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Antenatal and neonatal antecedents of executive dysfunctions in extremely preterm children

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Abstract

To find out why children born extremely preterm are at heightened risk of executive dysfunctions (ED), we assessed 716 10-year-olds born extremely preterm whose IQ ≥ 70. A working memory dysfunction (WMD) (N = 169), an inhibition dysfunction (ID) (N = 360), a switching dysfunction (SD) (355), and all 3 (ED) ((N = 107), were defined on the basis of Z-scores ≤ −1 on the DAS-II working memory composite, and/or on the NEPSY-II Inhibition-Inhibition and Inhibition-Switching subtests. All risk profiles include an indicator of socioeconomic disadvantage. The risk profile of each of the 3 individual dysfunctions includes an indicator of the newborn's immaturity, and the risk profiles of the ID and SD also include an indicator of inflammation. Only the SD dysfunction was associated with fetal growth restriction. The risk factors for ED can be subsumed under the four themes of socioeconomic disadvantage, immaturity/vulnerability, inflammation, and fetal growth restriction.

Keywords

extremely preterm; school performance; learning disabilities; mathematics; reading; special educational needs

Introduction

Children born very preterm are at higher risks of executive dysfunctions (variously defined at various ages) than children born at term.[1–10] Among children born extremely preterm, those who have executive function impairments have poorer academic outcomes than their peers.[11,12] Academic deficits in children who were born extremely preterm and had

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executive dysfunctions probably limit their “long-term economic and civic potential and productivity.”[13]

In our search for explanations why preterm newborns are at heightened risk of executive dysfunctions, we found only five reports that have in the title both ‘executive function’ and either ‘predict’ or ‘risk.’[5,14–17] None of these, however, reported the results of a systematic examination of a moderately large number of candidate characteristics and/or exposures in a relatively large number of high-risk children.

One possibility reflects the association between executive function limitations and low intelligence. However, even when adjustment is made for low IQ, children born extremely preterm or at an extremely low birth weight are more likely than their peers to have executive function limitations.[18]

Another possibility is that children born preterm who have executive function limitations are more likely than others to have early-identified structural abnormalities of the brain.[19–22] This might be a consequence of the extremely preterm newborn’s propensity to have systemic inflammation,[23] which appears to increase the risk of brain damage.[24–26] This prompted us to evaluate the contribution of inflammation-provoking exposures, as well as other exposures and perinatal characteristics to the risk of executive dysfunctions.

In light of the view that executive functions comprise three separable but interacting components: working memory, inhibitory control, and mental shifting/cognitive flexibility, [28,29] we assessed children’s performance on three corresponding measures: DAS-II Working Memory composite, NEPSY-II Inhibition-Inhibition, and NEPSY-II Inhibition-Switching, and sought the antecedents of limitations on each executive dysfunction component, as well as that of a composite comprised of all 3 limitations.

Methods

Participants

The ELGAN (**E**xtremely **L**ow **G**estational **A**ge **N**ewborn) Study is a multi-center observational study designed to identify characteristics and exposures associated with increased risk of structural and functional neurologic disorders in extremely preterm infants. [27] During the years 2002-2004, women delivering before 28 weeks gestation at one of 14 participating institutions were asked to enroll in the study. A total of 1249 mothers of 1506 ELGANs consented to participate. Enrollment and consent processes were approved by the individual institutional review boards.

Ten years later, we invited 966 children to return for an age-appropriate assessment of cognition, executive function, behaviors, and achievement (Table 1). They were selected because the concentrations of inflammation-related proteins in their blood collected during the first postnatal month had been measured. Of these 966 children, 889 (92%) returned for follow up and 874 were administered the neurocognitive tests. Enrollment and consent procedures for this follow up study were approved by the institutional review boards of all participating institutions.

Procedures at age 10 years

The families of all children whose development was assessed at age 2 years were contacted by mail and then by phone to invite them to participate in the 10-year follow up. Lost to follow-up families were searched for on state vaccination registries, and other openly-available websites. Facebook was also used where approved by the local institution's IRB.

Families willing to participate were scheduled for one visit during which all of the measures reported here were administered in 3 to 4 hours, including breaks. The assessments were selected to provide the most comprehensive information about neurocognitive and academic function in one testing session.

General cognitive ability (or IQ) was assessed with the School-Age Differential Ability Scales–II (DAS-II) Verbal and Nonverbal Reasoning scales.[30] For this study, we included only children with scores of 70 or higher on both scales.

The DAS-II Recall of Digits Backward and Recall of Sequential Order yielded a working memory composite score, while the NEPSY-II (A Developmental NEuroPSYchological Assessment-II) Inhibition-Inhibition subtest measured simple inhibition and the Inhibition-Switching subtest measured inhibition in the context of set shifting.[31] A low score on each assessment was defined as a Z-score of ≤ -1. We also created an indicator of executive dysfunction, which required a Z-score ≤ -1 on each of these three assessments.

Data analyses

We evaluated the generalized form of the null hypothesis that each measure of executive dysfunction is not associated with any prenatal, or early postnatal characteristic or exposure in children who are not cognitively impaired (*i.e.*, DAS-II ≥ 70). We began with univariate analyses (Appendix Tables 1-8), which identified candidate variables for the multivariate logistic regression analyses (Table 2). Because postnatal phenomena can be influenced by antepartum phenomena, the variables entered into the logistic regression analyses were ordered temporally, with the earliest occurring predictors/covariates of the risk of each measure of executive dysfunction entered first and not displaced by later occurring covariates.[32]

We used a step-down procedure seeking a parsimonious solution without interaction terms. The contributions of relevant variables are presented as risk ratios with 95% confidence intervals. The risk ratio for each variable expresses the increased or decreased risk of each measure of executive dysfunction in one category of a characteristic or exposure relative to the other.

Data interpretation—We found that even though the correlates of socio-economic disadvantage are so highly correlated, different sets of socio-economic correlates were associated with each of the four executive dysfunction entities. This prompted us to try to group the similar findings for each of the four executive dysfunction entities as themes that made sense in light of our familiarity with this data set.

Results

Of the 716 children who had an IQ ≥ 70 and had all 3 of the executive function subtests, 169 (24%) had a working memory Z-score ≤ −1, 350 (49%) had an Inhibition-Inhibition Z-score ≤ −1, 355 (50%) had an Inhibition-Switching Z-score ≤ −1, and 107 (15%) had a Z-score ≤ −1 on all 3. As might be expected, children who had a Z-score ≤ −1 on one subtest were likely to have a low Z-score on one of the other subtests. Specifically, 63% of all children who had a working memory Z-score ≤ −1, had a similarly low Z-score on the Inhibition-Inhibition subtest, and 80% had such a low Z-score on the Inhibition-Switching subtest (based on data in Appendix Table 1). Of all children who had an Inhibition-Inhibition Z-score ≤ −1, 34% had a similarly low Z-score on the working memory composite, and 69% had such a low Z-score on the inhibition-switching subtest, while 38% of the children who had an Inhibition-Switching subtest Z-score ≤ −1, had a working memory Z-score ≤ −1, and 70% had an Inhibition-Inhibition Z-score ≤ −1.

Univariable analyses (Appendix Tables 2-9)

Appendix Tables 2-9 display the prevalences of the four executive dysfunction entities among children classified by maternal, pregnancy, and newborn characteristics. The variables associated with each executive dysfunction are identified in the results section of the Appendix. Here we present these associations grouped by the variables that fit each of 4 themes. We identify each variable associated with each executive dysfunction entity with initials: W for working memory, I for Inhibition-Inhibition, S for Inhibition-Switching, and A for having all 3 limitations.

Theme #1: low socioeconomic characteristics

The indicators/correlates of mother’s low socioeconomic status associated with an increased risk of executive dysfunctions include self-identification as Black (W, S, A), young age at the time of the delivery (W, I, S, A), not married (W, S, A), low level of educational achievement (W, S, A), eligibility for government-provided medical-care insurance (W, S, A), not trying to get pregnant (A), did not seek conception assistance (W, S, A), less than one year since previous pregnancy (A), smoked cigarettes during the pregnancy (I, S), and exposure to the smoke of others (S).

Theme #2: inflammation

We divide inflammation into 2 categories, antenatal and postnatal. Among the indicators of antenatal inflammation associated with an increased risk of executive dysfunctions are mother-reported periodontal infection (I, S, A), consumption of a non-steroidal anti-inflammatory drug (I, S, A), recovery from the placenta parenchyma of multiple organisms (A), including Mycoplasma (W, A) and normal vaginal flora (A). Among the indicators of postnatal inflammation are postnatal antibiotic (W, I, S, A), postnatal bacteremia (S, A), tracheal colonization (S), “surgical” necrotizing enterocolitis (W, I, S), severe (W, I) and non-severe (S) bronchopulmonary dysplasia, retinopathy of prematurity (S).

Theme #3: immaturity/vulnerability

Low gestational age at birth (W, S, A), the quintessential indicator of immaturity and vulnerability, has many correlates that we view as conveying similar risk information. Those associated with an increased risk of executive dysfunctions include low birth weight (W, I, S), high illness severity score (SNAPPE II) (W, S, A), pulmonary deterioration (W, S), early and persistent pulmonary dysfunction (W, S), pneumothorax (W, S), pulmonary interstitial emphysema (S), pulmonary hemorrhage (W, I, S), tracheal colonization (S), retinopathy of prematurity (S), "surgical" necrotizing enterocolitis (W, I, S), severe (W, I) and non-severe (S) bronchopulmonary dysplasia, no antenatal corticosteroid exposure (W), no exposure to antenatal magnesium (A), high measurements of PaO_2 (S, A) and PCO_2 on 2 of the first 3 postnatal days (S), as well as postnatal receipt of surfactant (S), hydrocortisone (S), dexamethasone (A), a sedative (S), and recurrent transfusions (S).

Theme #4: fetal growth restriction

Low birth-weight Z-score, THE criterion for fetal growth restriction, was associated with all 3 executive dysfunctions (W, I, S), while correlates of fetal growth restriction in this sample, including fetal indication for delivery (W, A), mechanical ventilation (W and S most consistently, but also I for mechanical ventilation on day 21), early and persistent pulmonary dysfunction and pulmonary deterioration (W,S), severe bronchopulmonary dysplasia/chronic lung disease (W, I, S, A), and retinopathy of prematurity (S) exhibited more restricted associations.

Time-oriented risk models (TORMs)(Table 2)

This table is best viewed as the results of 4 regression analyses/models, each potentially consisting of variables from the three epochs, pre-pregnancy (*i.e.*, maternal socio-demographic characteristics), pregnancy characteristics/exposures, and early postnatal characteristics/exposures. The first epoch variables are entered first. They are retained and the second epoch (pregnancy) variables are then entered. The third epoch model retains the identified variables from the first and second epochs, while adding early postnatal characteristics and exposures.

a. working memory—The model for low working memory score included two maternal socio-demographic characteristics, Black self-identification and single marital status. When these were retained and pregnancy characteristics added, none were statistically significant. A high illness-severity score, which, to a large extent, reflects unstable/disturbed physiology during the first 12 postnatal hours was the only variable from the first postnatal month that supplemented risk information provided by the 2 socio-demographic variables.

b. Inhibition-Inhibition—Mother having no more than a high school education is the only socio-demographic variable associated with an increased risk of a low score on the Inhibition-Inhibition subtest. In contrast, three pregnancy variables provided supplemental information. They are consumption of a non-steroidal anti-inflammatory drug, chorionic plate inflammation of the placenta, and lack of exposure to magnesium sulfate. Low birth weight (≤ 750 grams) is the only early postnatal Variable that supplemented the risk information provided by the 4 variables already in the model.

c. Inhibition-Switching—The three separate socio-demographic variables associated with an increased risk of a low score on the Inhibition-Switching assessment were Black identification, no more than a high school education and single marital status. Although no pregnancy variable provided additional risk information, three early postnatal variables did, highest quartiles of P_aO_2 and PCO_2 on two of the first three postnatal days, and mechanical ventilation on day 21.

d. executive dysfunction composite measure—Only mother's eligibility for government-provided insurance provided information about the risk of the executive dysfunction composite.

Summary of Time-oriented risk models (Table 3)

We created this summary table to show the similarities and differences among the 4 executive dysfunction entities. We did this, in part, because we see each antecedent as a representative of other antecedents contained within the same theme.

Theme #1: Sociodemographic—All 4 entities have risk profiles that include at least one socio-demographic variable, with 2 entities, low scores on the working memory and Inhibition-Switching assessments, having the same 2 antecedents, Black-identification and not-married. No more than a high school education was shared by low scores on both the Inhibition-Inhibition and the inhibition-switching assessments.

Theme #2: Inflammation—The risk profiles of the working memory and executive dysfunction surrogate entities did not include an inflammation variable. In contrast, the risk profile of the entity characterized by a low score on the Inhibition-Inhibition assessment included 3 variables that conveyed information about inflammation, consumption of a non-steroidal anti-inflammatory drug, inflammation of the chorionic plate of the placenta, and no exposure to magnesium sulfate.

Mechanical ventilation on day 21 was the only inflammation-related variable associated with increased risk of a low score on the Inhibition-Switching assessment. In the ELGAN Study, "prolonged" mechanical ventilation (*i.e.*, beyond 2 weeks) was associated with systemic inflammation.[33]

Theme #3: Immaturity/vulnerability—The risk profile of each of the 3 components of executive dysfunction included an immaturity/vulnerability indicator, but the risk profile of the executive dysfunction surrogate did not. The risk profile of a low score on the Inhibition-Inhibition assessment included an extremely low birth weight (*i.e.*, ≤ 750 grams), while the risk profile of a low score on the working memory assessment was associated with a high illness severity score (*i.e.*, SNAP-PE 45+), indicative of physiologic instability and immaturity.[34–36] In contrast, the risk profile of a low score on the Inhibition-Switching assessment included 3 separate, but highly related indicators of physiologic instability and immaturity, highest quartiles of PaO_2 and PCO_2 on 2 of the first 3 days, and need for mechanical ventilation on postnatal day 21.

Theme #4: Fetal growth restriction—The only fetal growth restriction correlate identified by Time-oriented risk models was mechanical ventilation on day 21 as a risk factor for a switching limitation.

Discussion

Our main findings are that the risk profiles of executive function limitations appear to be best viewed as including indicators of socio-demographic disadvantage, inflammation, and immaturity/vulnerability.

SES

Children whose family is at socioeconomic disadvantage are at heightened risk of executive dysfunction regardless of whether they were born at term,[37–40] late preterm (34 to 36 weeks' gestation),[41] or preterm.[17,42–48] Among the biological mechanisms hypothesized to mediate the effects of social adversity on developmental outcomes of these preterm infants are an increased risk of giving birth preterm,[49,50] inflammation,[51–56] epigenetic phenomena ((*i.e.*, DNA methylation, histone modifications, and mRNAs),[57–59] exposure to neurotoxins, and sub-optimal parenting.[60] We expand on these.

Allostasis is the term applied to the stress that accompanies/follows from the need for constant adaptation.[61] When intense or persistent over long periods of time, the resulting allostatic overload disturbs a variety of systems,[62] including inflammatory immune activity,[63–65] as well as brain function[66] and maturation.[67]

"Environmental inequality'[68] and environmental injustice[69] are terms used to describe the increased likelihood of low socioeconomic adults and children to be exposed to violence, disorganization in school environments, crowding, and noise,[70] as well as toxins, some of which are known neurotoxins.[71]

Poor families face significant economic pressure and prejudice as they struggle to earn a living, pay bills, and make decisions about what is absolutely essential.[72] The resulting stress and dysfunction among parents that head many of these families may render them less able than others to provide nurturing, stimulation, and responsiveness to their children's needs.[60] Such lower-quality parenting has been associated with executive function limitations in the child.[15] Previously institutionalized children, who are presumed to have not received the equivalent of high-quality parenting, are also at increased risk.[73]

In preclinical models, stressing the gravida adversely influences the fetal brain.[74] In humans, too, maternal stress, some of which is related to social disadvantage, appears to have detrimental effects on the fetal brain.[75–79]

Immaturity

Compared to their peers born at term, children born very preterm or at very low birth weight are more likely to have executive dysfunction limitations.[1–10,14,46–48] However, even within groups of children defined by low gestational or low birth weight, the lower the gestational age, the higher the risk usually,[1,14,80,81] but not always.[17]

Several studies have also found that correlates of immaturity, such as high scores on the Neurobiological Risk Score (NBRS), a composite measure of neonatal risk,[82] low weight gain during the first 6 weeks,[2] and number of surgeries[14] were associated with one or more indicators of executive dysfunctions.

The gravida or placenta provides the fetus with neurotrophic proteins that the fetus is not yet able to synthesize in adequate amounts. These neurotrophic proteins promote the survival and differentiation of the brain cells in the fetus and newborn,[83] and are capable of promoting repair of brain damage,[84,85] Birth before having the ability to synthesize adequate amounts of these needed developmentally-regulated proteins limits the extremely preterm newborn's capacity to protect the brain, and to initiate repair.

Another disadvantage of immaturity in this sample is the intensity of the inflammatory response. In the ELGAN Study, concentrations of inflammation-related proteins in blood collected during the first 2 postnatal weeks tended to decrease with increasing gestational age, regardless of whether or not the placenta was inflamed.[86]

These 2 characteristics of immaturity are but just a few of those that have been identified. Consequently, we view indicators of immaturity as surrogates for all the unmeasured and unidentified developmentally regulated processes that might be associated with adversity,[87] including increased risk of executive dysfunctions.

Inflammation

Children who have executive dysfunctions are more likely than others to have been exposed to inflammatory phenomena such as necrotizing enterocolitis,[88] bronchopulmonary dysplasia,[43] and bacteremia.[89] Because children who have executive dysfunctions are more likely than their peers to have brain image abnormalities related to their executive function limitations,[20,22,90–100] it is possible that the inflammation, especially if prolonged or recurrent, contributes to executive dysfunctions via structural changes in the developing brain.[23,24,26,101–105]

Non-steroidal anti-inflammatory drugs were among the over-the-counter drugs recommended for fever and malaise during the second trimester of pregnancy.[106] Thus this variable is likely to convey information about infection/inflammation during pregnancy. Histologic inflammation of the placenta's chorionic plate speaks for itself. During 2002–2004 when newborns were recruited for the ELGAN Study, magnesium sulfate was most often given to women who had severe preeclampsia. It was also used as a tocolytic, but less often. Thus, the absence of magnesium sulfate exposure can serve as an indicator of an inflammation-associated medical indication for extremely preterm delivery, as well as an indicator that the children not exposed to magnesium might have been deprived of magnesium's neuroprotective[107] and anti-inflammatory capabilities.[108,109]

Fetal growth restriction

Children in the ELGAN study who had fetal growth restriction were less likely than their peers to have abundant concentrations in the blood of proteins with neurotrophic properties.[110] In addition, they were more likely to display an inflammatory surge after the first

postnatal week.[111] These two phenomena might explain why growth restricted extremely preterm newborns who experience systemic inflammation are at especially heightened risk of cognitive limitations.[112]

Vulnerability as an integration of all four themes

The four themes of socioeconomic disadvantage, immaturity, inflammation, and fetal growth restriction are so interrelated that it is difficult to distinguish the contribution of each from the others to the etiology of executive dysfunctions. We offer the unifying concept of vulnerability. Each theme contributes information about (brain) vulnerability of ELGANs.[112–118] Indeed, the co-occurrence of risk factors representing multiple themes might have a more adverse effect than the sum of the contribution of factors representing only one theme.[119]

Methodologic considerations

Categorization of outcome—We acknowledge that our dysfunction criterion of a score one or more standard deviations below the normative mean is arbitrary. Indeed, no sharp break (or discontinuity) in scores separates those with an executive dysfunction from their peers. As epidemiologists, we prefer to study categorical entities rather than continua. This is in keeping with our discipline's tendency to establish cut-offs for continuous measures of function/dysfunction (*e.g.,* hypertension, diabetes mellitus, glaucoma).[120]

Executive function assessments—While other investigators who sought to identify the risk factors for executive dysfunctions did not use either the NEPSY-II Inhibition-Inhibition and Inhibition-Switching assessments, others have used low scores on these measures to define executive function limitations.[121,122]

Heterogeneity of categorization of executive dysfunctions—We also acknowledge that the three executive dysfunction indicators tend to occur together, resulting in our assessing not isolated dysfunctions, but overlapping non-independent dysfunctions. Because each form of dysfunction might have its own risk profile, our including children who also had other executive dysfunctions impedes our ability to identify specific risk profiles.

Time-oriented Risk Models—Our Time-oriented risk models (TORMs) categorize sets of antecedents by the time they occurred or were identified. Only those variables in each epoch are retained that provide unique discriminating information. We do not allow variables from subsequent models to remove variables identified in previous epochs. What we are left with is a parsimonious model that might not be the most relevant from a biologic perspective, although it is from a discriminating perspective. That is why we emphasize themes rather than individual variables.

The multifactorial view of what contributes to the occurrence of dysfunctions —The multifactorial view of what contributes to dysfunction/disease postulates that the occurrence of every disorder/dysfunction reflects multiple factors.[123–126] This has been our experience in the ELGAN Study. For example, the risk of a low mental development index (on the Bayley Scales-II) is increased among children who had indicators/correlates of

socioeconomic disadvantage,[32,127,128] immaturity,[34,127] were growth restricted at birth,[112,128,129] were exposed to antenatal inflammation,[130] and had systemic inflammation.[130,131] These observations have reinforced our acceptance of a multifactorial view of the etiology of executive dysfunctions, even among children with an IQ in the normal range.

Limitations and strengths of this study—Our arbitrary definition of dysfunction undoubtedly resulted in some misclassification. We are unable, however, to know the extent and nature of such misclassification.

Even though we restricted our sample to those who had an IQ ≥ 70, thereby reducing the potential confounding of low IQ, this might not have been adequate to eliminate all residual confounding.

We create our models by selecting the variables that provide the most discriminating information. An unfortunate consequence might be that variables closely associated with this variable are not identified as risk factors.

With our large number of children who had each of the four executive dysfunction categories we assessed, we were able to appreciate risk ratios as low as 1.4 as statistically significant. Other strengths are the selection of infants based on gestational age (and not birth weight),[132] prospective collection of all data, and modest attrition.

Conclusions—In this sample of 10-year-old children born extremely preterm, increased risks of scores of one or more standard deviations below the normative mean individually on three assessments, DAS-II Working Memory, NEPSY-II Inhibition-Inhibition, and NEPSY-II Inhibition-Switching, as well as on all three together, were associated with perinatal antecedents that could be gathered under the headings of socio-economic disadvantage, immaturity, inflammation, and fetal growth restriction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is known

Very little is known about the antecedents of executive dysfunctions in children born at an extremely low gestational age.

What this study adds

This study confirms that socioeconomic disadvantage and immaturity are important risk factors for these dysfunctions. It also suggests that inflammation, both antenatal and postnatal, might also be important.

Table 1

Sample description

	Yes	No
Enrolled	1506	
Returned for an assessment at age 10 years	889	
DAS-II IQ ≥ 70	739	
All relevant assessments completed	716	
Working memory (WM) Z-score ≤ −1	169	547
Inhibition-Inhibition (I-Inhib) Z-score ≤ −1	360	356
Inhibition-Switching (I-Swich) Z-score ≤ −1	355	361
Z-score ≤ −1 on all 3: WM, I-Inhib, I-Switch	107	609

Table 2

Odds ratios and 95% confidence intervals for the association of each learning limitation with the antecedents listed on the left. These are based on a time oriented logistic regression model that added variables sequentially as they were identified. Earlier occurring variables could not be displaced. The selection of variables to offer the model is based on what was seen in earlier tables. Children with each of the learning limitations are compared to the same referent group of children who did not have that learning limitation.

A. Working Memory (WM)			
	Socioeconomic	**Socioeconomic & Pregnancy**	**Socioeconomic, Pregnancy & Early postnatal**
Socioeconomic			
Black identification	2.1 (1.4, 3.1)	2.1 (1.4, 3.1)	1.9 (1.3, 2.9)
Single marital status	2.0 (1.3, 2.9)	2.0 (1.3, 2.9)	1.9 (1.3, 2.9)
Pregnancy			
Nothing		-----	-----
Early postnatal			
SNAPPE-II 45+			1.8 (1.2, 2.7)

B. Inihibition-Inihibition (I-Inhib)			
	Socioeconomic	**Socioeconomic & Pregnancy**	**Socioeconomic, Pregnancy & Early postnatal**
Socioeconomic			
Maternal education ≤12 years	1.7 (1.2, 2.3)	1.6 (1.2, 2.2)	1.6 (1.2, 2.2)
Pregnancy			
NSAID during pregnancy		2.2 (1.2, 4.1)	2.1 (1.1, 3.9)
Chorionic plate inflammation		1,5 (1.03, 2.3)	1.5 (1.02, 2.3)
No magnesium sulfate		1.7 (1.2, 2.3)	1.7 (1.2, 2.4)
Early postnatal			
Birth weight ≤ 750 grams			1.5 (1.1, 2.1)

C. Inihibition-Switching (I-Switch)			
	Socioeconomic	**Socioeconomic & Pregnancy**	**Socioeconomic, Pregnancy & Early postnatal**
Socioeconomic			
Black race	2.4 (1.6, 3.6)	2.4 (1.6, 3.6)	2.8 (1.8, 4.5)
Maternal education ≤12 years	1.4 (1.03, 2.1)	1.4 (1.03, 2.1)	1.0 (0.7, 1.6)
Single marital status	1.6 (1.1, 2.2)	1.6 (1.1, 2.2)	1.9 (1.2, 2.8)
Pregnancy			
Nothing		-----	-----
Early postnatal			
Highest Q highest P_aO_2 *			2.0 (1.3, 3.1)
Highest Q highest PCO_2 *			2.1 (1.4, 3.2)
Mech ventilation, day 21 *MV*			1.8 (1.2, 2.5)

D. Executive Dysfunction composite (All)			
	Socioeconomic	**Socioeconomic & Pregnancy**	**Socioeconomic, Pregnancy & Early postnatal**
Socioeconomic			
Eligible for public insurance	2.2 (1.4, 3.3)	2.2 (1.4, 3.3)	2.2 (1.4, 3.3)
Pregnancy			
Nothing		-----	-----
Early postnatal			
Nothing			-----

*Extreme quartile for gestational age on two of the first three postnatal days

MV Includes conventional mechanical ventilation and high frequency ventilation

Table 3

Single table summary of the four parts of Table 2

	Antenatal	Pregnancy	Early Postnatal
Low socioeconomic status			
Black	WM, I-Switch		
Single marital status	WM, I-Switch		
Maternal education ≤12 years	I-Inhib, I-Switch		
Public insurance	All		
Inflammation			
NSAID during pregnancy		I-Inhib	
Chorionic plate inflammation		I-Inhib	
No magnesium sulfate		I-Inhib	
Mechanical ventilation, day 21			I-Switch
Immaturity			
Birth weight ≤ 750 grams			I-Inhib
SNAP-PE 45+			WM
Highest Q P_aO_2*			I-Switch
Highest Q PCO_2			I-Switch
Mechanical ventilation, day 21			I-Switch
Fetal growth restriction			
Mechanical ventilation, day 21			I-Switch