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# Maternal socioeconomic disadvantage is associated with transcriptional indications of greater immune activation and slower tissue maturation in placental biopsies and newborn cord blood

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ABSTRACT

Children from economically disadvantaged families experience worse cognitive, psychiatric, and medical outcomes compared to more affluent youth. Preclinical models suggest some of the adverse influence of disadvantage could be transmitted during gestation via maternal immune activation, but this hypothesis has not been tested in humans. It also remains unclear whether prenatal interventions can mitigate such effects. To fill these gaps, we conducted two studies. Study 1 characterized the socioeconomic conditions of 79 women during pregnancy. At delivery, placenta biopsies and umbilical blood were collected for transcriptional profiling. Maternal disadvantage was associated with a transcriptional profile indicative of higher immune activation and slower fetal maturation, particularly in pathways related to brain, heart, and immune development. Cord blood cells of disadvantaged newborns also showed indications of immaturity, as reflected in down-regulation of pathways that coordinate myeloid cell development. These associations were independent of fetal sex, and characteristics of mothers (age, race, adiposity, diabetes, pre-eclampsia) and babies (delivery method, gestational age). Study 2 performed the same transcriptional analyses in specimens from 20 women participating in CenteringPregnancy, a group-based psychosocial intervention, and 20 women in traditional prenatal care. In both placenta biopsies and cord blood, women in CenteringPregnancy showed up-regulation of transcripts found in Study 1 to be most down-regulated in conjunction with disadvantage. Collectively, these results suggest socioeconomic disparities in placental biology are evident at birth, and provide clues about the mechanistic origins of health disparities. They also suggest the possibility that psychosocial interventions could have mitigating influences.



## 1. Introduction

Children's life outcomes differ as a function of their family's economic conditions. The slope of this socioeconomic gradient varies across countries (Elgar et al., 2015) and, even in nations where it is steep, a sizeable minority of disadvantaged youth still achieve positive outcomes (Masten and Narayan, 2012). Yet on the whole, disadvantaged children fare worse than their affluent peers, and these disparities are apparent in a variety of cognitive, psychiatric, and biomedical outcomes (Hertzman and Boyce, 2010; Shonkoff

*Abbreviations:* BMI, body mass index; EMT, epithelial-mesenchymal transition; IL, interleukin; NF-κB, nuclear factor kappa B; TFBM, transcription factor binding motif; TNFα, tumor necrosis factor alpha; TELiS, transcription element listening system; TOA, transcript origin analysis.

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and Garner, 2012). With regard to cognition, childhood disadvantage forecasts slower language acquisition, worse executive function, and lower educational attainment (Duncan and Murnane, 2011). Disadvantage also portends higher psychiatric risks (Reiss, 2013). In the National Comorbidity Survey Replication Study, financial hardships during childhood presaged higher probability of first-onset anxiety, mood, behavioral, and substance disorders, and did so at all stages of the lifecourse (McLaughlin et al., 2011). In the realm of physical health, disadvantage is associated with the incidence and severity of obesity, diabetes, and asthma in childhood (Chen et al., 2002), and with increased vulnerability to cardiovascular disease, functional disability, and premature death in adulthood (Galobardes et al., 2008; Montez and Hayward, 2014; Miller et al., 2011).

Mechanistic accounts of these disparities generally focus on characteristics of the postnatal environment, e.g., socioeconomic variations in children's exposure to cognitive stimulation, sensitive caregiving, dietary imbalances, and environmental toxins. Although these characteristics undoubtedly contribute to socioeconomic disparities (Kundakovic and Champagne, 2015; Hackman et al., 2010; Wright and Subramanian, 2007; Schreier and Chen, 2013), mounting evidence suggests that some of the relevant exposures could occur prenatally, and become "embedded" in aspects of physiology during sensitive windows of fetal development (Hertzman and Boyce, 2010; Entringer et al., 2012). Indeed, socioeconomic disadvantage often co-occurs with psychological stress, depressive symptoms, cortisol dysregulation, poor nutrition, and toxin exposure (Wright, 2011; Evans, 2004). Experimental studies in animals indicate these exposures can affect the gestational milieu, with implications for offspring brain development, cognitive functioning, psychiatric disorders, and a host of allergic, metabolic, and cardiac diseases (Bale, 2015; Hanson and Gluckman, 2014; Prescott, 2006; Pryce et al., 2005).

The placenta is likely to be a key route by which these exposures are transmitted from mother to offspring. It functions as a barrier that protects the fetus from maternal immunity and potential teratogens, and the interface where gases, nutrients, and waste are exchanged. These functions are dysregulated in animals subjected to experimental conditions that parallel human disadvantage, like psychological stress, glucocorticoid excess, and nutrient restriction (Bronson and Bale, 2016; Braun et al., 2013; Coe and Lubach, 2014). In many of these models, excessive activation of maternal immunity is a key pathway by which gestational manipulations predispose animals to altered patterns of neural, cognitive, and behavioral development (Bilbo and Frank, 2013; Estes and McAllister, 2016; Meyer, 2013; Bale, 2015; Nusslock and Miller, 2015). These phenotypes are thought to emerge because maternal immune activity interferes with placental nutrient transfer, slowing maturation of fetal brain, heart, and liver (Arck and Hecher, 2013; Dimasuay et al., 2016)

Despite these observations, studies have not yet examined how maternal socioeconomic conditions relate to placental immune activation in humans, or explored the implications for fetal maturation. Here, we attempted to begin to filling these gaps in knowledge by assessing the socioeconomic conditions of pregnant women and assembling transcriptional profiles of their placentas. Based on the findings in animal models outlined above (Bronson and Bale, 2016; Hanson and Gluckman, 2014; Arck and Hecher, 2013; Braun et al., 2013; Coe and Lubach, 2014), we hypothesized that maternal disadvantage would be associated with transcriptional indications of greater immune activation and slower tissue maturation in women's placental biopsies. We also expected maternal disadvantage would be associated with transcriptional indications of slower leukocyte maturation in newborn cord blood cells.

In a small follow-up study, we also considered the possibility these disparities might be ameliorated through a prenatal intervention. CenteringPregnancy is group-based model of prenatal care, wherein 8–10 women of the same gestational age meet together on a weekly basis with a nurse or midwife. Patients receive all the obstetric components of traditional prenatal care, but the sessions also focus on building social support, and include discussions of nutrition, parenting, stress reduction, patient-provider communication, and other topics typically reserved for childbirth preparation classes (Hale et al., 2014). In multiple large-scale evaluations, Centering has improved birth outcomes, particularly among low-income minority women (Ickovics et al., 2007, 2016; Picklesimer et al., 2012). For example, in an initial randomized clinical trial of 1047 women, Ickovics reported that participation in Centering led to a 33% reduction in preterm birth compared with traditional prenatal care (Ickovics et al., 2007). These benefits were replicated in a follow-up randomized trial of 1148 women, which also found a 34% reduction in babies delivered small for gestational age (Ickovics et al., 2016). Given that Centering reduces the prevalence of adverse birth outcomes in low-income women, and simultaneously lowers distress, facilitates social connections, and improves lifestyle (Ickovics et al., 2011; Heberlein et al., 2016), we hypothesized it would ameliorate some of the transcriptional dysregulation associated with disadvantage.

## 2. Patients & methods

### 2.1. Patients

Study 1 involved 100 women recruited from the obstetric clinics of NorthShore University Hospital in Evanston, Illinois. To participate, women had to be $\geq$18 years old, fluent in English, $\leq$26 weeks gestational age, and with a singleton pregnancy. To maximize generalizability, we included women regardless of whether they delivered vaginally or by Caesarean section. Exclusion criteria included fetal congenital anomaly, chromosomal abnormality, and treatment with oral corticosteroids during pregnancy or progesterone after 14 weeks' gestation. All women gave written consent before participating, and the Institution Review Boards of Northwestern University and NorthShore University HealthSystem approved the protocol.

Study 2 involved 40 women delivering at Greenville Memorial Hospital in Greenville, South Carolina. At admission to Labor and Delivery, resident physicians in Obstetrics and Gynecology identified women who had participated in CenteringPregnancy and screened them for eligibility. Criteria were identical to Study 1, with the additional stipulation that women had attended at least 5/10 Centering sessions. (The average number of sessions attended was 7.2, with a standard deviation of 1.1.) After enrolling a Centering participant, residents approached consecutively admitted women until they identified an eligible Control, defined as a patient who met Study 1 criteria and had not attended Centering. All women gave written consent and the Greenville Health System Institution Review Board approved the protocol.

### 2.2. Disadvantage

In Study 1, socioeconomic conditions were assessed during second trimester with a structured interview developed by the MacArthur Network on SES and Health. We calculated a composite disadvantage score (Miller et al., 2014a) that assigned one point for each of these indicators: household income below federal poverty threshold; savings less than one month of living expenses; receipt of TANF, WIC, SNAP, CHIP, SSI, or Medicaid; education less than two-year college degree; and inability to afford suitable housing.