**REVIEW ARTICLE**

Placental programming, perinatal inflammation, and neurodevelopment impairment among those born extremely preterm

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Individuals born extremely preterm are at significant risk for impaired neurodevelopment. After discharge from the neonatal intensive care, associations between the child’s well-being and factors in the home and social environment become increasingly apparent. Mothers’ prenatal health and socioeconomic status are associated with neurodevelopmental outcomes, and emotional and behavioral problems. Research on early life risk factors and on mechanisms underlying inter-individual differences in neurodevelopment later in life can inform the design of personalized approaches to prevention. Here, we review early life predictors of inter-individual differences in later life neurodevelopment among those born extremely preterm. Among biological mechanisms that mediate relationships between early life predictors and later neurodevelopmental outcomes, we highlight evidence for disrupted placental processes and regulated at least in part via epigenetic mechanisms, as well as perinatal inflammation. In relation to these mechanisms, we focus on four prenatal antecedents of impaired neurodevelopment, namely, (1) fetal growth restriction, (2) maternal obesity, (3) placental microorganisms, and (4) socioeconomic adversity. In the future, this knowledge may inform efforts to detect and prevent adverse outcomes in infants born extremely preterm.

**PEDIATRIC RESEARCH**

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**IMPACT:**

- This review highlights early life risk factors and mechanisms underlying inter-individual differences in neurodevelopment later in life.
- The review emphasizes research on early life risk factors (fetal growth restriction, maternal obesity, placental microorganisms, and socioeconomic adversity) and on mechanisms (disrupted placental processes and perinatal inflammation) underlying inter-individual differences in neurodevelopment later in life.
- The findings highlighted here may inform efforts to detect and prevent adverse outcomes in infants born extremely preterm.

**BACKGROUND**

Extremely preterm birth (birth before 28 weeks of gestation) accounts for <1% of US births; however, due to their greatly increased risk of chronic health and developmental disorders, individuals born extremely preterm contribute a disproportionate fraction of children with cerebral palsy, cognitive impairment, epilepsy, and autism spectrum disorder. Early life predictors of chronic health and developmental disorders among survivors of extreme prematurity is the focus of this review of findings from the Extremely Low Gestational Age Newborn (ELGAN) Study and similar cohorts. The ELGAN cohort was recruited in the years 2002–2004, at 14 hospitals in five states in the United States, and has been evaluated through 15 years of age, although this review will be restricted to findings through 10 years of follow-up. The premises of this review are that: (1) more effective promotion of positive health outcomes among individuals born preterm depends on greater understanding of risk factors for chronic disorders and the mechanisms that link these risk factors to adverse outcomes and (2) interventions that target early life risk factors hold greater potential benefit than those which target factors later in life. For this reason, we focus on prenatal risk factors and highlight biological mechanisms including placenta reprogramming and perinatal systemic inflammation that may be targeted to interrupt the relationships between exposures during fetal life to childhood health outcomes.

Over the past half century in which advances in obstetrical and neonatal care resulted in dramatic improvements in the survival of babies born extremely preterm, the major focus of epidemiological studies (both observational and interventional) has been neonatal morbidities attributable to immaturity of multiple organs, including lungs, brain, eyes, kidneys, and gastrointestinal tract. Related to this immaturity are high risks of acute disorders, such as respiratory distress, necrotizing enterocolitis (NEC), sepsis, and more chronic conditions such as bronchopulmonary dysplasia (BPD), perinatal brain injury, and severe retinopathy of prematurity (ROP). Each of these neonatal morbidities is predictive of...
adverse neurodevelopmental impairment. To the extent that neonatal morbidities lie on a causal pathway connecting extremely preterm birth to adverse child health and neurodevelopmental outcomes, interventions that target antecedents of BPD, NEC, sepsis, severe brain injury, and ROP have the potential for increasing the likelihood that an extremely preterm birth will remain free from chronic health or developmental problems.

In comparison to the neonatal morbidities, prenatal antecedents of adverse health and developmental outcomes among extremely preterm neonates have been relatively understudied. Prenatal risk factors for adverse outcomes potentially could be linked to both neonatal morbidity, as a mediating factor, and also could have direct links to adverse outcomes, without involving neonatal morbidity as mediator. As examples of prenatal antecedents of neonatal morbidities and/or chronic disorders of health or development, we will review four that have been investigated within the ELGAN cohort: (1) fetal growth restriction (FGR), (2) maternal obesity, (3) placental microorganisms, and (4) socioeconomic adversity (Fig. 1). By considering ELGAN Study findings about these four antecedents, we also illustrate that two mechanisms, namely, placental reprogramming and perinatal inflammation, may underlie the developmental origins of health and disease (DOHaD). By modifying the prevalence of these antecedents and/or targeting mechanistic links between early life predictors and later life outcomes, health and development can be optimized for individuals born extremely preterm.

A detailed discussion of the methods used to identify neurodevelopmental impairments is beyond the scope of this review, but can be found elsewhere. Nonetheless, it is important to emphasize that in many studies of neurodevelopmental impairment among extremely preterm infants, the follow-up period extended only through late infancy, when the predictive accuracy of assessments is at best modest. Thus, an important research priority are studies of adults born extremely preterm.

MECHANISM 1: PERINATAL INFLAMMATION AND NEURODEVELOPMENT

The central hypothesis of the ELGAN Study that perinatal inflammation contributes to the neurodevelopmental impairments, which disproportionately affect children born extremely preterm, had its origins >45 years ago when Floyd Gilles and Alan Leviton observed a 34-fold increase in the odds of autopsy-confirmed perinatal white matter damage among infants with postmortem bacteremia, despite the finding of no bacteria in their brains. In preclinical models, animals treated with lipopolysaccharide (LPS) or viral mimetics develop systemic inflammation that can then lead to microglial activation and increased local transcription of chemokines in the brain. Chemokine induction leads to a transient recruitment of neutrophils and monocytes to the brain, and accumulation of macrophages and other immune cells that can extravasate from blood vessels and/or cerebrospinal fluid to infiltrate the brain parenchyma. Experimental (e.g., LPS-induced) inflammation leads to neonatal cerebral white matter damage in kittens, rodents, rabbits, dogs, pigs, and non-human primates. The propensity to develop neuroinflammation in association with peripheral immune activation is influenced by genetic background, sex, and postnatal age.

In humans, antecedents of perinatal brain injury and resultant neurodevelopmental impairments that might be mediated by systemic inflammation include maternal factors, such as socioeconomic status (SES) indicators, pre-pregnancy obesity, and FGR; perinatal infections, such as sepsis, tissue damage, as can occur with NEC and ventilator-induced lung injury; and pre- and postnatal exposure to environmental chemicals, as well as treatments given to neonates as a component of neonatal intensive care. The heightened inflammatory response to LPS in male neonates, as compared to females, might contribute to males’ higher risk of neurodevelopmental impairments.

As has been found in preclinical models, human neonates with sustained or multiple intermittent episodes of inflammation are at increased risk for perinatal brain injury as compared to those with a single episode of inflammation. Consistent with this possibility is the finding that in the ELGAN Study, infants with both placenta inflammation and neonatal systemic inflammation were more likely to develop brain ultrasound indicators of cerebral white matter damage and developmental impairments at 24 months of age than were infants who had only placenta inflammation or only neonatal systemic inflammation. Similarly, among infants born before 33 weeks of gestation, three or more infections was associated with a higher likelihood of magnetic resonance imaging-detectable white matter abnormalities lower scores on developmental assessments. A molecular mechanism that might underlie the apparent “sensitization” of the brain by an initial exposure to inflammation is the increased expression of Toll-like receptors that follows LPS treatment, and, as a consequence, increased sensitivity to inflammation in life.

Additional, albeit indirect, evidence that early life inflammation contributes to the risk of neurodevelopmental impairment comes from studies of genetic polymorphisms in inflammatory genes. Single-nucleotide polymorphisms (SNPs) in the genes for...
interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and IL-1β have been associated with an increased risk of cerebral palsy among very preterm infants, and a SNP in the mannose-binding lectin gene has been associated with worse neurodevelopmental outcome. Consistent with inflammation having a mediating role between early life antecedents and neurodevelopment outcome, the recovery of Lactobacillus from placenta was associated with variation in placental DNA CpG methylation of inflammation-related genes, decreased neonatal systemic inflammation, and decreased risk of cognitive impairment among children born extremely preterm.

Particularly compelling evidence of a relationship between perinatal inflammation and disrupted brain development comes from studies of the relationship of biomarkers of inflammation, such as TNF-α and IL-1, -6, -8, and -9. In one of the earliest biomarkers studies, neonates born at term with elevated levels of inflammatory biomarkers in the first several postnatal days were more likely to subsequently develop cerebral palsy, with the strongest association being with spastic diplegia. In a meta-analysis of 37 studies, the protein biomarkers most consistently predictive of neurodevelopmental impairments were IL-6, IL-8, and, to a lesser extent, TNF-α and IL-1β. In the ELGAN Study, elevated levels in neonatal blood of multiple inflammation biomarkers, most prominently IL-8, were associated with neonatal brain ultrasound indicators of white matter damage, cognitive impairment, cerebral palsy, autism spectrum disorder, and attention deficit hyperactivity disorder symptoms, as well as decreased cortical and deep gray matter, cerebellar, and brainstem volumes as measured with magnetic resonance at 10 years of age.

A detailed description of the cellular and molecular events that could explain a causal relationship between perinatal inflammation and neurodevelopmental impairments is beyond the scope of this review, and the interested reader is referred to several excellent reviews of this topic. Briefly, systemic inflammation disrupts the blood–brain barrier and allows movement of molecular inflammation mediators into the brain or by stimulating secretion from endothelial cells of inflammatory mediators into the brain parenchyma. Microglial activation to an immune-responsive state not only increases microglial production of molecules that are toxic to neighboring neurons but also reflects from developmental microglial functions that support axonal connectivity and synaptic formation. The neuroimmune system is central not only to neuronal injury but also to brain plasticity and manifests as both reparative and pathological activity. One implication of these dual roles of neuroinflammation is that great caution is needed when designing therapeutic interventions targeting neuroinflammation.

**MECHANISM 2: DISRUPTED PLACENTAL PROGRAMMING AND NEURODEVELOPMENT**

Evidence is growing that the mechanisms by which maternal exposure to stressors is associated with later life neurobehavioral dysfunction likely initiate within the placenta. As such, placental development and function are important features of the DOHaD framework. As the conduit between the mother and fetus, the placenta serves as a transient organ, yet the master regulator of fetal growth and development through numerous functions, such as metabolism, neuroendocrine signaling, and immunologic control. In humans, the decidua, composed of maternal uterine and immune cells, controls the immunological tolerance of the embryo. Trophoblast cells of fetal origin predominate in the basal plate where they serve as the source for the synthesis and secretion of endocrine factors into both maternal and fetal circulations. In contrast, chorionic villous trophoblasts located between the maternal and fetal vasculature are critical for the exchange of oxygen, nutrients, and waste through diffusion and macro- and micronutrient transporters. Disruption of these critical functions has adverse effects on fetal development, including the brain and primordial germ cells. Sex-specific reprogramming occurs in response to maternal stress and manifests as sex differences in placental size, gene expression, and CpG methylation. Sex-specific placental abnormalities predict offspring outcome in pregnancies complicated by maternal asthma and preeclampsia.

Evidence of a role for the placenta in relation to child health outcomes in ELGANs is several studies that have integrated placental programming, including gene expression and mechanisms that control gene expression, such as altered DNA (i.e., CpG) methylation signatures with later life health. Specifically, ELGAN researchers have provided evidence of the relationship between CpG methylation and gene expression of genes in critical biological pathways, including genes involved in the hypothalamic-pituitary-adrenal (HPA) axis and health outcomes in children born preterm. Specifically, placental CpG methylation levels of the glucocorticoid receptor gene, nuclear receptor subfamily group 3C member 1 (NR3C1) and brain-derived neurotrophic factor (BDNF) were significantly associated with increased odds in developing moderate/severe adverse cognitive impairment at age 10 years. In terms of the mechanistic basis for this relationship, related to placental function, NR3C1 is highly expressed and plays a role in regulating fetal exposure to cortisol. BDNF has been shown to promote trophoblast growth, and cell survival during placental development. Low expression levels of BDNF in the placenta have been associated with pregnancy complications, such as preeclampsia and preterm birth. In support of these data, differences in the methylation and subsequent altered expression of NR3C1 and FKBP5 in the placenta have been associated with adverse neurobehavioral outcomes. CpG methylation in humans occurs at the fifth position of the pyrimidine ring of the cytosine residues within CpG sites to form 5-methylcytosines. The presence of multiple methylated CpG sites in CpG islands of promoters often causes stable silencing of genes, although this gene silencing can also be initiated by other mechanisms.

The placental also serves as a sensor and transducer of environmental signals, such as prenatal exposure to tobacco, air pollution, and environmental pollutants, which have been tied to both neonatal morbidities and perinatal inflammation. Important questions remain in relation to the role of specific biological pathways in the placenta that when perturbed can lead to child health or disease. Through interrogation of molecular signatures in the placenta including the placental epigenomic and transcriptome, we anticipate that novel links between protective prenatal factors, placental molecular functions, and health outcomes in children will be identified.

Below, we discuss four antecedents of neurodevelopmental impairment for which there is at least preliminary evidence of associations with inflammation, placenta epigenetic variation, and neurodevelopmental impairment.

**ANTECEDENT 1: FGR**

FGR and neurodevelopment FGR, as reflected in unusually low birth weight for the infant’s gestational age, can arise from pathological conditions within the mother, fetus, or placenta. Among neonates born extremely preterm, FGR has been associated with an increased risk of BPD, NEC, and cerebral white matter injury (identified with ultrasound). The association between FGR and BPD is particularly strong among infants with relatively normal pulmonary function in the first 2 weeks of life, among whom the odds ratio (OR) for the association between FGR and BPD was 26 (95% confidence interval (CI) 7–95). Interventions that have the potential for...
mitigating risks associated with FGR include aspirin for women at high risk of developing preeclampsia and calcium supplemen-
tation among women with low calcium intake (<800 mg per day).99

In the ELGAN cohort, the disorder that was most strongly
associated with FGR was autism spectrum disorder without
intellectual deficit.100 FGR also was associated with severe early
cognitive impairment (a Bayley Scale Mental Development Index
<55) at 2 years of age,101 although the association between FGR
and a low intelligence quotient at 10 years of age was not
statistically significant when adjusted for confounders.102 Among
girls, FGR was associated with delayed motor development at 2
years of age,103 but was not associated with an increased risk of
cerebral palsy.98 Sex differences in outcome of fetuses with
FGR might result from sex-specific changes in the structure
and function of the placenta in response to processes that
underlie FGR.104

Fetal growth restriction and inflammation-related proteins
Potential molecular mechanisms that might underlie associations
between fetal growth restriction and BPD, NEC, and cerebral white
matter include insufficiency of growth factors, such as insulin-like
growth factor-1, and neurotrophic factors, such as neurotrophin-4
and brain-derived neurotrophic factor.105,106 as well as increased
expression, during the first postnatal month, of inflammatory
proteins in neonatal blood, including cytokines (IL-1β, IL-6, TNF-α,
and IL-8), chemokines (monocyte chemoattractant protein-4),
adhesion molecules (E-selectin and intracellular adhesion
molecule-1 and -3), and matrix metalloproteinase-9.31 Although
ELGAN Study infants with FGR, as well as those born to mothers
with preeclampsia, were less likely than infants without FGR to
have systemic inflammation on the first postnatal day, they were
more likely to have systemic inflammation in the second week of
life.31 In addition, FGR could sensitize the fetal brain so that the
adverse effect of postnatal inflammation is accentuated. Consis-
tent with a “two-hit” model of pathogenesis,107,108 among ELGAN
cohort infants with FGR, those with elevated blood concentrations
of IL-1β, TNF-α, or IL-8 during the first 2 postnatal weeks were at
higher risk of severe early cognitive impairment as compared to
FGR infants without systemic inflammation and non-FGR infants
with systemic inflammation.109

Fetal growth restriction and placental programming
Among pregnancies delivered at term, differences in DNA CpG
methylation have been found when comparing placenta from
neonates with and without fetal growth restriction.114 However,
in human studies it is not possible to definitively determine if altered
profiles of DNA methylation are a response of the placenta to the
intrauterine environment and/or growth restriction, or whether
these methylation differences precede, and contribute to, growth
restriction. In the ELGAN cohort, the most common pregnancy
complication associated with FGR was preeclampsia.103 Pree-
clampsia is associated with differential methylation of genes in the
transforming growth factor-β signaling pathway, a regulator of
placental trophoblast invasion and migration.115 Another epige-
netic mediator is microRNA, and in the ELGAN cohort, 268 miRNAs
were identified as associated with birth weight.116 some of which
regulate important biological pathways, including glycoprotein VI
(the major receptor for collagen), human growth, and hepatocyte
growth factor signaling. Environmental chemicals such as
inorganic arsenic115 and cadmium114 are associated with epige-
netic modifications that might mediate associations between
these chemical exposures and fetal growth restriction.

**ANTECEDENT 2: MATERNAL OBESITY**

Maternal obesity and neurodevelopment

Over a third of all women of childbearing age in the United States
are obese (BMI ≥ 30 kg/m²).115 Confirming findings from other
cohorts,116–119 among ELGAN Study participants, newborns of
obese mothers, as compared to those born to mothers with
normal BMIs, were more likely to have Bayley Scales of Mental and
Motor scale scores >3 standard deviations below the reference
mean (mental: OR = 2.1; 95% CI 1.3, 3.5) (motor: OR = 1.7; 95% CI
1.1, 2.7) and these associations were more prominent in children
who did not have intermittent or sustained systemic inflammation
(mental: OR = 4.6; 95% CI 1.6, 14) (motor: OR = 3.7; 95% CI 1.5, 8.9).120 Similarly, based on evaluations at ten years of age,
individuals in the ELGAN Study whose mothers were obese prior
to pregnancy were more likely to have low scores on intelligence
tests, measures of processing speed and visual fine motor control,
and spelling achievement tests.121 However, ELGAN Study
children who were born to mothers with pre-pregnancy obesity
were not more likely to develop cerebral palsy.122

In studying associations between maternal obesity and off-
spring outcomes, a number of potential confounding factors
should be considered. Obese women are more likely to experience
adversities and exposures arising from low SES, and more often
experience micronutrient deficiencies, emotional distress, and
mental health dysfunctions.30 Studies of molecular mechanisms,
such as inflammation and placenta programming, could increase
understanding of the putative link between maternal obesity and
offspring outcome.

Maternal obesity and inflammation
Systemic inflammation is one molecular mechanism that might
contribute to the observed association between maternal obesity
to less favorable neurodevelopmental outcomes. In the ELGAN
cohort, among the pregnancies delivered as a result of maternal
or fetal indications, such as preeclampsia or severe fetal growth
restriction, infants born to mothers who were overweight (BMI
>25 but <30) or obese (BMI ≥ 30) were more likely to have elevated levels of protein biomarkers of inflammation, such as
C-reactive protein, E-selectin, intracellular adhesion molecule-3, and
receptors for TNF and vascular endothelial growth factor.29 In
addition, when assessed at 10 years of age, ELGAN individuals
who were exposed to pre-pregnancy maternal overweight or
obesity were more likely to be overweight or obese, outcomes
that would be expected to result in a chronic proinflammatory state123 and could have deleterious effects on brain structure and
function across the life span.124–129

Maternal obesity and placental programming
Disrupted placenta signaling is a second molecular mechanism
that likely plays a role in early life programming of fetuses
exposed to maternal obesity. Maternal obesity preceding or
during pregnancy is associated with variations in DNA CpG
methylation in umbilical cord blood.130,131 A study of siblings born
either before or after their mothers underwent bariatric surgery for
weight identified 5698 differentially methylated genes, with a
disproportionate representation of glucoregulatory, inflammatory,
and vascular disease genes.131 One of the largest studies (n = 9340) of the relationship of maternal obesity and offspring
epigeneic provides robust evidence of associations between
maternal adiposity and variations in newborn blood DNA
methylation.132 In most of the CpG sites that were differentially
methylated in cord blood, the association with maternal BMI was
also found in blood collected during adolescence, suggesting
existence of epigenetic “marks”. About 90% of the associations
between maternal BMI and offspring CpG methylation were most
likely explained by shared mother–offspring genetic and postnatal
environmental factors, but ~10% were most likely attributable to a
causal intrauterine mechanism. Other molecular mechanisms
that might mediate links between maternal obesity and offspring
neurodevelopment include an increase in oxidative stress and
altered maternal microbiome, both of which could alter placental
immune and metabolic functions.133
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ANTECEDENT 3: PLACENTAL MICROORGANISMS

Placenta microorganisms and neurodevelopment

Previously we have described the relationship between placental microorganisms and neurodevelopmental outcomes. Microorganisms in the placenta are associated with intrauterine infection and preterm labor. Pathogenic bacteria can colonize the placenta by hematogenous spread or invasion from the vagina. Although somewhat controversial, some researchers posit that even among uncomplicated pregnancies a placental microbiome exists, comprising non-pathogenic commensal microorganisms. Studies that utilized culture techniques optimized for detection of pathogenic organisms might fail to detect commensal organisms, while newer culture-independent techniques, such as 16S ribosomal RNA (rRNA) gene sequencing, can detect a more diverse set of organisms and less abundant organisms, but do not differentiate between living and dead bacteria and are susceptible to contamination from dust or commercial reagents. Notwithstanding this methodological concern, studies using 16S rRNA sequencing have detected microorganisms in the placenta that also are found in the vagina and oral cavity. In studies of extremely preterm births, conventional culture techniques detected non-pathogenic bacteria in the placenta, but these results might not apply to normal pregnancies.

In the ELGAN cohort, the presence of Ureaplasma urealyticum was associated with increased risk of brain ultrasound indicators of intraventricular hemorrhage and cerebral white matter injury. The presence of any aerobe in the placenta was associated with a 4-fold increase in the odds of diparesis, and the presence of two or more species of bacteria was associated with a 5.2-fold increase in odds. The recovery of any anaerobe or of two or more species of bacteria were associated with an approximate doubling of the odds of quadriparesis. Placental microorganisms were not associated with an increased risk of low scores on the Bayley Scales Mental Development Index, assessed at 2 years of age. However, assessments of the ELGAN cohort at 10 years of age indicated that recovery of U. urealyticum, Corynebacterium sp., Escherichia coli, or alpha-Streptococcus from placenta was associated with low scores on mathematics achievement tests, and recovery of U. urealyticum or Staphylococcus was associated with low scores on oral and written language tests. In contrast, recovery of Lactobacillus from placenta was associated with a lower risk of cognitive impairment and higher scores on language assessments.

Placenta microorganisms and inflammation

In the ELGAN cohort, biopsies of the subamniotic placenta parenchyma were taken around the time of delivery and were cultured and evaluated for specific histologic patterns of inflammation in a blinded fashion. Excluding cases with prolonged membrane rupture, microorganisms were recovered from 41% of placentas. High-grade chorionic plate inflammation and fetal vasculitis were found more frequently in placentas from which the following organisms were recovered: Actinomycetes, Prevotella bivia, Corynebacterium sp., E. coli, Peptostreptococcus magnus, multiple species of Streptococci, and Mycoplasma sp., including U. urealyticum.

Consistent with the premise that perinatal inflammation is a mediator of associations between the presence in placenta of specific microorganisms and altered risks of neurodevelopmental impairments, in the ELGAN cohort, the presence in placenta of either U. urealyticum or alpha-Streptococcus was associated with an increased likelihood of elevated levels of IL-8 in neonatal blood on day 1, whereas the presence in placenta of Lactobacillus was associated with a lower likelihood of elevated IL-8 levels. Among the 28 inflammation-related proteins measured in neonatal blood, IL-8 was the most strongly associated with neurodevelopmental impairment.

As discussed above, placental microorganisms are associated with both inflammation within the placenta and in the extremely preterm neonate’s blood. Within the placenta, inflammation might alter epigenetic processes, as suggested by the finding that acute chorioamnionitis is associated with altered DNA methylation in placentas from preterm deliveries, with DNA methylation profiles consistent with activation of the innate immune response. In the ELGAN cohort, placental microorganisms were associated with differential methylation within genes coding for growth and transcription factors, the immune response, and the inflammatory response, specifically the nuclear factor-κB pathway. These observations support the concept that microorganisms in the placenta could influence health and development in the offspring by altered placenta epigenetic programming. Further support for this concept is being sought in ongoing studies of the relationship of microorganisms to the placental transcriptome within the ELGAN cohort.

ANTECEDENT 4: SOCIOECONOMIC ADVERSITY

Socioeconomic adversity and neurodevelopment

In analyzing a child’s health, the concept of socioeconomic adversity illustrates aspects of the network of disadvantages leading to poor health outcomes. In the ELGAN cohort, factors indicative of socioeconomic disadvantage are associated with short and long health outcomes. Indicators of mother’s low SES that are associated with an increased risk of executive dysfunctions include young age at the time of the delivery, not married, low level of educational achievement, eligibility for government-provided medical-care insurance, and smoking cigarettes during pregnancy. Low education status at time of birth is also associated with substantial neurodevelopmental impairment with scores ≥2 standard deviations below normative expectation. Conversely, maternal educational advancement in child’s first 10 years of life is associated with modestly improved neurocognitive outcomes, even when adjusting for confounders, including gestational age, fetal growth restriction, maternal IQ, and minority ethnic/racial status. In the ELGAN Study maternal educational status serves as a proxy measure of SES and is strongly associated with household income, as reflected by eligibility for public (government-provided) health insurance (i.e., Medicaid). Follow-up studies of adults born prematurely indicate that maternal socioeconomic hardship at birth are associated with worse cognitive outcomes.

Socioeconomic adversity and inflammation

Recent research has focused on the potential biological mechanisms linking socioeconomic adversity and poor outcomes; much of this work has pointed to systemic inflammation. In the ELGAN Study, indicators of socioeconomic disadvantage (education) are associated with modestly increased risk of systemic inflammation in postnatal blood during the first postnatal month and with a slightly reduced risk of a neurotrophic signal, but do not confound relationships between inflammatory proteins and outcomes.

Socioeconomic adversity and placental programming

Advances in the developmental origins of chronic illness suggest that multiple environmental stressors are linked to variations in fetal–placental development, which involve DNA that can alter gene expression and set pathways linked to later life illness. In utero exposure to environmental stressors (i.e., socioeconomic adversity) can alter the expression of HPA axis-associated genes. Furthermore, adversity in fetal life can shape the maturation of stress-regulating pathways, leading to altered stress responsivity during adulthood. Although associations between epigenetic changes and health outcomes have been established, the extent to which maternal socioeconomic adversity affects CpG methylation in...
extremely preterm children is rarely demonstrated. In an epigenome-
wide DNA methylation in 426 placentas from ELGAN cohort, we
found that DNA methylation in 33 CpG sites (representing 21 genes)
associated with either a summative socioeconomic adversity
cumulative score or individual component exposures, including
maternal status, maternal education, and food security. Placentas
from female pregnancies showed more robust differential CpG
methylation than placentas from male pregnancies. Maternal socio-
economic adversity was associated with differential methylation of
genes involved in gene transcription and placental function
potentially altering immunity and stress response. These findings
suggest that socioeconomic adversity is associated with imprints on
the epigenome and may be linked to biological embedding of
socioeconomic adversity, which could affect long-term child
outcomes.

SUMMARY
Early life factors that influence health and development of
individuals born extremely preterm include prenatal factors such
as maternal BMI, placental microorganisms, fetal growth restric-
tions, and lower maternal socioeconomic status.

The body of evidence reviewed here suggests at least two broad
causal pathways between early life predictors and childhood out-
comes. These factors, which are not mutually exclusive, include:
(1) increased neonatal systemic inflammation, which consistently has been associated with later life impairments; and
(2) disrupted placental programming that may be controlled, at
least in part, through epigenetic mechanisms.

Novel findings from the ELGAN cohort that support the
hypothesis that placental CpG methylation is an intermediate
linking prenatal exposures to later life neurodevelopmental
outcomes include: (1) prenatal factors, such as maternal health
and socioeconomic adversity, are predictive of placental CpG
methylation, and (2) placental CpG methylation is predictive of
neurodevelopmental outcomes.

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