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Review Article

Born early and born poor: An eco-bio-developmental model for poverty and preterm birth

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Abstract. Poverty is associated with adverse long-term cognitive outcomes in children. Poverty is also linked with preterm delivery which, in turn, is associated with adverse cognitive outcomes. However, the extent of the effect of poverty on preterm delivery, as well as proposed mechanisms by which they occur, have not been well described. Further, the impact of poverty on preterm school readiness has not been reviewed. As the childhood poverty level continues to increase in the U.S., we examine the evidence around physiological, neurological, cognitive and learning outcomes associated with prematurity in the context of poverty. We use the evidence gathered to suggest an Eco-Bio-Developmental model, emphasizing poverty as a toxic stress which predisposes preterm birth and which, via epigenetic forces, can continue into the next generation. Continued postnatal social disadvantage for these developmentally high-risk preterm infants is strongly linked with poor neurodevelopmental outcomes, decreased school readiness, and decreased educational attainment which can perpetuate the poverty cycle. We suggest social remedies aimed at decreasing the impact of poverty on mothers, fathers, and children which may be effective in reducing the burden of preterm birth.

Keywords: Stress, neurodevelopment, poverty, prematurity

1. The scope of poverty and preterm birth

Poverty is associated with significant adverse life outcomes such as decreased health care access, increased injury, increased rates of chronic disease, food insecurity, and decreased academic performance throughout childhood [1–3].

Approximately 20% (15.75 million) of all American children lived in poverty in 2010 [4]. The recent economic recession increased the number of children in poverty by 1.1 million and the rate of childhood poverty has continued to increase over the past decade [1, 4, 5].

The federal poverty level is calculated based on the assumption that food represented one third of overall

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expenses [1, 6]. Thus in 2015, the federal poverty rate was $24,250 for a family of four [7]. However this number is controversial, as today families spend greater percentages of income on housing and child care costs and only one fifth of their budget on food, making the poverty rate calculation less valid for today's families. The concept of "Living Wage" is an alternative solution to better estimate minimum needs. This measure takes into account actual spending and includes housing and childcare expenses, and deemphasizes the contribution of food expenses. While varying by region, a living wage is estimated at approximately 200% of the federal poverty level [1, 8]. Most studies, however, adopt the federal definition.

There are significant racial and ethnic disparities between children living in poverty and those who are not. Although African-American children constitute only 14% of the child population, they account for 26% of impoverished children [4]. Furthermore, while 23% of U.S. children are Hispanic/Latino, this group accounts for 32% of American children in poverty [4].

Paralleling rates of childhood poverty are the rates of preterm (<37 0/7 weeks gestation age) birth. Though data illustrate a recent decrease in the rate of premature births in 2012 [9], this decrease is likely due to reduced elective birth in the late preterm gestational age range (34–36 6/7 weeks gestational age) [10]. More importantly, the percentage of very preterm infants (below 32 weeks completed gestation) – those who require the greatest healthcare resources per capita and are at highest risk of developmental complications – has been stable at approximately 2.0% over the same time span [9]. Concurrent high rates in both childhood poverty and preterm birth suggest a potential association.

Assessing the effect of economic poverty, per se, on birth outcomes is confounded by the association of low levels of education, teenage or unwed motherhood, smoking, and race with both poverty and birth outcomes [11]. In general, low income is associated with poor birth outcomes such as stillbirth, low birthweight and neonatal and post-neonatal mortality [11–13]. Using Missouri data, DeFranco et al. attempted to determine the independent effect of county-level poverty on preterm birth [14]. Defining preterm birth as less than 35 weeks gestation, the authors found significant differences in risk of preterm birth related to high-vs.-low poverty quartiles (adjusted odds ratio 1.18, Confidence intervals 1.03–1.35) [14]. Similar analysis for preterm birth less than 32 weeks demonstrated an even stronger association [14]. These data strongly implicate the socio-economic environment as a contributor to preterm delivery.

Other studies have shown the magnitude of odds of having a preterm delivery in the setting of poverty is 1.94 (1.73–2.17 [15], 2.42 (1.60–3.66) [11, 16]; 1.67 (1.42–1.96 [11]. To give a context to these relationships, the relative risk of a mother who herself was born prematurely of having preterm offspring is 1.85 (1.52–2.27) [17]. On the other hand the odds of a preterm delivery in the setting of cocaine use is 10.4 (5.5–20.0) [18]. The odds of prematurity in the setting of chorioamnionitis is highest for the most premature; with odds of preterm spontaneous delivery of 9.6 (8.7–10.6) for <28 weeks gestation, 4.5 (3.9–5.2) for 28–31 weeks, and 1.0 (1.0–1.1) for 32–36 weeks [19]. In summary, poverty is as important a risk factor for prematurity as heredity, but not as strong as infection or illicit substance use.

This review will discuss possible mechanisms by which poverty contributes to preterm birth; in turn, we review how preterm birth is associated with long-term cognitive impairment. We then will propose potential remedies to the problems identified. The randomized control trial is the gold standard in assessing causality. However, as randomized control trials are neither feasible nor ethical in determining the relationship between poverty and prematurity, epidemiologists have studied variables related to poverty and prematurity in an effort to assess relationships between and among multiple interactive and complicated social and environmental factors. Lucas and McMichael in 2005 summarized the utility of the Hill criteria, precepts aimed at assessing causality from epidemiologic studies [20]. These principles include 1. Strength, 2. Consistency, 3. Specificity, 4. Temporality, 5. Biological gradient, 6. Plausibility, 7. Coherence, 8. Experiment, and 9. Analogy [20].

In the setting of poverty, across studies and meta-analyses as cited above, the strength of the association is approximately one and a fifth to two times higher risk of preterm birth [11, 14–16]. Multiple studies are consistent with this degree of risk spanning United States regions as well as England [11, 14–16]. The narrow 95% confidence intervals listed above across these studies support a specific relationship between poverty and preterm birth [11, 14–16]. The criteria of temporality is re-enforced by the observation that women with lower socioeconomic status during pregnancy had an increased risk of preterm delivery, a relationship that persisted in the study's adjusted model [21]. The

biological gradient criteria is similar to dose-response, where Smith et al. in 2007 showed a gradation of higher very preterm birth across worse deciles of poverty [15].

There are many plausible biologic mechanisms of poverty causing prematurity which we detail subsequently. Coherence is established by the lower rates of preterm birth in countries with less poverty and universal healthcare [22]. Increased government investment in reducing poverty in England was associated with lower rates of extreme prematurity underlying the experimental criteria [1]. One key analogy-link in the poverty-prematurity outcome relationship is stress: in both poverty and prematurity, there are similar stress-related downstream pathophysiologies related to the neuro-hormonal-immuno axis [23, 24].

2. Mechanisms of poverty's effects on preterm birth

2.1. Environmental

Multiple studies have demonstrated an association of preterm birth and low birth weight with lower socioeconomic status across a diverse array of geographic areas [11, 14–16, 25–31]. An analysis of four studies using area deprivation scores which account for poverty by using location data, found an odds ratio of 1.67 (95% Confidence Interval 1.42–1.96) for preterm birth when comparing regions with the lowest and highest indices of socio-economic status [11].

The association of poverty and preterm birth is clear. However, to determine causality requires examination of mechanisms by which the social comorbidity of poverty may predispose to preterm birth. Environmental hazards do not fall equally on all income groups: poor families are more likely to have adverse environmental exposures [32]. For example, air pollution exposure, including particulate matter, nitric oxide species and sulfur dioxide occurs more frequently in mothers with preterm delivery [32, 33]. Families from lower socio-economic groups are also more likely to live in older housing, increasing risk of exposure to lead from dust or paint [34, 35]. Data suggests that women who experienced preterm delivery had higher lead levels than mothers of full term infants (4.53 vs 3.72ug/dl with higher odds of preterm delivery) [32, 36]. Cigarette smoke exposure – rates of which track with lower family income – has been clearly linked to preterm delivery as well [37, 38]. Areas with high levels of preterm birth overlap with areas of poor water quality, suggesting a link, though a specific toxin has not been identified [39].

2.2. Poverty as a "Toxic Stress"

Poverty's social impact imparts a chronic, toxic stress on preconception and pregnant women, predisposing them to epigenetic changes across generations [40–43]. Crowded home environments, smoke exposure, nutritional deprivation, unemployment and decreased social support all qualify as "toxic" stressors [40–42]. Experiencing these events early in life chronically activate the neuro-hormonal-immuno axis based stress response and is strongly associated with higher rates of preterm birth [24, 44, 45]. Animal models demonstrate that excessive fetal glucocorticoid exposure increases DNA methyltransferase activity in the placenta, conferring elevated Nuclear Factor Kappa B levels, a potent inducer of Interleukin 6 (IL-6) synthesis, leading to inflammatory response and resultant preterm birth [46, 47]. This may partially explain why pro-inflammatory cytokines are altered in women with preterm birth who have no other signs of a pro-inflammatory state such as infection [48–50]. These chronic stressors then impart epigenetic sequelae such as DNA methylation and histone deacetylation, depositing the biologic underpinnings of subsequent adverse long-term health outcomes [42]. Miller and Chen have demonstrated that these effects may be modulated by parental style [23]. Children from families that were less nurturing manifested increased IL-6, resistance to the anti-inflammatory effects of cortisol, despite socioeconomic strata [23]. These data suggest that more nurturing parenting styles can mitigate the effects of poverty-related stress on health [23].

Poverty induced stress, an epigenetic-mediated pro-inflammatory state, is speculated to remain embedded in the mother's epigenome [51, 52]. Such a hypothesis may explain why mothers born into poverty but who subsequently move to higher socioeconomic levels still maintain an increased incidence of adverse birth outcomes [53, 54]. An epigenetic change promoting inflammation is heritable [42, 55] and may partially explain why preterm birth in African-American women occurs across generations even if the next generation is not impoverished and why maternal grandmother's socioeconomic status is an independent risk factor for low birthweight [54]. Although transgenerational effects of poverty are plausible, and have

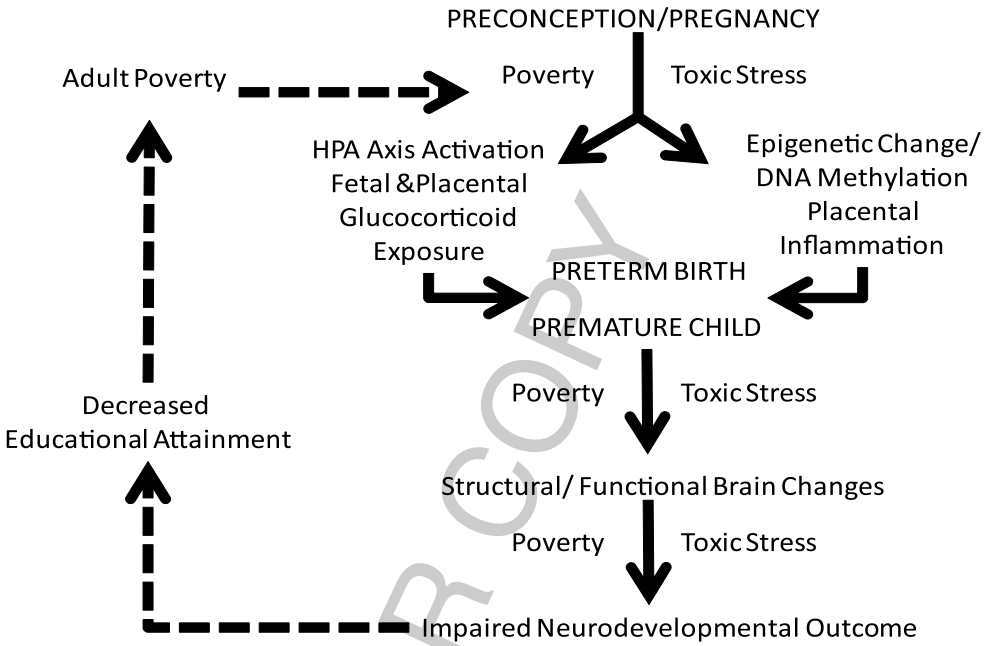

Fig. 1. Eco-Bio Developmental Model of Poverty and Preterm Birth: This figure outlines the multi-faceted effect of poverty on the public health issue of preterm birth. Poverty, acting as a "Toxic Stress" imparts chronic inflammatory changes in the preconception/pregnant mother, creating a chronic cytokine-mediated stress response and imparting inflammatory changes in the uterus/placenta – predisposing to preterm birth. After delivery, the high-risk preterm infant, growing up in an impoverished environment is less likely to be cognitively stimulated, resulting in decreased school readiness and educational attainment, resulting in lower wages in adulthood and perpetuation of the poverty cycle.

been observed in the setting of poverty and low birth weight [53, 54], little epidemiological data exist for the transgenerational effect of poverty on preterm birth.

Integrating the biologic effects of stress and environmental toxins at a time of critical cognitive development is the hallmark of an Eco-Bio-Developmental Model of disease, which has gained attention for its ability to assimilate health policy, molecular and developmental biology with research on optimal growth and development [42]. Adopting this model, Ecology (social and physical environment) and Biology (neuroendocrine axis as well as genetic predisposition) act together to increase the risk of preterm delivery and future problematic neurodevelopment (Fig. 1).

3. Poverty and long-term outcomes in premature infants

The independent effects of poverty on outcomes of preterm infants are difficult to isolate because other concurrent morbidities of prematurity [birthweight, postnatal corticosteroids, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL)] are related to poorer neurodevelopmental outcomes [56–59]. However, among all birthweights and gestational ages, parental incomes and socioeconomic status remain strong independent predictors of health and neurocognitive outcomes [60–65].

Though lower socioeconomic status remains a risk factor for developmental delay when assessed at two years, the influence of socioeconomic status persists as formerly preterm children reach school age [65]. Less school readiness leads to poorer academic performance, reduced educational attainment and subsequent decreased economic productivity, thus contributing to the perpetuation of the poverty cycle [66–69] (Fig. 1).

Hillemeier et al. examined the contribution of poverty on neurodevelopment in premature infants by using data from the Early Childhood Longitudinal Study Birth Cohort, and performing a modified Bayley Assessment as an outcome measure (Bayley Short Form-Research Edition) at 24 months and cognitive testing at 48 months [70]. Based on multivariate logistic regression models, the authors found the risk for cognitive delay at the 24 month time point increased with low birth weight (less than 1500 grams), education and race/ethnicity, but not for families with low

Table 1
Summary of the Known Differences in Brain Development in Children from Low versus High Socio-Economic Strata. Documented structural changes in the brain, along with functional correlates for children raised in poverty are listed

Region of brain	Effect of poverty/low socio-economic status	Functional correlate	Reference
Amygdala	decreased volume, greater reactivity,	emotional processing	77–79
Hippocampus	decreased overall volume (l > r)	stress regulation/emotional processing	78, 79
White matter	decreased	processing across gray matter	78
Cortical gray matter	decreased volume	speech, emotion, decision-making, self-control	78
Left inferior frontal Gyrus	decreased specialization, decreased volume	language expression	75
Left fusiform gyrus	correlation with activation and phonological awareness, increased distractibility	visual word recognition	73, 76
Right middle frontal Gyrus	Increased activity	novel task performance/rule learning	81
Perisylvian region	larger region activated in phonological task	phonologic awareness	76

incomes. However, the risk for delay was significantly higher in poorer families and those with lower education at 48 months compared with parents of higher socioeconomic means [70]. At the 48 month age, extreme poverty exerted a greater effect than very low birthweight or prematurity on cognitive outcomes, suggesting the experience of wealthier children between 24–48 months mitigated intrinsic cognitive deficits conferred by preterm birth [70].

Hoobler et al. found low socioeconomic status (as measured by the Hollingshead Index of Social Position) provided a greater relative contribution to lower school readiness at 5–6 years of age than the neonatal sequelae of IVH and PVL in a predominantly Black population of preterm infants with respiratory distress syndrome (mean gestational age 27.5 weeks) [69].

At school age, children of wealthier families, despite their NICU course, benefit from socioeconomic advantage. Several studies have confirmed that former preterm infants from wealthier families performed better in measures of language, school readiness, and school performance and were less likely to require special education than gestational-aged, matched preterm controls drawn from poorer families [62, 65, 71]. Very low birthweight infants equaled their siblings in first grade school performance, but only if they came from families with high social position [72].

4. Poverty's anatomic and structural effect on brain development

Functional deficits in language development, school readiness, and school performance appear to have structural correlates [73, 74]. Studies of children from lower socioeconomic strata exhibit potential decreases in the specialization of the Left Inferior Frontal Gyrus, containing Broca's area and a relationship with activity in the left fusiform gyrus, an area involved in word recognition [73, 75]. Functional Magnetic Resonance Imaging technology has demonstrated that phonological awareness is more strongly associated (at lower socioeconomic levels) with left fusiform activation, a region important for language development [76]. Volumetric analysis has shown that poor children are at higher risk for decreased cortical gray and white matter, as well as lower hippocampal and amygdala volumes, but increased amygdala reactivity [73, 77–80]. A summary of known variations in regional brain size attributed to poverty is shown in (Table 1).

These architectural changes in the brain are associated with difficulty learning new tasks [81]. Children from mothers with lower educational attainment (a surrogate for socioeconomic status) exhibit increased electrical activity as measured by event related potentials while listening unattended to two stories, suggesting easy distractibility [73]. Delays in learning novel information, essential for education, are also seen in impoverished versus wealthier children and are associated with changes in the right middle frontal gyrus [73, 81].

Although the exact molecular mechanisms of these anatomic and functional differences have not been fully elucidated, the home environment of the premature infant has been implicated as a modifying factor of neurodevelopment [82, 83]. Watson et al. demonstrated that the parenting domains in academic stimulation, language stimulation, and learning stimulation were all significantly lower in poorer households of preterm infants ($\leq$ 37 weeks) with birthweights less than 2500 grams [83]. Using a cohort from eight cities, Bradley et al. determined that the percentage of premature

infants in poverty who attained normal cognitive and physical growth at 3 years was only 12% [82]. However, these well-functioning children were more likely to have a safe play area and be exposed to more learning materials than their under-performing peers [82]. Therefore, poverty is intertwined with a deficient caregiving environment which may worsen the neurodevelopmental effects of prematurity alone. Nevertheless, parenting style and household environment are modifiable and thus, if optimized, may mitigate the effects of poverty and prematurity on the developing brain.

Taken together, these studies support an Eco-Bio-Developmental mechanism of poverty and prematurity, whereby poverty exacerbates cognitive outcomes during a period of rapid postnatal neurodevelopmental growth of the already susceptible population of preterm infants [41, 42]. These deficits have structural correlates in the brain which result in decreased school readiness, leading to poorer academic performance, reduced educational attainment, and lower economic productivity across the lifespan - thus tending to perpetuate the poverty cycle (Fig. 1).

5. Remedies

On an individual patient or family level, parenting styles and home environment can mitigate the effects of poverty [23, 78, 82, 83]. Parents can be taught effective and nurturing techniques and can be alerted to the importance of early vocabulary stimulation [82–84]. Given that the discrepancy in achievement widens over time for preterm infants in poverty, community services which target these high-risk children in early childhood may mitigate their adverse cognitive outcomes at a later school age [65, 68]. Families in impoverished environments have decreased numbers of books and circumscribed developmental environments for children [82–85]. Over time the home experience plays a far greater role in impacting school readiness than NICU comorbidities [70, 82, 83]. Increasing the developmental stimulation of a child's environment with such programs as book sharing may be effective for preterm infants, as has been shown in full term infants [82, 84, 86]. Given the life-long decrease in economic productivity associated with poverty across all birthweights, the cost-effectiveness of these strategies may be highly favorable [87].

There is a lack of data linking the influence of social programs aimed at reducing poverty on the rates of preterm birth and the resulting diminished educational attainment of preterm children. However some studies link specific government policies to improved birthweights. The Earned Income Tax Credit (a government program to reduce tax liability for low-wage workers), Temporary Assistance for Needy Families (cash assistance credit), and expansion of the Supplemental Nutrition Assistance Program have all correlated with improved birthweight [88, 89]. However, antenatal and postnatal home visitation programs which seek to increase patient compliance, improve health care access, and reduce hospital readmission, have not been consistently shown to decrease rates of low birthweight [90–92].

The return on investment from programs which address social determinants of health and which provide minimum standards for self-sufficiency (ie. housing and nutrition) is well described [93, 94]. Use of our proposed Eco-Bio-Developmental Model of preterm birth will allow physicians to better articulate the wide ranging implications of poverty on the public health issue of preterm birth. With their scientific and clinical expertise, physicians are ideal advocates at the individual, community, and policy level to promote an intergenerational lifecourse perspective of prematurity and to promote measures aimed at reducing the ill health effects of poverty. Physicians' comprehensive knowledge of social history – assessing patients across the spectrum of preconception, pregnancy and child development – will allow earlier connection of families with appropriate community resources. Beyond counseling their patients, physicians may bring expertise on prematurity to those in the educational and public policy sectors, educating them and encouraging them to systematically address poverty's effects through regional, state, and federal advocacy. Tackling the deleterious relationship between poverty, prematurity and negative long term outcomes will take a concerted effort by many stakeholders. Physicians can play a major role in educating policymakers and citizens on issues of poverty and prematurity, and breaking the intergenerational poverty cycle.

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