low to moderate alcohol consumption are less definitive.[7]

In addition, PAE is associated with increased rates of preterm birth and both prenatal and postnatal growth deficiency.[1,5,40,41] Because alcohol can harm any organ or system in the growing fetus, many comorbidities, particularly learning and behavioral disorders, are associated with

FASD.[3,6,21] Results from a systematic review and meta-analysis conducted in 2016 revealed 428 comorbid conditions with FASD, found in 18 out of 22 chapters of the International Classification of Diseases, Version 10 (ICD-10).[21] Some of the most prevalent comorbidities found were related to congenital malformations (including of the spine), mental and behavioral disorders, language disorders, hearing loss, and vision problems.[21]

The type and severity of health outcomes resulting from PAE are influenced by factors both related and not related to maternal alcohol consumption patterns. Important metrics of alcohol exposure include the dose, frequency, and gestational timing of PAE.[5,16] Binge drinking during pregnancy, which is variably defined as 3-5+ drinks per occasion, poses the greatest risk and causes the most harm to fetal development.[15,16,42] Research has also confirmed that high, sustained levels of alcohol consumption during pregnancy are associated with a greater range of dysmorphic features.[5,17] The evidence is less clear when it comes to lower levels of alcohol consumption, but research suggests that even low to moderate PAE, especially when continued across gestation, is associated with certain psychological, behavioral, and neurodevelopmental deficits.[5,16,32]

Other factors may protect against or amplify adverse outcomes resulting from PAE. Maternal risk factors and environmental influences that may exacerbate the effects of PAE include maternal depression, genetic predispositions, socioeconomic stressors, poor access to resources, maternal smoking, and other teratogenic exposures.[16,43,44] Maternal nutritional status plays an important role in either protecting against or worsening the teratogenic effects of alcohol. Chronic alcoholics and those who regularly consume large amounts of alcohol may experience altered metabolism, malabsorption, or simply a deficiency in key nutrients.[29,44] Inadequate dietary intake before and during pregnancy is a co-risk factor for FASD, but

multivitamin use may provide some protection to infants exposed to alcohol during gestation.[18,29,43,44] Finally, PAE increases the chance of preterm birth, and shortened gestation may both directly and indirectly influence alcohol's harm to development.[8,41]

2.4 Maternal Predictors of Prenatal Alcohol Consumption

Research shows that some maternal predictors of prenatal alcohol consumption vary by country and setting, but others are common across groups. Socioeconomic status, race/ethnicity, tobacco use, maternal education, maternal age, gravidity/parity, and marital status are a few of the predictors often found in the literature.[42] Specifically, women are more likely to drink during pregnancy, and thus are at a higher risk of having a child with FASD, when they consumed alcohol prior to pregnancy, are older, smoke tobacco, did not intend to get pregnant, are exposed to abuse or violence, have a prior mental illness, use illicit drugs (especially marijuana), are single or unmarried, have a partner who consumes alcohol, and are non-Hispanic white ethnicity.[18,19,42,45-57] The scientific evidence on income, education, and parity/gravidity as predictors of prenatal alcohol consumption is conflicting, with some studies reporting that women with lower education and income are more likely to consume alcohol during pregnancy and other studies reporting the opposite.[18,42,45-47,49,50,52,56,57] Likewise, some evidence suggests that prenatal alcohol consumption is more likely in women with a higher number of children and pregnancies, while other evidence suggests women who are nulliparous are more likely to drink during pregnancy.[18,42,50,54]

2.5 Breastfeeding

The WHO and United Nations Children's Fund (UNICEF) recommend that infants are exclusively breastfed for the first six months of life, and then continuing breastfeeding alongside complementary foods up to two years or longer.[58] The Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) also recommend exclusive breastfeeding for the first six months of life with continued breastfeeding and complementary foods for at least one year.[59] Whereas PAE is associated with developmental deficits, breastfeeding is associated with benefits to infant growth and development. One benefit that has been of particular interest to researchers is improved neurodevelopment in infants who are breastfed.[9-12,60-62] Neurodevelopment refers to development of function of the nervous system that includes a number of functional domains, such as attention, behavior, cognition, academic achievement, language development, memory, and motor development.[7]

One prospective cohort study conducted in Ireland aimed to assess the effect of breastfeeding on infant neurodevelopment at 9-months of age. The study included 11,134 infants and measured neurodevelopment using the Ages and Stages Questionnaire (ASQ, 2nd edition), which, according to the authors, is comparable to the BSID-II. Infants who were ever breastfed had significantly higher odds of passing fine motor, gross motor, problem solving, and personal-social modules of the ASQ at 9-months, compared to those who were never breastfed. The study's findings suggest that *any* breastfeeding is beneficial to infants and may be associated with advantages on standardized neurodevelopmental assessments.[62] Likewise, a systematic review and meta-analysis conducted in 2015 by Horta et al. looked at the evidence of an association between breastfeeding and intelligence. All 17 included studies indicated benefits of breastfeeding on intelligence test performance, though only 12 of these were significant. Using

pooled effect estimates, researchers found that breastfed infants had a mean difference of 3.44 points higher than those who were not breastfed. Even the studies that controlled for maternal IQ showed a benefit, with a mean difference of 2.62 points higher.[61]

The mechanisms for the benefits of breastfeeding on infant neurodevelopment are still unclear. Some research suggests that mothers who breastfeed are simply more likely to provide cognitively stimulating environments for their infants or that breastfeeding is a marker of practices that encourage healthy child development. This would imply that the improvements in cognition are due to family environment, rather than nutritional benefits. On the other hand, the presence of long chain polyunsaturated fatty acids, such as arachidonic acid and docosahexaenoic acid, in breastmilk may also help improve cognitive development.[60,61] Finally, breastfeeding may just provide a means of bonding between mothers and their children, which contributes to healthy neurodevelopment.[61]

2.6 Maternal Predictors of Infant Breastfeeding

As with prenatal alcohol consumption, there is evidence that mothers who breastfeed may have similar characteristics. One prospective cohort study that included 540 mother-infant pairs in Crete, Greece found that mothers who were older, had university education, and did not smoke during pregnancy or after birth were more likely to breastfeed their infant longer.[11] Similarly, another cross-sectional study conducted in Australia with 17,564 infants found that younger mothers (<20 years) and mothers who smoked tobacco during pregnancy were more likely to cease exclusive breastfeeding in the first four weeks postpartum.[63] The same Australian study also found that mothers experiencing intimate partner violence, lower socioeconomic status, and

pre-existing mental health problems also were more likely to cease breastfeeding in the early postpartum period.[63]

A concern with many of the maternal factors associated with breastfeeding is that these factors also influence prenatal alcohol consumption. In fact, another prospective cohort study in Brazil with 833 infants found that women who consumed alcohol during pregnancy had an 88% higher risk of early breastfeeding cessation compared to mothers who did not consume alcohol in pregnancy. Consistent with the other studies, women who were younger and smoked tobacco during pregnancy were also less likely to continue breastfeeding.[64] The overlapping predictors of PAE and cessation (or not initiating) breastfeeding may be one reason for some of the current research gaps in this field.

2.7 Current Research Landscape

Significant strides in the research on FASD, PAE, infant neurodevelopment, and breastfeeding have been made, particularly in the last forty years; yet many scientific gaps remain.[20] Significantly, there are multiple systems to diagnose FASD and a lack of agreement on some aspects of case definition, leading to discrepancies in the results of research evaluating the adverse effects associated with PAE.[2,6,16] Biomarkers, such as epigenetic markers, may meaningfully improve identification of PAE and diagnosis of FASD.[6,32] A continued understanding of the maternal predictors of PAE and breastfeeding is also needed.

2.8 Study Objectives

Although few studies have examined whether continued alcohol consumption during lactation increases the risk of FASD relative to abstaining during lactation,[65,66] to our knowledge,

no studies on how breastfeeding specifically benefits infants exposed to alcohol in-utero could be found. For this reason, this analysis may provide a crucial introduction to the importance of promoting breastfeeding, especially among women who consume alcohol during pregnancy. The public health research gap that we aim to fill is the lack of scientific research looking at the neurodevelopmental benefits of breastfeeding on infants exposed to alcohol in pregnancy. Though evidence suggests breastfeeding improves infant neurodevelopment and PAE has negative effects, researchers have yet to evaluate the benefits of breastfeeding on infants exposed to alcohol in gestation, whether they have received an official FASD diagnosis or not. The research question posed in this study will be, "Is breastfeeding associated with neurodevelopment at 6- or 12-months of age, and is any association modified by pattern of prenatal alcohol use?" Based on the review of key scientific literature, we hypothesize that breastfeeding will be associated with infant neurodevelopment at 6- and 12-months of age, and this association will be stronger in infants exposed to higher levels of PAE.

CHAPTER 3: METHODS

3.1 Study Design and Sample

The prospective cohort study was carried out in Western Ukraine as one of the studies included in the Collaborative Initiative on Fetal Alcohol Spectrum Disorder (CIFASD), which is a multidisciplinary initiative established in 2003 for the purpose of better understanding the effects of PAE and improving diagnosis, prevention, and treatment of FASD. CIFASD is funded by the National Institutes of Health (NIH), National Institute on Alcohol Abuse and Alcoholism (NIAAA) and has involved research in several countries.[15,42-44,67] Women who reported at least weekly binge episodes of 4 to 5 alcohol drinks/occasion, at least 5 episodes of 3 to 4 drinks, or at least 10 episodes of 1 to 2 drinks in the month around conception and/or in the most recent month of pregnancy were recruited. Following identification of an exposed participant, the next minimally exposed or unexposed woman (<2 drinks per occasion and no more than 2 drinks per week in the month around conception and no alcohol in the most recent month of pregnancy) was recruited.[17,43,44] In the parent study, women were randomized to multivitamin supplements provided by the study after enrollment. Half of those randomized to multivitamin supplements were also randomized to an additional choline supplement. The control group received health information on the importance of prenatal vitamin use and may or may not have used supplements.[42-44]

The analytic sample includes pregnant women who enrolled between 2008 and 2014 and were followed until their infants were 12-months old. Data were collected through interview, infant medical records, direct examination, and developmental assessment. This study was previously approved by the Institutional Review Boards (IRB) at the University of California, San Diego and Lviv Medical University in Ukraine.[42-44]

Women were enrolled at two locations in Western Ukraine, the Rivne Regional Medical Diagnostic Center and the Khmelntsky Perinatal Center – both of which are affiliated with OMNI-Net, a network of research and education sites aimed at preventing birth defects.[44,68] Data collection for the study included interviews with women twice during pregnancy (at enrollment and around 32 weeks' gestation) and after delivery to collect information on subjects' demographics, alcohol consumption patterns, other exposures, and pregnancy history. Infant growth and birth outcomes were collected from medical records, and the Bayley Scales of Infant Development (2nd edition) (BSID-II) was used to assess infant neurodevelopment at 6- and 12-months.[70] Specific measures from the BSID-II that were used in this analysis are the Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI).[5,20,42,43] During the 6-month postnatal visit, individuals reported whether they had initiated breastfeeding, and whether they continued to breastfeed.

3.2 Measures

Prenatal alcohol exposure clusters were based on maternal report at specific timepoints and extrapolated across pregnancy. Specifically, women who reported any drinking in their lifetime completed a survey assessing the type, quantity, and frequency of typical standard drinks per day over a 7-day period around the time of conception. This intake level was assumed to continue (extrapolated) until the gestational week pregnancy was recognized. Women were then asked to report the number of standard drinks over a 14-day period prior to the gestational week of study enrollment. This intake level was extrapolated from gestational week at pregnancy recognition to the interview at around 32 weeks' gestation. Finally, women reported the number of standard drinks per day at 32 weeks' gestation, if different from previous reports, and this was

assumed to continue until delivery. The quantity and frequency of alcohol consumption at each phase was converted into absolute ounces of alcohol (ozAA) per day, with one standard drink equivalent to 0.5 ozAA.[5,69]

Five trajectory groups were originally created by Bandoli et al. using longitudinal cluster analysis across gestation to classify women with similar drinking patterns (dose, frequency, and gestational timing) into distinct groups.[5] The original five trajectories – A. Minimal or no PAE throughout gestation; B. Low-to-moderate PAE with discontinuation early in gestation; C. Low-to-moderate PAE sustained across gestation; D. Moderate-to-high PAE with reduction early in gestation; and E. high PAE sustained across gestation – were combined into three groups to increase power for analysis.[5] As shown in Figure 1 in the Appendix, group A was categorized as 'Low PAE Exposure,' groups B and C were combined and categorized as 'Medium PAE Exposure,' and groups D and E were combined and categorized as 'High PAE Exposure.'

Infant neurodevelopment was measured at 6- and 12- months through the Bayley Scales of Infant Development, second Edition (BSID-II).[70] Specifically, the Mental Developmental Index (MDI) assessed problem solving and prelinguistic development, while the Psychomotor Developmental Index (PDI) assessed fine and gross motor skills. This standardized measure was appropriate due to its worldwide use and availability in a Russian translation, which is preferable to an English translation. Two Ukrainian child psychologists, who were trained and supervised by the research team, administered the assessment while children were seated on the lap of their caregiver. PDI and MDI scores were both standardized to a scale with a mean of 100 and a standard deviation (SD) of 15. Scores were also standardized for prematurity (gestational age <37 weeks), sex, and age of the child at the time of testing.[5,43,44,71] Low scores on either scale

may indicate developmental delay, and 1 SD below the mean (score of 85 or below) is often set as the threshold to prompt further evaluation.[71,72]

Breastfeeding length was assessed at the 6-month interview from maternal report and categorized for each infant as either none, breastfed 1-3 months, or breastfed 4+ months. Because breastfeeding was assessed at the 6-month interview, it was not possible to collect exact breastfeeding durations and use a continuous variable for breastfeeding length. Additionally, mothers were not asked about exclusive breastfeeding versus supplementing with formula.

3.3 Covariates

Vitamin use (prenatal vitamins either due to maternal use or through parent study assignment), maternal age at study enrollment, and smoking during pregnancy were included as covariates because they are expected to be associated with PAE and neurodevelopment. A previous study using the same cohort also identified maternal age and smoking during pregnancy as significant predictors of alcohol consumption in pregnancy and alcohol-related birth defects.[42] Another study found that prenatal multivitamin use can reduce the negative impact of alcohol use during pregnancy on specific developmental outcomes.[44] Additional covariates included were socioeconomic status and sex of the infant. Socioeconomic status (SES) was a binary (high/low) variable based on the Hollingshead score, which was calculated from maternal report of maternal and paternal occupation and education.[43,73] Hollingshead scores <30 were considered low SES, while scores $\geq$30 were considered high SES.[5] Because the BSID-II scores were already standardized for gestational age, preterm (versus term) births were not included as a covariate.[5,43,44]

3.4 Statistical Analyses

All data analysis were conducted using R-Studio.[74] Descriptive statistics were calculated and stratified by breastfeeding category (no breastfeeding, breastfed 1-3 months, and breastfed 4+ months) in one table and by PAE trajectory group (low, medium, and high) in another table. Multivariable linear regression models were created to estimate the effect of breastfeeding length (none, 1-3 months, and 4+ months) on infant neurodevelopment (measured by MDI and PDI scores) at 6 and 12 months of age. Four separate models with unique beta coefficients resulted, and all models adjusted for PAE group, prenatal vitamin use, maternal age, smoking status, SES, and infant sex. An interaction term was then added to each of the models to assess the joint effects of PAE level and breastfeeding length on infant neurodevelopment. The significance level for the interaction terms was determined a priori to be 0.05. Given the low power to assess interaction, we also tested for effect measure modification by stratifying on PAE group and assessing the association between breastfeeding and neurodevelopmental measures. The stratified models were also adjusted for prenatal vitamin use, SES, maternal age, smoking status, and infant sex.

CHAPTER 4: RESULTS

4.1 Sample Description

Of the 401 infants included in the initial dataset, 9 were removed due to missing breastfeeding data. Analysis was conducted using the remaining 392 infants with data for two maternal pregnancy visits, breastfeeding information, and a 6- and/or 12-month neurodevelopmental assessment. Participants who missed the 6-month assessment were still eligible to complete the assessment at 12-months, so analysis included infants with either 6-month scores, 12-month scores, or both. 345 infants (88%) completed the MDI and PDI at 6 months, and 338 infants (86%) completed the MDI and PDI at 12 months. All infants were singletons, as the 2 twin sets were removed when the original PAE trajectory groups were created by Bandoli et al.[5]

Table 1 in the Appendix describes the maternal characteristics stratified by breastfeeding category. Most infants (n=261, 66.6%) were breastfed 4+ months, 103 (26.3%) were breastfed 1-3 months, and 28 (7.1%) were not breastfed at all. Among the breastfeeding groups, there was no significant difference between maternal age, gestational age at birth, and vitamin use in pregnancy. There were, however, significant differences in maternal drinking patterns during pregnancy, smoking status, college attendance, marital status, SES, and alcohol intake (measured by absolute ounces of alcohol [ozAA] per day) between the three breastfeeding categories. As breastfeeding length increased, the mean ozAA per day for all three trimesters and the proportion of mothers who smoked, attended college, were married, and had a high SES all increased. Additionally, there were significant differences in the scores on both the MDI and PDI at 6 and 12 months with scores increasing as breastfeeding duration increased.

Maternal characteristics by PAE group are reported in Table 2. Overall, 62.2% of infants (n=244) were exposed to low levels, 22.7% (n = 89) to medium levels, and 15.1% (n = 59) to high levels of PAE. The average ozAA per day was significantly different between exposure groups in all three trimesters. All three PAE categories had the highest exposure levels in the first trimester, compared to the second and third, with means of 0.006 oz/day, 0.221 oz/day, and 1.159 oz/day for low, medium, and high PAE groups, respectively. PAE groups differed significantly in maternal age, gestational age at birth, smoking status, college attendance, marital status, and SES. Finally, the MDI and PDI scores at 6 and 12 months all decreased as PAE increased; however, only PDI and MDI at 6 months and PDI at 12 months were significantly different between groups.

4.2 PAE and Neurodevelopment

We examined the main effects of PAE on neurodevelopment (results shown in Table 3). Compared to the low PAE group, the medium PAE group was associated with a statistically significant decrease in MDI scores at 12 months. Specifically, infants exposed to medium levels of PAE had a mean decrease of 3.57 points on the MDI at 12 months compared to infants exposed to low levels of PAE. Infants exposed to high levels of PAE had statistically significant negative associations with the MDI and PDI at both 6 and 12 months. Compared to infants exposed to low levels of PAE, infants exposed to high levels had a mean decrease of 4.55 points on the PDI at 6 months, 5.77 points on the MDI at 6 months, 4.94 points on the PDI at 12 months, and 6.17 points on the MDI at 12 months.

4.3 Breastfeeding and Neurodevelopment

Next, we assessed the main effects of breastfeeding on infant neurodevelopment among the full sample of infants. Figure 2 provides a visual depiction of the PDI and MDI scores for all infants at 6 and 12 months based on their breastfeeding length. The boxplots for MDI and PDI at 6 months show an increase in score as the length of breastfeeding increased; while those for MDI and PDI at 12 months show that scores are similar across all three breastfeeding categories. Four linear regression models were computed using PDI and MDI scores at 6- and 12-months as the outcomes, controlling for PAE group, prenatal vitamin use, maternal age, smoking status, SES, and sex of the infant. Among the full sample of infants, breastfeeding was found to have a statistically significant positive association with PDI and MDI scores at 6 months (shown in Table 3). Infants breastfed 1-3 months had a mean increase of 5.41 points on the PDI and 5.46 points on the MDI at 6 months compared to infants who were never breastfed. Infants breastfed 4+ months had a mean increase of 6.88 points on the PDI and 7.98 points on the MDI at 6 months compared to infants who were never breastfed. Breastfeeding was not significantly associated with PDI and MDI scores at 12 months.

4.4 Interaction between PAE and breastfeeding

An interaction term was then added to each of the models to assess the joint effects of PAE and breastfeeding. Prenatal vitamin use, maternal age at enrollment, smoking status, SES, and sex of the infant were again controlled for. The interaction terms for breastfeeding and PAE shown in Table 3 were significant at the 0.05 level for all four tests, indicating that there was an interaction effect above and beyond PAE and breastfeeding alone.

4.5 Effect Measure Modification of breastfeeding and neurodevelopment by PAE

Figures 3, 4, and 5 depict the PDI and MDI scores after stratifying by PAE group. Stratification by PAE group was also applied to the models to better understand the effects of breastfeeding on infant neurodevelopment. These models again controlled for prenatal vitamin use, maternal age, smoking status, SES, and infant sex. Table 4 includes beta coefficients for all models separated into low, medium, and high PAE. Among infants exposed to low PAE (shown in Figure 3), breastfeeding only had a positive statistically significant association on the MDI at 6 months. Specifically, infants breastfed 1-3 months had a mean increase of 6.82 points and infants breastfed 4+ months had a mean increase of 7.71 points on the MDI compared to infants who were never breastfed.

Among infants exposed to medium levels of PAE (shown in Figure 4), breastfeeding only had a statistically significant association with PDI scores at 12 months; however, this association was negative. Compared to infants who were never breastfed, infants breastfed 1-3 months had a mean decrease of 10.75 points and infants breastfed 4+ months had a mean decrease of 12.75 points on the MDI at 12 months.

Among infants exposed to high levels of PAE (shown in Figure 5), breastfeeding had a positive statistically significant association with PDI and MDI scores at both 6 and 12 months. Infants breastfed 1-3 months had a mean increase of 15.23 points on the PDI at 6 months, 11.61 points on the MDI at 6 months, 17.43 points on the PDI at 12 months, and 14.04 points on the MDI at 12 months compared to infants who were never breastfed. This relationship was stronger in the highest breastfeeding length category. Infants breastfed 4+ months had a mean increase of 19.67 points on the PDI at 6 months, 18.25 points on the MDI at 6 months, 22.28 points on the

PDI at 12 months, and 20.25 points on the MDI at 12 months compared to infants who were never breastfed.

CHAPTER 5: DISCUSSION

5.1 Summary of Findings & Comparison of Literature

In this prospective cohort study of pregnant women, we found evidence that PAE has a negative effect and breastfeeding has a positive effect on infant neurodevelopment as measured by the BSID-II PDI and MDI at 6 and 12 months of age. The positive effects of breastfeeding were primarily evident in infants exposed to higher levels of PAE.

As the breastfeeding length increased from none to 1-3 months to 4+ months, the proportions of mothers who smoked decreased, were married increased, attended college increased, and had low SES decreased. This aligns with previous literature, which states that women who are married, do not smoke, attended college, and have a higher SES are more likely to breastfeed.[11,75,76] A prospective cohort study conducted in Brazil examined predictors of breastfeeding cessation before 6 months among 833 infants and found that women with less education and who smoked during pregnancy were more likely to stop breastfeeding early.[64] Another cross-sectional study in Australia with 17,564 infants found that mothers who smoked during pregnancy, had lower SES, and poor partner support were more likely to cease exclusive breastfeeding in the first four weeks after delivery.[63] Though marital status does not necessarily equate to having a supportive partner, it may be more likely that couples who are married have greater commitment to and support of one another.

There were significant differences between PAE groups in maternal age, gestational age at birth, smoking status, college attendance, marital status, and SES. Specifically, as alcohol report increased, maternal age and gestational age at delivery decreased. Additionally, there were differences between PAE groups when it came to maternal smoking, with higher proportions of women smoking in the categories of higher alcohol consumption. This result agrees with those of

past studies.[52,53] The proportion of high SES and college attendance increased from low to medium but then decreased among the high PAE levels. This is consistent with a cross-sectional conducted in France in 2017 with 3,603 pregnant, breastfeeding, or postpartum women, which showed that moderate drinking during pregnancy is associated with higher education level.[52] Another study in the Netherlands using data from two nationwide surveys found that the proportion of women who consumed alcohol during pregnancy increased with level of education.[57] The increase in SES and education from low to moderate PAE levels and then decrease from moderate to high PAE levels demonstrate one explanation for the conflicting results when it comes to SES and education as predictors of prenatal alcohol consumption. Rather than a linear pattern, it appears that these predictors may follow more of a curvilinear pattern where women with higher education and higher SES are more likely to consume moderate levels of alcohol during pregnancy, but women with less education and lower SES are more likely to consume high levels of alcohol.

Our full model demonstrated that, when controlling for PAE group, prenatal vitamin use, maternal age, smoking status, SES, and infant sex, breastfeeding had a statistically significant positive association with both the PDI and MDI at 6 months but not at 12 months. A prospective cohort study in Brazil with 205 infants looked at the benefits of breastfeeding on BSID-II scores at the ages of 1 day, 10 days, each month from one to six months, nine months, and then one year. Researchers found that exclusive breastfeeding was associated with small, though statistically significant, benefits to infant MDI score at 1 month; however, no additional benefits to MDI scores were found with longer durations of breastfeeding. This study also found no benefit of breastfeeding on the PDI.[77] Another birth cohort study conducted in Spain with 504 infants examined PDI and MDI at 14 months and found no association between breastfeeding

and PDI; however, they did find that MDI scores increased an average of 5.48 points in infants exclusively breastfed for 6 months. This relationship was not significant when infants were exclusively breastfed for less than four months or between 4-6 months.[78] Unfortunately, it is possible that the categorical rather than continuous variables used in this study prevented analysis at the level of detail needed to determine a significant relationship between breastfeeding and infant neurodevelopment.

The interaction term for breastfeeding and PAE was introduced to each of the models and found to be significant at the 0.05 level for all four tests, indicating a joint effect of PAE and breastfeeding on infant neurodevelopment. Additionally, our subgroup analysis provided evidence of heterogeneity of the effects of breastfeeding on neurodevelopment across levels of PAE. Specifically, the benefits of breastfeeding were strongest in those with the highest PAE, suggesting that they may receive additional benefit from human milk relative to infants with lower levels of PAE. Among infants exposed to low levels of PAE, breastfeeding only had a statistically significant positive association with the MDI at 6 months. The results for the medium PAE group models were unexpected, as breastfeeding had a significant negative association with the PDI at 12 months. The reason for these results is unclear, but future research should seek to understand why this association exists. It will be important to include all five prenatal drinking patterns and ensure there is enough power to evaluate each group separately.

Breastfeeding appeared to have the greatest impact on neurodevelopment among infants exposed to high levels of PAE, as suspected. A significant positive association was found for all four models, and the positive relationship was stronger among infants breastfed longer (4+ months versus 1-3 months). It is especially noteworthy that effect size seen in the high PAE group was so large, as this indicates practical implications of breastfeeding's effect on

neurodevelopment among infants exposed to high levels of PAE. The mean increases in PDI and MDI scores associated with breastfeeding were close to or beyond 15 points (1 SD), which demonstrates the value in efforts to increase breastfeeding initiation and continuation. If infants exposed to high levels of PAE receive distinct benefits from breastfeeding beyond those received by unexposed infants, then mothers who consumed alcohol during pregnancy would benefit the most from breastfeeding interventions.

5.2 Strengths

A key strength in this analysis is that, to our knowledge, this is the first study evaluating the effects of breastfeeding on infants exposed to varying levels of PAE. While researchers have investigated the effects of alcohol consumption both during pregnancy and breastfeeding, none have determined how breastfeeding might help counteract the negative neurodevelopmental effects of PAE. While abstinence from alcohol during pre-conception and gestation is the ideal solution, breastfeeding may provide key nutrients that mitigate PAE. The large effect size seen in the high PAE group is also a strength, as it demonstrates how breastfeeding may be especially important for the neurodevelopment of infants exposed to alcohol during gestation.

5.3 Limitations

The results should be viewed in light of the limitations. Breastfeeding was assessed as a categorical variable to maintain sufficient power for the study. We were not able to know if the infants were exclusively breastfed and for how long, or if breastmilk was supplemented with formula. Additionally, the dataset did not include information on when and what solid foods were introduced. We also did not know if and how much alcohol was consumed by mothers

during breastfeeding, which would have important implications on infant neurodevelopment. It is likely some women in the higher alcohol groups continued to consume alcohol during lactation, which could have attenuated results based on previous studies of a detrimental effect of postnatal alcohol exposure via human milk. The study population only included Ukrainian women who were relatively homogenous regarding race/ethnicity, marital status, and education level. This limits the generalizability of the results, though they do still provide insights for future research. Finally, the original five prenatal alcohol exposure trajectories utilized in Bandoli et al. had to be combined into three groups to improve the power of the analysis.[5] Future research is needed to elucidate if the benefits of breastfeeding differ for infants who experience sustained PAE across gestation versus PAE that is discontinued or decreased early in gestation.

5.4 Conclusions

This analysis showed that breastfeeding may provide distinct benefits to infants exposed to high levels of PAE. Though breastfeeding exclusively for 6 months and then continuing alongside solid foods up to 2 years or longer is recommended for all infants, women who consume alcohol during pregnancy might be further encouraged to do so.[58] Future studies on this topic will help provide insight into any dose-response relationship between breastfeeding and neurodevelopment, as well as the ideal breastfeeding duration to mitigate deficits resulting from PAE. It will be important for future research to include more specific estimates of breastfeeding length, alcohol use during lactation, as well as information on exclusive versus mixed feeding (supplementing breastfeeding with formula feeding), introduction of solid foods, and factors in the home environment that may provide neurodevelopmental stimulation. Additionally, a larger sample that allows for more granular PAE trajectory groups will provide additional details to

help characterize PAE. For now, this analysis provides encouraging evidence that longer durations of breastfeeding may optimize infant neurodevelopment, particularly those with higher PAE. These implications could have life-long improvements in individual's learning and cognitive abilities.

APPENDIX

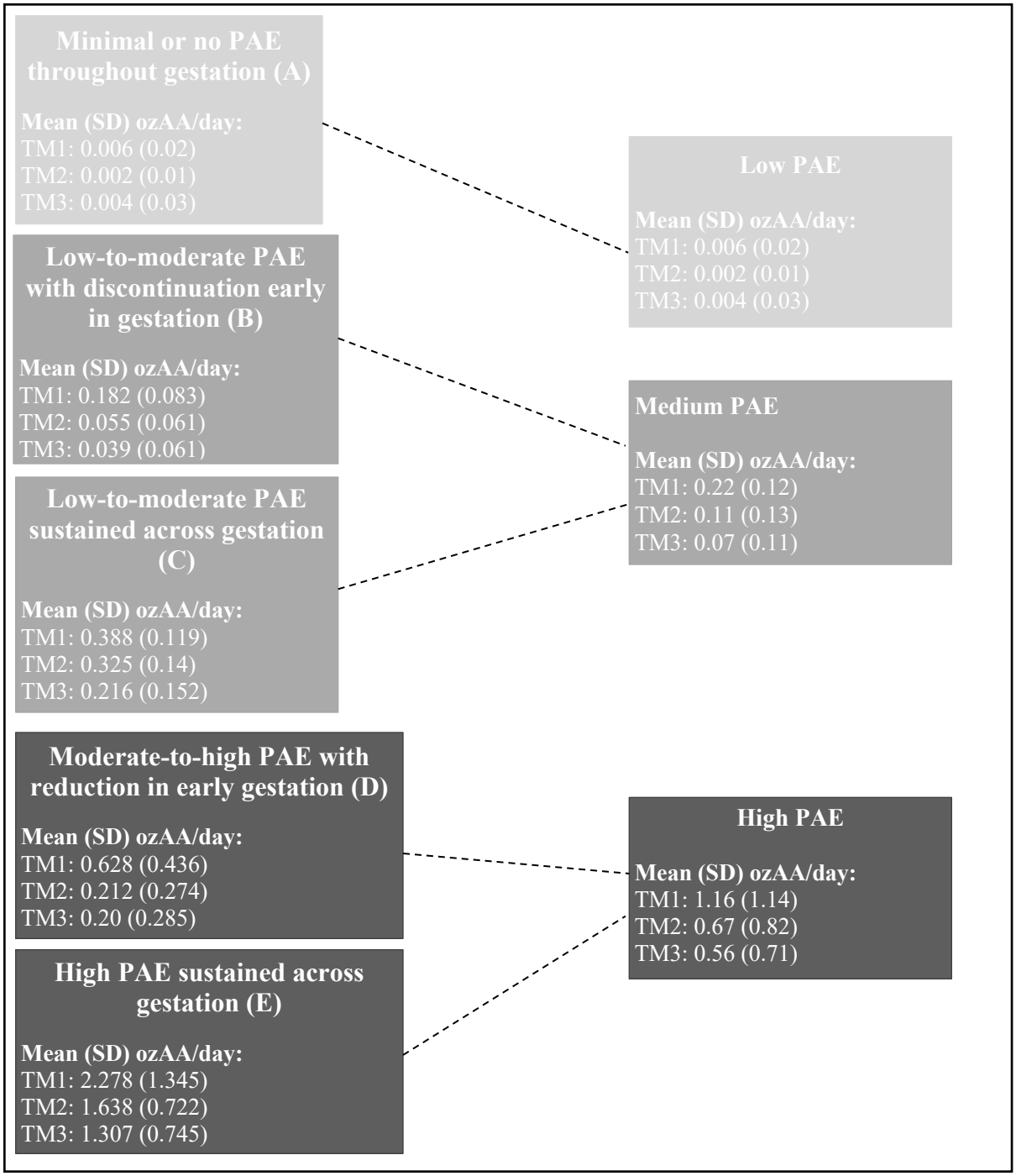

Figure 1: Original Five Trajectories from Bandoli et al. combined to increase power
ozAA = Absolute ounces of alcohol; SD = Standard Deviation; TM = Trimester

Table 1: Maternal Characteristics by Breastfeeding Category (N=392)

	Breastfeeding Group			
	None	**1-3 months**	**4+ months**	
Maternal Characteristics	n = 28 (7.1%)	n = 103 (26.3%)	n = 261 (66.6%)	**P-Value**
Drinking pattern – n (%)				
Low	11 (39.3%)	56 (54.37%)	177 (67.8%)	
Medium	11 (39.3%)	32 (31.07%)	46 (17.6%)	
High	6 (21.4%)	15 (14.56%)	38 (14.6%)	0.005*
Mom Age (yrs)				
Range	19 – 37	16 – 43	16 – 40	
Mean (SD)	26.7 (5.4)	25.8 (5.7)	26.4 (4.8)	0.53
Gestational Age at delivery (wks)				
Mean (SD)	39.0 (2.0)	39.5 (1.6)	39.6 (1.3)	0.35
Smoking– n (%)				
Yes	12 (42.8%)	38 (36.9%)	61 (23.4%)	
Unknown	1 (3.6%)	2 (1.9%)	3 (1.1%)	0.005*
College[1] – n (%)				
Yes	4 (14.3%)	47 (45.6%)	148 (56.7%)	<0.001*
Married – n (%)				
Yes	23 (82.1%)	91 (88.3%)	247 (94.6%)	0.02*
Vitamin Use – n (%)				
Yes	21 (75%)	75 (72.8%)	203 (77.8%)	0.60
SES – n (%)				
High (HH ≥30)	16 (57.1%)	76 (73.8%)	220 (84.3%)	<0.001*
ozAA/day by trimester Mean (SD)(Oz)				
TM1	0.616 (1.398)	0.227 (0.476)	0.187 (0.477)	<0.001*
TM2	0.344 (0.692)	0.140 (0.385)	0.098 (0.350)	
TM3	0.238 (0.446)	0.108 (0.358)	0.086 (0.315)	
6-month Bayley: MDI Mean (SD)	82.26 (15.23)	88.06 (9.62)	90.93 (6.45)	
Missing	5 (17.9%)	8 (7.8%)	34 (7.8%)	<0.001*
6-month Bayley: PDI Mean (SD)	82.22 (15.05)	87.88 (12.28)	89.94 (9.76)	
Missing	5 (17.9%)	8 (7.8%)	34 (7.8%)	0.002*
12-month Bayley: MDI Mean (SD)	86.96 (17.03)	88.45 (10.46)	90.27 (10.43)	
Missing	5 (17.9%)	19 (18.4%)	30 (18.4%)	0.01*
12-month Bayley: PDI Mean (SD)	94.48 (16.27)	96.54 (12.65)	98.54 (11.59)	
Missing	5 (17.9%)	19 (18.4%)	30 (18.4%)	0.05*

*Indicates values significantly different by group at 0.05 level.
1. College defined as any schooling beyond high school
ozAA = Absolute ounces of alcohol; TM = Trimester; SES = Socioeconomic Status; MDI = Mental Developmental Index; PDI = Psychomotor Developmental Index; HH = Hollingshead score; SD = Standard Deviation

Table 2: Maternal Characteristics by Drinking Trajectory Group (N=392)

	Drinking Pattern Group			
	Low	**Medium**	**High**	
Maternal Characteristics	n = 244 (62.2%)	n = 89 (22.7%)	n = 59 (15.1%)	**P-value**
Breastfed – n (%)				
Never	11 (4.5%)	11 (12.4%)	6 (10.2%)	0.005*
1-3 m	56 (23.0%)	32 (35.9%)	15 (25.4%)	
4+ m	177 (72.5%)	46 (51.7%)	38 (64.4%)	
Mom Age (yrs)				
Range	16 – 43	16 – 42	16 – 40	
Mean (SD)	26.3 (4.5)	26.4 (6.1)	25.9 (5.7)	0.01*
Gestational Age at delivery (wks)				
Mean (SD)	39.7 (1.3)	39.4 (1.7)	39.2 (1.8)	0.03*
Smoking – n				
Yes	31 (12.7%)	51 (57.3%)	29 (49.2%)	<0.001*
Unknown	4 (1.6%)	1 (1.1%)	1 (1.7%)	
College[1] – n (%)				
Yes	146 (59.8%)	30 (33.7%)	23 (39.0%)	<0.001*
Married – n (%)				
Yes	235 (96.3%)	79 (88.8%)	47 (79.7%)	<0.001*
Vitamin – n (%)				
Yes	193 (79.1%)	67 (75.3%)	39 (66.1%)	0.11
SES – n (%)				
High (HH ≥30)	213 (87.3%)	59 (66.3%)	40 (67.8%)	<0.001*
ozAA/day by trimester				
Mean (SD)(Oz)				
TM1	0.006 (0.018)	0.221 (0.121)	1.159 (1.137)	<0.001*
TM2	0.002 (0.012)	0.107 (0.134)	0.671 (0.815)	
TM3	0.004 (0.026)	0.073 (0.110)	0.556 (0.706)	
6-month Bayley: MDI				
Mean (SD)	90.91 (7.51)	89.50 (8.10)	84.37 (10.83)	0.02*
Missing	33 (13.5%)	9 (10.1%)	5 (8.5%)	
6-month Bayley: PDI				
Mean (SD)	90.09 (10.12)	88.56 (11.16)	84.48 (13.31)	0.02*
Missing	33 (13.5%)	9 (10.1%)	5 (8.5%)	
12-month Bayley: MDI				
Mean (SD)	91.54 (10.40)	87.47 (10.38)	84.96 (12.40)	0.08
Missing (%)	35 (14.3%)	13 (14.6%)	6 (10.2%)	
12-month Bayley: PDI				
Mean (SD)	99.55 (10.99)	95.91 (13.27)	93.40 (14.04)	0.04*
Missing	35 (14.3%)	13 (14.6%)	6 (10.2%)	

*Indicates values significantly different by group at 0.05 level.

1. College defined as any schooling beyond high school

ozAA = Absolute ounces of alcohol; TM = Trimester; SES = Socioeconomic Status; MDI = Mental Developmental Index; PDI = Psychomotor Developmental Index; HH = Hollingshead score; SD = Standard Deviation

Table 3: Main effects (Bs) of Breastfeeding and PAE on Neurodevelopment (N = 392)

	PDI 6 M	MDI 6 M	PDI 12 M	MDI 12 M
Breastfeeding				
None	Reference	Reference	Reference	Reference
1-3 m	5.41 [0.37, 10.46]*	5.46 [1.73, 9.19]*	1.33 [-4.26, 6.93]	0.64 [-4.32, 5.61]
4+ m	6.88 [2.03, 11.73]*	7.98 [4.40, 11.57]*	2.64 [-2.62, 7.90]	2.00 [-2.67, 6.67]
PAE				
Low	Reference	Reference	Reference	Reference
Medium	0.02 [-3.13, 3.17]	0.13 [-2.20, 2.46]	-2.51 [-6.08, 1.06]	-3.57 [-6.74, -0.40]*
High	-4.55 [-7.97, -1.12]*	-5.77 [-8.30, -3.23]*	-4.94 [-8.89, -0.99]*	-6.17 [-9.68, -2.67]*

*Significant – null value not included in the 95% confidence interval
Controlled for maternal age, smoking during pregnancy, prenatal vitamin use, SES, and infant sex.

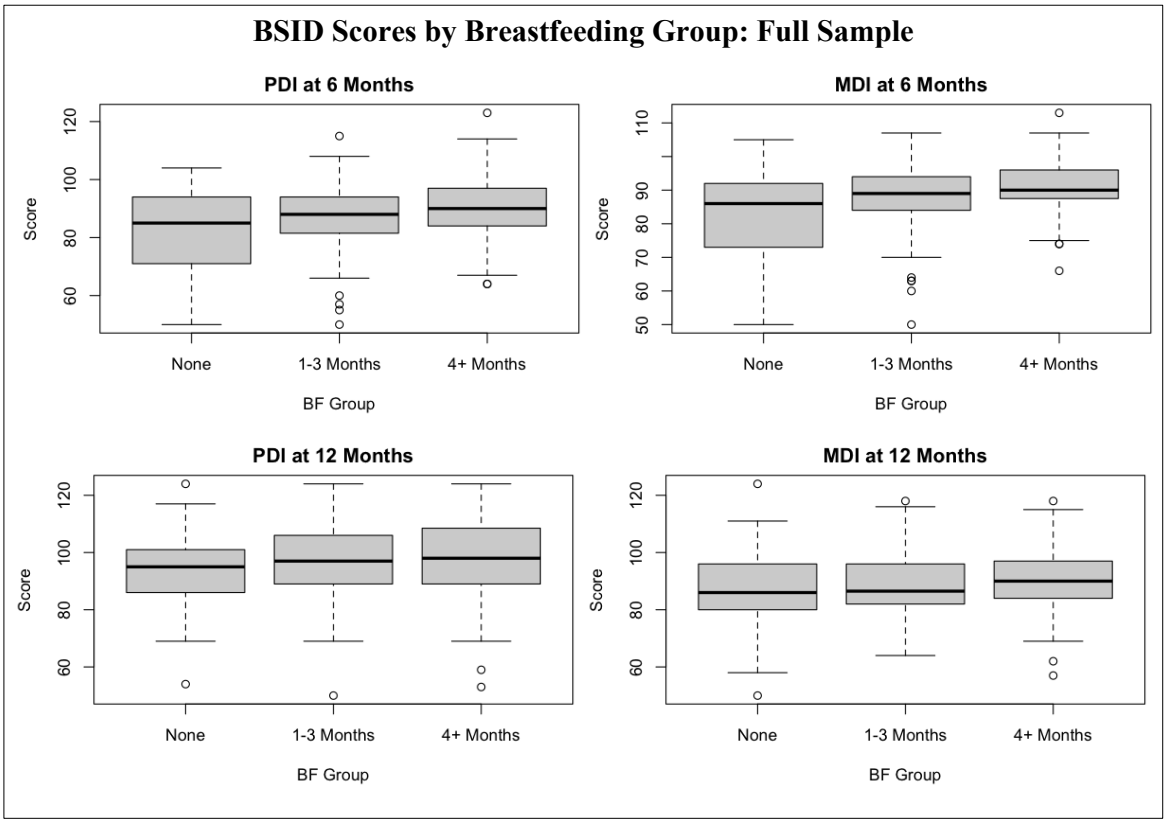

Figure 2: PDI and MDI scores at 6 and 12 months by Breastfeeding Group: Full Sample (N = 392)

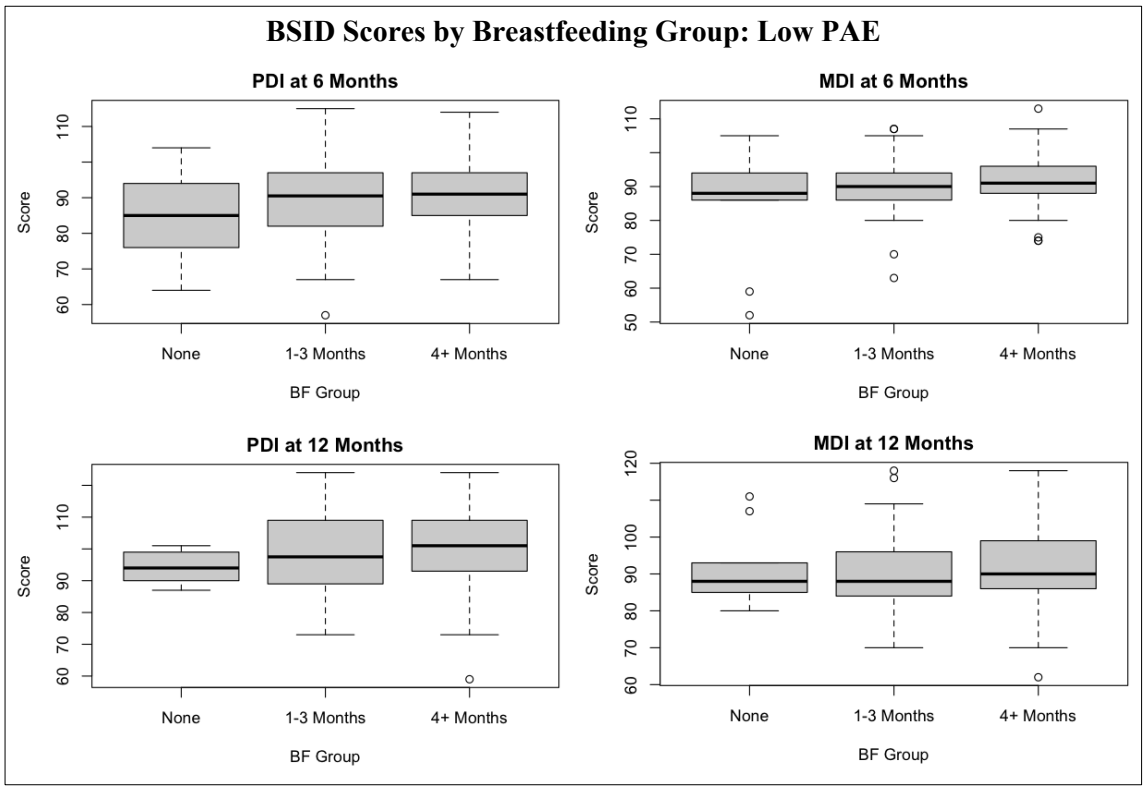

Figure 3: PDI and MDI scores at 6 and 12 months by Breastfeeding Group: Low PAE (N = 244)

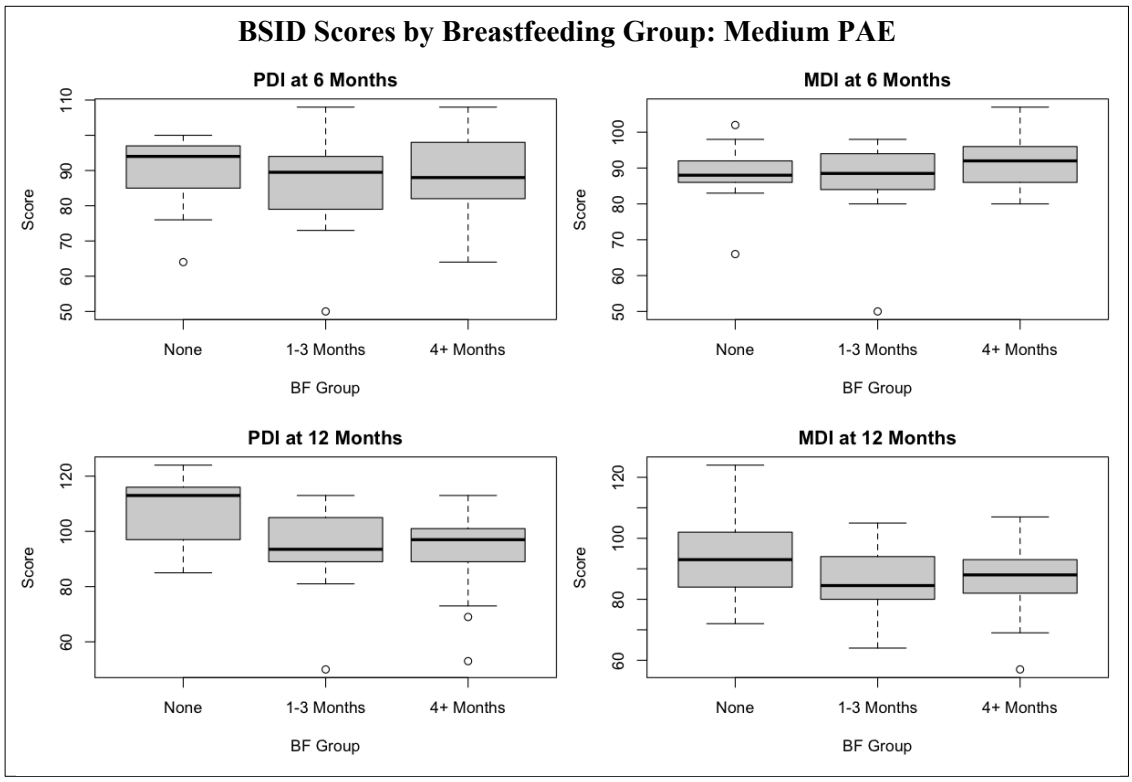

Figure 4: PDI and MDI scores at 6 and 12 months by Breastfeeding Group: Medium PAE (N = 89)

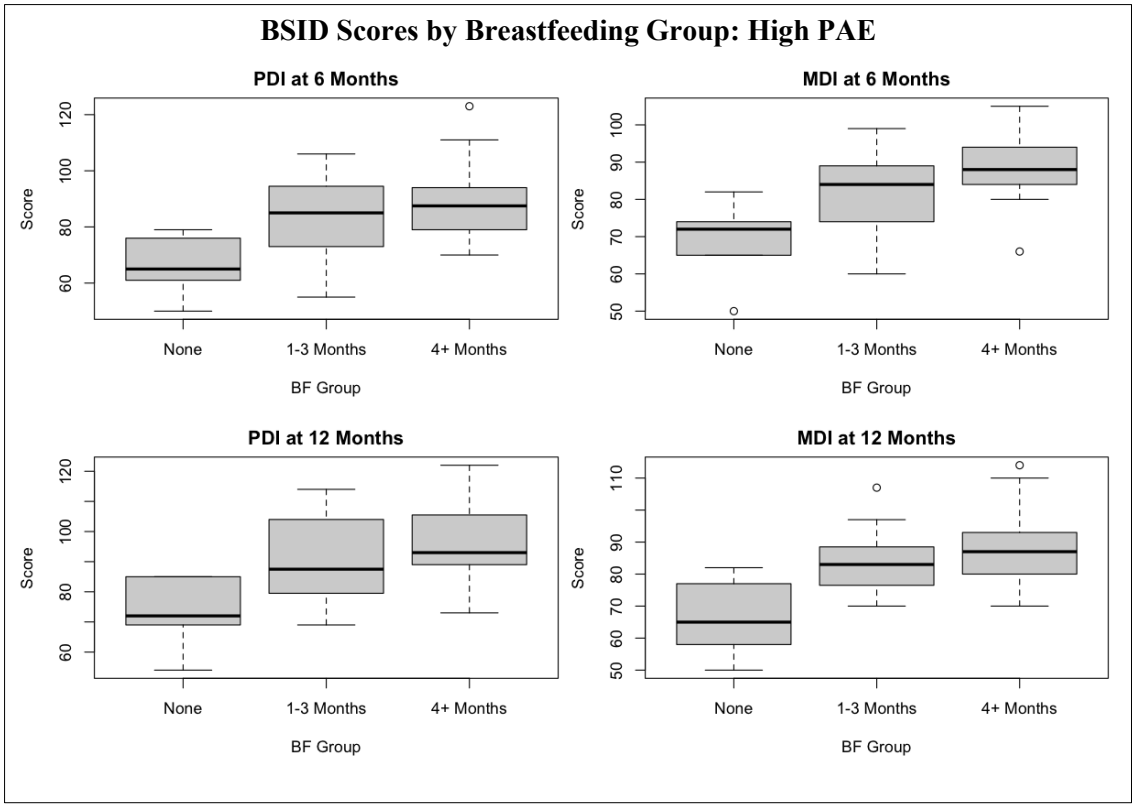

Figure 5: PDI and MDI scores at 6 and 12 months by Breastfeeding Group: High PAE (N = 59)

Table 4: Main effects (Bs) of Breastfeeding on Neurodevelopment stratified by PAE group

	PDI 6 M	MDI 6 M	PDI 12 M	MDI 12 M
LOW PAE				
Breastfeeding				
None	Reference	Reference	Reference	Reference
1-3 m	6.36 [-1.41, 14.13]	6.82 [1.10, 12.54]*	4.18 [-3.91, 12.27]	0.15 [-7.52, 7.81]
4+ m	6.21 [-1.13, 13.56]	7.71 [2.31, 13.12]*	5.30 [-2.24, 12.85]	0.64 [-6.50, 7.79]
MEDIUM PAE				
Breastfeeding				
None	Reference	Reference	Reference	Reference
1-3 m	0.37 [-8.08, 8.83]	2.17 [-3.84, 8.18]	-10.75 [-20.70, -0.81]*	-7.21 [-15.32, 0.90]
4+ m	2.91 [-5.36, 11.19]	4.94 [-0.94, 10.82]	-12.75 [-22.27, -3.23]*	-7.37 [-15.13, 0.39]
HIGH PAE				
Breastfeeding				
None	Reference	Reference	Reference	Reference
1-3 m	15.23 [1.56, 28.91]*	11.61 [0.71, 22.51]*	17.43 [2.91, 31.95]*	14.04 [1.50, 26.59]*
4+ m	19.67 [6.92, 32.41]*	18.25 [8.09, 28.41]*	22.28 [9.48, 35.08]*	20.25 [9.19, 31.32]*
Breastfeeding & PAE Interaction Term p-value	0.02*	0.01*	<0.001*	0.001*

*Significant – null value not included in the 95% confidence interval
Controlled for maternal age, smoking during pregnancy, prenatal vitamin use, SES, and infant sex.

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