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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

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CONFLICTS OF INTEREST

None of the authors reports a (1) biomedical financial interest or (2) potential conflict of interest related to this study.

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.

Keywords

Early life stress; poverty; inflammation; placenta; neurodevelopment

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 & 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 & Boyce 2010; Shonkoff & Garner 2012). With regard to cognition, childhood disadvantage forecasts slower language acquisition, worse executive function, and lower educational attainment (Duncan & 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 & 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 & Champagne 2015; Hackman et al. 2010; Wright & Subramanian 2007; Schreier & 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 & 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 & 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 & Bale 2016; Braun et al. 2013; Coe & 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 2013; Estes & McAllister 2016; Meyer 2013; Bale 2015; Nusslock & 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 & 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 & Bale 2016; Hanson & Gluckman 2014; Arck & Hecher 2013; Braun et al. 2013; Coe & 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; Ickovics et al. 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.

PATIENTS & METHODS

Patients

Study 1 involved 100 women recruited from the obstetric clinics of NorthShore University Hospital in Evanston, Illinois. To participate, women had to be ≥ 18 years old, fluent in English, ≤ 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.

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. Reflecting the independence of these indicators, their average inter-correlation was .29 (range .08–.62). The sample had the full range of scores on the composite (0–5), but only 3 women scored 4 or 5. Accordingly, we compressed the composite into a four-level variable. In the analytic sample, the distribution of scores was 0 (57%), 1 (13.9%), 2 (11.4%), and ≥ 3 (17.7%).

Placenta Biopsy and Cord Blood Collection

Both studies used the same protocol to collect placenta biopsies and umbilical blood. Within two hours of childbirth, trained staff on Labor and Delivery units collected 0.5-cm^3 biopsies of fetal chorionic villi, the inner placenta layer where nutrient exchange occurs. To minimize the effects of clonal variation, biopsies were collected from four separate cotyledons.

Immediately following collection, the specimens were rinsed in PBS, stabilized in RNAlater (Qiagen), and frozen at −80 C. After completing the placenta biopsy, staff drew 2.5 ml of umbilical vein blood into a PAXgene Blood RNA Tube (Qiagen), and immediately froze the specimen at –80° C. At the end of the study, biopsies were thawed, then dissociated and homogenized on a gentleMACS Instrument (Miltenyi Biotec). Each woman's biopsies were pooled into a single lysate and frozen at −80° C.

RNA Extraction and Transcriptional Profiling

From placental lysates and PAXgene specimens, total RNA was extracted using PCR-clean and RNAse-free techniques with a commercially available kit (Qiagen RNeasy). After extract purity and integrity had been verified on NanoDrop 1000 and Agilent TapeStation instruments, fluorescently-labeled cRNA targets were synthesized with a commercially available kit (Ambion TotalPrep), and hybridized to Illumina HT-12 v4 bead arrays, which were read on an Illumina iScan Station at the UCLA Neuroscience Genomics Core. This array covers 34,000+ transcripts including the vast majority of named human genes. Detailed descriptions of our methods are provided elsewhere (Miller et al. 2009; Cole et al. 2011).

Covariates

On an a priori basis, we selected a panel of covariates that pattern by socioeconomic status and forecast perinatal outcomes, and abstracted values from electronic medical records. The covariates were maternal age, race (coded as European descent vs. Other), body mass index (BMI) before pregnancy, gestational diabetes, pre-eclampsia, delivery method (coded as vaginal vs. Caesarean), fetal sex, and gestational age at delivery.

Statistical Analyses

Data analytic methods have been previously detailed (Cole et al. 2005; Miller et al. 2009; Miller et al. 2008). Briefly, transcript abundance was estimated using default algorithms in Illumina GenomeStudio, and raw data were quantile-normalized and $\log_2$-transformed. Linear models were used to estimate the magnitude of differential gene expression across the disadvantage composite (Study 1) or between intervention and comparison groups (Study 2). All models included the panel of a priori selected covariates. In Study 1, genes showing ≥ 1.25-fold differential expression over the range from lowest to highest disadvantage served as input into higher-order bioinformatics analyses, which examined transcription control pathways (Cole et al. 2005) cellular origins (Cole et al. 2011), and mesenchymal vs. epithelial polarization (Choi et al. 2010). Statistical testing was based on standard errors derived from bootstrap resampling of linear model residual vectors (controlling for correlations across genes). In Study 2, we limited analyses to a subset of genes that showed the largest differential expression in Study 1. This approach directly addressed the mitigation question, asking whether Centering was associated with a reversal of differences related to disadvantage. The number of analyzed transcripts was selected by optimizing the ratio of observations to parameters (with four genes, 160:21). Mixed-effect linear models with unstructured covariance matrices were used, treating the four genes as repeated measures.

STUDY 1 RESULTS

Preliminary Analyses

Placenta tissue and umbilical blood were collected in 88/100 deliveries. (The remainder involved precluding emergencies or unplanned deliveries elsewhere.) To avoid confounding effects of prematurity, we excluded 9 deliveries that occurred before 37 weeks, leaving an analytic sample of 79 full-term pregnancies. The sample's characteristics are described in Table 1.

In preliminary analyses, we estimated associations between disadvantage and the panel of covariates, using Pearson's correlations for continuous outcomes and Spearman's correlations for categorical outcomes. To the extent they were disadvantaged, women tended to be younger ($r = -.31$, $p = .005$) and identify as African-American ($r = -.62$, $p < .0001$). They also tended to have higher pre-pregnancy BMI ($r = .45$, $p = .001$), and were more likely to have gestational diabetes ($r = .22$, $p = .05$) and pre-eclampsia ($r = .27$, $p = .02$). Disadvantage was not associated with delivery method ($r = .12$, $p = .30$), gestational age at delivery ($r = -.18$, $p = .09$), or fetal sex ($r = -.07$, $p = .57$). Regardless, these characteristics are still likely to influence transcriptome profiles, so we included all of them as covariates in subsequent analyses of Study 1 data. This strategy helps to minimize risks of residual confounding.

Placenta Transcriptome

Net of the covariates, linear mixed models identified 344 transcripts showing ≥ 1.25-fold differential expression across the range of disadvantage (online Table S1). The 111 up-regulated genes included multiple transcripts involved in immune activation (*CXCL14, CCL13, IL2B*, *SPP1*, *STAT4, TNFRSF21*, *TNFSF10*), prostaglandin synthesis (*PTGES, PTGDS*), and tissue remodeling (*COL1A1*, *COL1A2*, *COL5A1 COL5A2*, KRT6A, KRT6C, KRT24, KRT7). Prominent among the 233 transcripts down-regulated with disadvantage were pregnancy-specific glycoproteins (*PSG5*, *PSG7*, *PSG11*) and the chorionic gonadotropin beta/luteinizing hormone beta gene cluster (*CGB*, *CGB1*, *CGB5*, *CGB7*, *CGB8, LGB*), which all have roles in fetal immune tolerance (Martinez et al. 2013; Bansal et al. 2012). Other down-regulated transcripts included suppressors of cytokine signaling (*SOCS2, A2M, PIK3AP1*), and inhibitors of histamine and prostaglandin activity (*PGT*, *ABP1*), as well as mediators of fetal nutrient access, blood supply, and organ maturation (*CGB*, *CGB1*, *CGB5*, *CGB8*, *MMP12*), and transcripts found to be hypermethylated in association with nutrient deficiency (*MEG3*, *PEG10, SLC38A2*, and *LEP*) (Tobi et al. 2015). Also down-regulated were the *CRH* gene, which regulates the timing of parturition, and genes involved in maturation of the bones, heart, brain, and kidneys (*FRZB*, *GPNMB, INSL4*, *LEP, NUCB2, INSIG1, GADD45G, SEMA3B, HOXB2, NDRG1, TEAD3, TFAP2A*).

Role of Covariates

The project was not designed to examine the influence of the demographic and obstetrical covariates themselves. Nevertheless, for interested readers we present the full results of the linear mixed models in online Table S2. For each of the 34,000+ measured transcripts,

coefficients reflecting the influence of demographic and obstetrical covariates are displayed. When examining these results, it is important to keep in mind that most of the covariates have limited variability. As a result, the coefficients are likely to be imprecise estimates of their true (population) effects.

To roughly quantify the influence of covariates, we compared results from crude models, where the only predictor was disadvantage, to those from covariate-adjusted models. For placental transcripts identified as up-regulated, the average crude association for disadvantage was .44 $\log_2$ expression units and the average covariate-adjusted association for disadvantage for these transcripts was .26 $\log_2$ units. These results imply that 40.4% of the total association between disadvantage and expression of these transcripts was attributable to the demographic and obstetrical covariates. Accordingly, the residual 59.6% was attributable to either direct effects of disadvantage and/or other (unmeasured) mediating pathways. Similarly, among the placental transcripts identified above as down-regulated, the average disadvantage coefficient in crude models was −.45 $\log_2$ units and the average covariate-adjusted coefficient for these transcripts was −.33. Thus, for the down-regulated transcripts, covariates explained 27.3% of the association with disadvantage, whereas the remaining 72.7% was attributable to direct influences of disadvantaged and/or other (unmeasured) mediating pathways.

Upstream Regulatory Pathways

As in past research (Cole et al., 2011; Miller et al., 2008), our goal was not to discover individual mRNAs that mediate health disparities, but instead to use the pool of differentially expressed genes to glean insights about the activity of upstream transcriptional networks. Accordingly, this pool of genes served as input for TELiS, a bioinformatics tool that quantifies the prevalence of transcription factor binding motifs (TFBMs) in promoters of differentially expressed genes (Cole et al. 2005). Results appear in Figure 1 and online Table S3. Consistent with hypotheses regarding immune activation, TELiS results linked disadvantage to up-regulation of multiple transcription pathways involved in macrophage and lymphocyte activity (AP-1, GATA-1, EGR2, EGR4, MAF, EBF1). Disadvantage also was associated with down-regulated activity of NF-κB, which as we discuss later may be a reflection of its role in embryonic development (Espín-Palazón & Traver 2016).

Also consistent with hypotheses, results linked disadvantage to down-regulation of multiple transcription pathways involved in tissue development (Figure 1 and Table S3). These pathways included homeobox factors (CDX, PBX1), which control body plan and cell fate (Rezsohazy et al. 2015); members of the ETS family (ETS1, ELK1), which play roles in hematopoiesis (Ciau-Uitz et al. 2013), and NKX2-5, a key driver of cardiomyocyte development (McCulley & Black 2012). Of particular interest here were results indicating that disadvantage was associated with down-regulated activity of C/EBP-β, GFI1, PAX5, and CREB/ATF factors. These transcriptional pathways orchestrate brain maturation by promoting neurogenesis, dendrite formation, and synaptic plasticity (de la Torre-Ubieta & Bonni 2011; Blake & Ziman 2014).

Cellular Origins

Placental villi contain multiple leukocyte subsets as well as trophoblasts and fibroblasts. We used bioinformatic Transcript Origin Analyses in conjunction with reference datasets (Cole et al. 2011) to estimate how much each leukocyte population contributed to the transcriptional patterns described above. As shown in previous validation studies, this approach can accurately identify which specific cell type(s) mediate changes in gene expression within a heterogeneous pool of cell types (Cole et al. 2011). Results of these analyses identified monocytes and B-lymphocytes as major sources of the transcripts up-regulated in association with disadvantage (online Figure S1). No specific immune cell type was distinguished as an origin of down-regulated genes.

Fetal development entails a series of epithelial-mesenchymal transitions (EMTs) (Thiery et al. 2009). At the outset of pregnancy, EMTs mediate placental anchorage in the endometrium and remodel uterine circulation to perfuse the fetus. Later they facilitate tissue development by helping progenitor cells dislodge from epithelia, and acquire the specialized functions required to form organs. As these tissues mature, this process reverses to consolidate the cells into the well-structured epithelia characteristic of a mature organ. EMTs also play a role in mature tissue responses to injury. Consistent with a less fully mature or more injured tissue, TOA found disadvantage-related transcripts to be more predominately mesenchymal versus epithelial in status (online Figure S1).

Cord Blood Transcriptome

Net of covariates, linear mixed models identified 610 transcripts from cord blood cells that were differentially expressed by ≥ 1.25-fold across the range of disadvantage (online Table S4). Among the 379 up-regulated transcripts were genes involved with response to hypoxia (*HBG2*, *HBE1*, *HBB*, *HBM*, *HBBP1*) and anti-viral/cell-mediated immunity (*IL18*, *IFI27*, *ISG20*, *FOX04*, *CD8A, CD5*). The 231 down-regulated genes included transcripts involved in monocyte chemotaxis and activation (*CCL3*, *TLR4*, *IL1B*, *IL1R2, IL8*) and transcription factors involved in myeloid effector functions (*MAFB*, *EGR1*, *EGR2*, *CEBPA*). Also down-regulated were transcripts involved in B-cell activation and differentiation (*CD19*, *FCRLA*, *CD72*, *CD24, CD52*), and antigen presentation (*HLADQB1*, *HLADRB3, HLADRB4*, *HLADRB6, HLADOB*).

Role of Covariates

For readers interested in associations between demographic and obstetrical covariates and the umbilical transcriptome, online Table S2 displays the complete results of linear mixed models. As with the placenta results, readers should keep in mind that most of the covariates have limited variability and, as a consequence, the coefficients are likely to be imprecise estimates of their true (population) effects. To roughly quantify the nature of these effects, we again compared results from crude and adjusted models. Among the umbilical transcripts identified as up-regulated, the average crude association for disadvantage was .44 $\log_2$ units and the average covariate-adjusted coefficient for these transcripts was .42 $\log_2$ units. These patterns imply that less than three percent of disadvantage's total association with these transcripts was attributable to demographic and obstetrical covariates. For the transcripts identified as down-regulated, the average crude coefficient was −.43 and the average

covariate-adjusted coefficient for these transcripts was −.38, implying that covariates explained 11.8% of these relationships.

Upstream Regulatory Pathways

TELiS analysis of umbilical blood data (Figure 2, online Table S5) linked disadvantage with up-regulation of c-Myb, which mobilizes hematopoietic stem and progenitor cells, and a panel of transcription factors indicative of up-regulation of lymphoid lineage precursor cells (E2F, ETS1, ELK1, EGR1, EGR3) (Gómez-Martín et al. 2010). Results also linked disadvantage to a down-regulation of transcription factors involved in myeloid cell differentiation and mature effector activities (i.e., C/EBP-β, EVI1, TAL1, AP-1, STAT1, STAT3, NF-κB).

Cellular Origins

Umbilical blood contains multiple types of leukocytes. As with the placenta analyses, we used Transcript Origin Analyses in conjunction with leukocyte reference datasets (Cole et al. 2011) to estimate how much each of these cell types contributed to the transcriptional patterns described above. The results identified monocytes, dendritic cells, and macrophages as primary sources of downregulated cord blood transcripts (online Figure S2). B-lymphocytes were identified as a source of both upregulated and downregulated transcripts. One potential explanation for this biphasic pattern is that disadvantage is associated with a shift in B-lymphocyte differentiation patterns, e.g., in the balance of precursor vs. mature B-lymphocytes or naive vs. activated phenotypes).

STUDY 2 RESULTS

Study 2 collected placenta biopsies and cord blood from 20 women in CenteringPregnancy, and 20 comparison women in traditional prenatal care who delivered babies in the same clinical setting over the same time period. As Table 2 illustrates, women in this study were generally low in socioeconomic status, with 35% lacking a high-school diploma, and only 5% having completed a Bachelor's degree. The groups had similar demographic and obstetrical profiles except that women in Centering were slightly older. There also were hints of group differences in fetal sex, gestational age, diabetes, and preeclampsia (p's < .20). To minimize the risks of confounding, we included all five of these covariates (maternal age, fetal sex, gestational age, diabetes, and preeclampsia) along with Centering status in statistical models.

As noted in the Statistical Analyses section, analyses of transcriptional activity focused on a set of four placenta transcripts that were most strongly associated with disadvantage in Study 1. These transcripts were *CGB1*, *CCK*, *LHB*, and *KRTAP26-1*, and all of them were down-regulated in association with disadvantage in Study 1. Consistent with hypotheses, women in Centering showed higher average expression of these mRNAs relative to Controls, both in crude ($F = 12.56$, $p = .001$, $d = .63$; Figure 3a) and adjusted mixed-model analyses ($F = 11.10$, $p = .002$, $d = .59$).

We next conducted parallel analyses of the 4 cord blood transcripts most strongly associated with disadvantage in Study 1. They were *GH1*, *CSH1*, *CSHL1*, and *CSH2*; and again all

were down-regulated in connection with disadvantage in Study 1. Again, consistent with hypotheses, women in Centering showed higher average expression of these transcripts relative to Controls in mixed models (crude: $F = 11.75$, $p = .002$, $d = .96$; covariate-adjusted: $F = 19.75$, $p < .001$, $d = 1.27$; Figure 3b).

DISCUSSION

Economic hardship in childhood is associated with a variety of adverse outcomes across the lifecourse, spanning the cognitive, psychiatric, and biomedical domains. The prevailing mechanistic accounts of these disparities focus on variations in the postnatal environment. However, results of the studies presented here indicate that molecular correlates of maternal disadvantage are present in mRNA from the placenta's chorionic villous layer and newborn umbilical blood cells. These patterns are consistent with the possibility that some of the biological substrates of lifecourse disparities originate *in utero*. Because of the study's observational design, it is unclear whether these associations reflect a causal influence of disadvantage. However, experimental studies in animals demonstrate the biological plausibility of a causal effect, showing that gestational exposure to stressors associated with disadvantage can leave molecular footprints detectable in the nervous, immune, and metabolic systems of offspring (Bale 2015; Hanson & Gluckman 2014; Prescott 2006; Pryce et al. 2005; Coe & Lubach 2014).

The findings also provide clues about the mechanistic origins of socioeconomic disparities. Several themes emerged, all paralleling experimental models of pregnancy stress (Blois et al. 2005; Friebe et al. 2011; Howerton et al. 2013; Hanson & Gluckman 2014). First, disadvantage was associated with multiple indications of perturbed immune homeostasis in the placenta. The patterns suggest a scenario where disadvantage impairs maternal immune tolerance of the fetal allograft, as reflected in decreased expression of pregnancy-specific glycoproteins, chorionic gonadotropins, and other anti-inflammatory mediators (Martinez et al. 2013; Bansal et al. 2012). This diminution of tolerance is permissive of immune activity in the chorionic villi, as reflected in up-regulation of the AP-1, GATA-1, EGR2, EGR4, and MAF transcriptional pathways, which collectively are hallmarks of macrophage and lymphocyte activation (Gómez-Martín et al. 2010; Natoli et al. 2011; Naito et al. 2011; Geissmann et al. 2010). Consistent with this interpretation, bioinformatic analyses suggested these differential transcription profiles were orchestrated by monocytes and macrophages, B-lymphocytes, and to a lesser extent, dendritic cells. The villi are an immune privileged site, with a pivotal role in nutrient exchange. To the extent that immune activity disrupts nutrient transfer (Dimasuay et al. 2016), it could underlie a second prominent theme in the results, the down-regulation of transcriptional pathways that orchestrate tissue maturation. Indeed, disadvantage was associated with bioinformatic indications of reduced activity of transcription factors that control body plan, and promote maturation of the heart, brain, and immune system (Rezsohazy et al. 2015; Ciau-Uitz et al. 2013; de la Torre-Ubieta & Bonni 2011; Blake & Ziman 2014; McCulley & Black 2012). Cellular origin analyses substantiated these results, revealing patterns characteristic of mesenchymal cells engaged in organ development.

Whether these transcriptional patterns are sufficient to functionally alter trajectories of organ development is not yet clear. But socioeconomic disparities in phenotypic development are apparent in early childhood, particularly in the brain. By 6 months, socioeconomic differences in the functional connectivity of default-mode and sensori-motor networks are apparent (Gao et al. 2015). By school age, there are well-established socioeconomic disparities in amygdala and hippocampal volume, as well as cortical grey matter (Hanson et al. 2013; Luby et al. 2013). The placenta gene expression findings reported here could be gestational manifestations of these later phenotypic variations in brain maturation. Consistent with the developmental relevance of our observations in the placenta, analyses revealed transcriptional correlates of disadvantage in umbilical blood cells, suggesting that newborns enter the world with distinct immunologic profiles, which pattern by socioeconomic conditions. The transcription profile of disadvantaged newborns was consistent with a relative immaturity of myeloid cells, as reflected in down-regulation of pathways that orchestrate functions like phagocytosis, antigen processing and presentation, and tissue remodeling (Gómez-Martín et al. 2010; Ciau-Uitz et al. 2013). These newborns also showed up-regulation of pathways that control mobilization of lymphoid progenitors, and commitment and differentiation of B-lymphocytes (Medvedovic et al. 2011; Phelan et al. 2010). Research is needed to clarify the functional significance of these variations for subsequent immune functioning and health outcomes.

Broadly speaking, the perturbed immune homeostasis seen here is consistent with results of earlier research on transcriptional correlates of socioeconomic disadvantage (Chen et al. 2009; Powell et al. 2013; Miller et al. 2009; Levine et al. 2015). But in several regards there were substantive differences in the pattern of results. First, in placenta biopsies disadvantage was generally associated with transcriptional indications of immune activation, as reflected in up-regulation of the AP-1, GATA-1, EGR2, EGR4, and MAF pathways (Gómez-Martín et al. 2010; Natoli et al. 2011; Naito et al. 2011; Geissmann et al. 2010). However, these analyses simultaneously indicated down-regulated activity of NF-κB, a pivotal pro-inflammatory transcription factor, which has shown up-regulation in previous studies of disadvantage and adversity more generally (Cole 2014; Chen et al. 2009; Powell et al. 2013; Miller et al. 2009; Cole et al. 2011; Miller et al. 2014b; Cole et al. 2007). Future research will be required to determine why the NF-κB up-regulation previously associated with social adversity in the blood cells of more developmentally mature humans is not observed here in the context of placental villi. However, it seems plausible that in trophoblasts, fibroblasts, and other cells of the placenta, NF-κB plays different functional roles from those of mature leukocyte populations observed in previous studies. Indeed, emerging research shows that during embryonic development, NF-κB signaling is crucial in maturation of the liver and brain, as well as limbs, muscle, and skin (Espín-Palazón & Traver 2016). If that is (primarily) what our measure of placental NF-κB activity reflects, the pattern of results could be understood as convergent with this study's other findings connecting disadvantage with transcriptional indications of slower tissue maturation. A second inconsistency with previous research is the pattern observed in umbilical blood cells. Here, disadvantage was associated with a bioinformatic profile suggesting relative down-regulation of myeloid cells functions and up-regulation of lymphoid cell functions. These patterns contrast markedly with the "Conserved Transcriptional Response to Adversity (CTRA)," seen in peripheral

leukocytes of more developmentally mature humans exposed to various forms of social adversity (Cole 2014; Cole 2010; Irwin & Cole 2011). Again, future research will be required to identify the basis for the observed differences, but we speculate that they might reflect (a) disparities between the cellular makeup of umbilical versus antecubital blood, and/or (b) disparities in these cells' developmental stage and historical exposure to microbial and hormonal stimulation. Either way, our results suggest that in umbilical vein cells from newborns, adversity does not manifest in the CTRA phenotype of increased pro-inflammatory and decreased anti-viral activity observed later in development. Instead, it appears to be associated with a profile indicative of relative hematopoietic immaturity, which is consistent with results of studies in non-human primates. When exposed to stress during the prenatal period, newborn monkeys display reductions in lymphocyte proliferation, natural killer activity, and cytokine production (Coe & Lubach 2005). If substantiated in future research, these findings would suggest significant developmental heterogeneity in the transcriptional response to adversity.

Consistent with other studies suggesting that early disadvantage can be mitigated (Campbell et al. 2014; Miller et al. 2014a), we found that participation in CenteringPregnancy was associated with favorable gene expression profiles in placenta biopsies and umbilical cells. These patterns suggest the possibility that Centering ameliorated some of the transcriptional disparities most strongly connected to disadvantage in Study 1. However, given the observational design of the study, the small number of participants, the potential for Type 1 error, and the fallibility of covariance procedures in rendering groups truly equivalent, these results should be interpreted cautiously. To ascertain the causal status of our observations, a randomized, controlled trial of Centering with the same outcomes is needed. If efficacious, this trial would also provide the opportunity to address questions about mechanisms of action. Centering reduces distress, improves lifestyle, and bolsters social support in high-risk women (Heberlein et al. 2016; Ickovics et al. 2011). Any of these changes might ameliorate immune activation in the placenta (Straub et al. 2014) and their role should be explored in follow-up studies.

In the meantime, further research is needed to substantiate our findings regarding disadvantage and elucidate their underpinnings and significance. After confirming the patterns seen here, research should identify the cellular actors involved, and clarify whether disadvantage is associated with their distribution, transcriptional patterns, or both. Research also should identify factors that connect disadvantage with transcriptional activity. Our study considered a host of demographic (age, racial/ethnic background) and obstetrical (BMI, diabetes, pre-eclampsia, delivery method, fetal sex, gestational age at delivery) factors. Collectively, they explained 3–40 percent of the associations between disadvantage and differential gene expression in both placenta biopsies and umbilical blood, which implies that other mechanistic pathways are substantial contributors to these relationships. Thus, future research should consider the role of other presumptive mediators, including variations in nutrition, glucocorticoid activity, toxin exposure, and intrauterine infection. Interestingly, many functions of the placenta are regulated by a circadian clock (Waddell et al. 2012). Given the marked socioeconomic variations in sleep and activity cycles (Laposky et al. 2016), clock-related disruptions are a potential mechanism to consider in follow-up research. Substance use might also play a role, although is unlikely to be a factor here. Only two

women drank alcohol during pregnancy (both < 1 drink weekly) and two others smoked (both < 5 cigarettes daily.) A more thorough assessment of characteristics and complications of delivery is also warranted; we did not have the statistical power or range of variation in risk factors to do that here. Finally, longitudinal research that tracks newborns' health into childhood is needed, so the phenotypic relevance of the differences we observed can be evaluated.

Despite these uncertainties, these results suggest that multiple dimensions of newborn gene expression are dysregulated following gestation in adverse socioeconomic conditions. The results also provide encouraging, albeit preliminary, suggestions that some of those alternations might be ameliorated by a prenatal intervention that emphasizes the importance of women's psychosocial environment alongside more conventional obstetric characteristics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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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Highlights

1. In pregnant women, socioeconomic disadvantage was associated with a placenta transcriptional profile indicative of higher immune activation and slower fetal maturation
2. These patterns were particularly evident in pathways related to brain, heart, and immune development
3. Cord blood cells of disadvantaged newborns also showed indications of immaturity, as reflected in down-regulation of pathways that coordinate myeloid cell development
4. A small follow-up study found preliminary support for the hypothesis that group-based prenatal care, focusing on women's psychosocial status, could ameliorate some of these socioeconomic differences

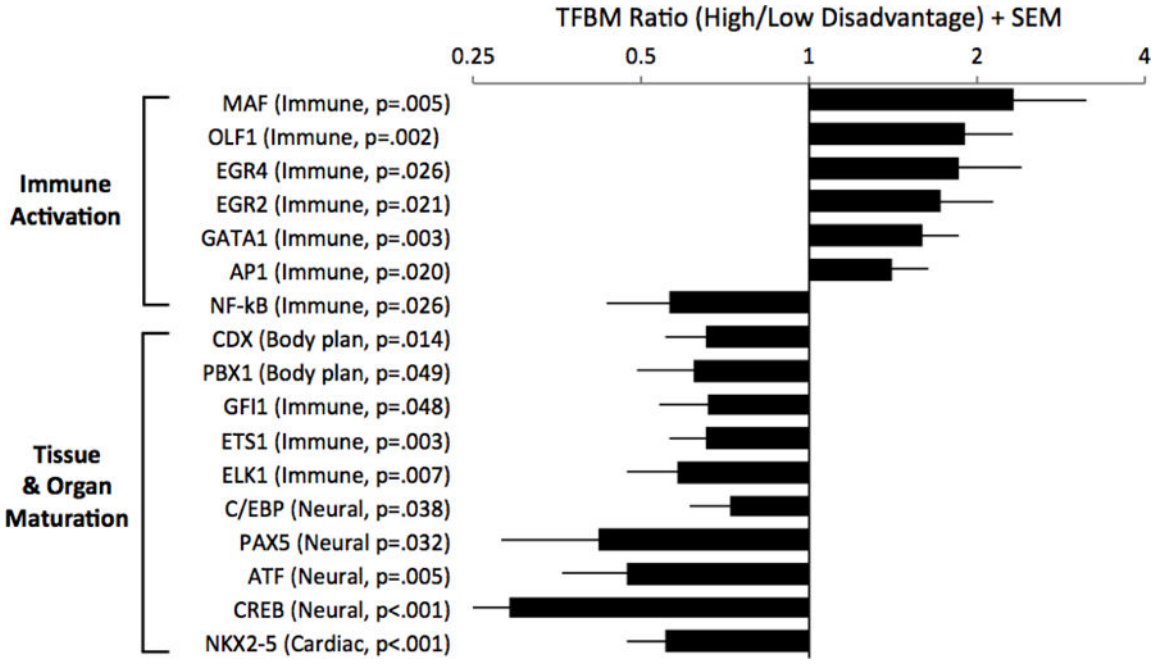

Figure 1. Placenta transcriptome

Genome-wide expression profiling was performed on biopsies of placental chorionic villi. Linear mixed models were used to estimate the magnitude of differential gene expression as a function of maternal socioeconomic disadvantage, adjusting for a panel of a priori selected covariates, with false discovery rate held at 5 percent. Genes showing ≥ 1.25-fold differential expression over the range from lowest to highest disadvantage served as input into higher-order bioinformatics analyses using the Transcription Factor Element Listening System. This platform quantified the prevalence of transcription factor binding motifs (TFBMs) in promoters of differentially expressed genes. TFBM ratios > 1 indicate specified transcriptional pathway is up-regulated with maternal disadvantage; ratios < 1 indicate converse.

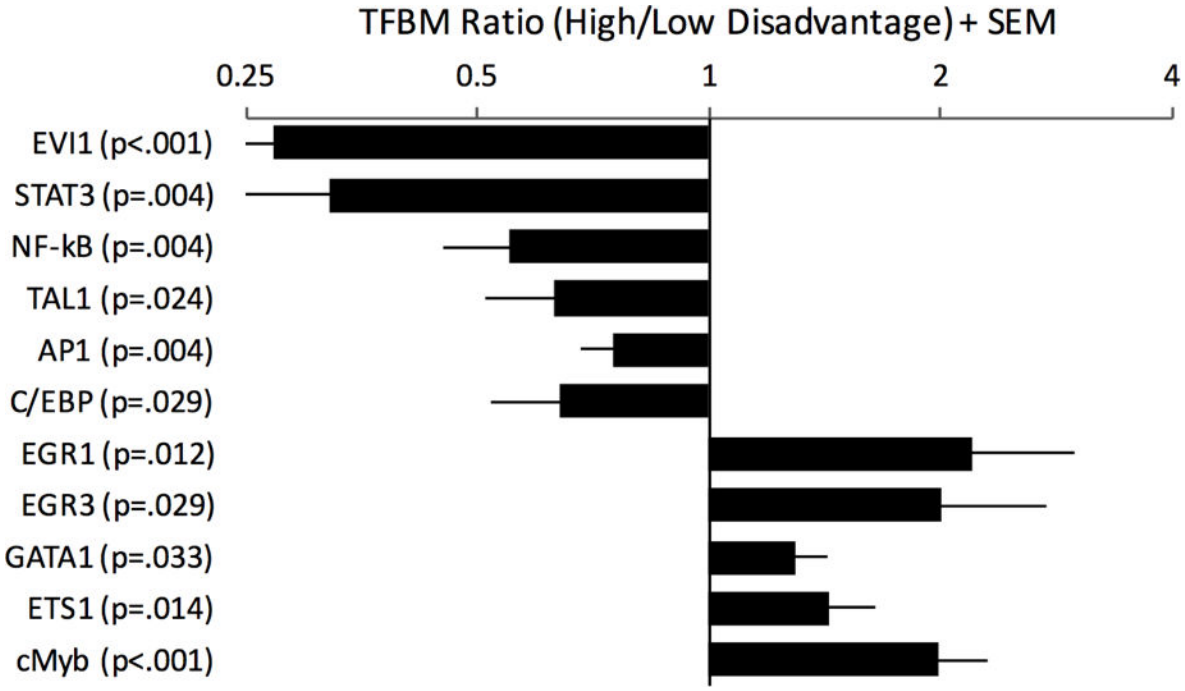

Figure 2. Cord blood transcriptome

Genome-wide expression profiling was performed on bulk cord blood cells (i.e., un-separated) from newborns. Linear mixed models were used to estimate the magnitude of differential gene expression as a function of maternal socioeconomic disadvantage, adjusting for a panel of a priori selected covariates, with false discovery rate held at 5 percent. Genes showing ≥ 1.25-fold differential expression over the range from lowest to highest disadvantage served as input into higher-order bioinformatics analyses using the Transcription Factor Element Listening System. This platform quantified the prevalence of transcription factor binding motifs (TFBMs) in promoters of differentially expressed genes. TFBM ratios > 1 indicate specified transcriptional pathway is up-regulated with maternal disadvantage; ratios < 1 indicate converse.

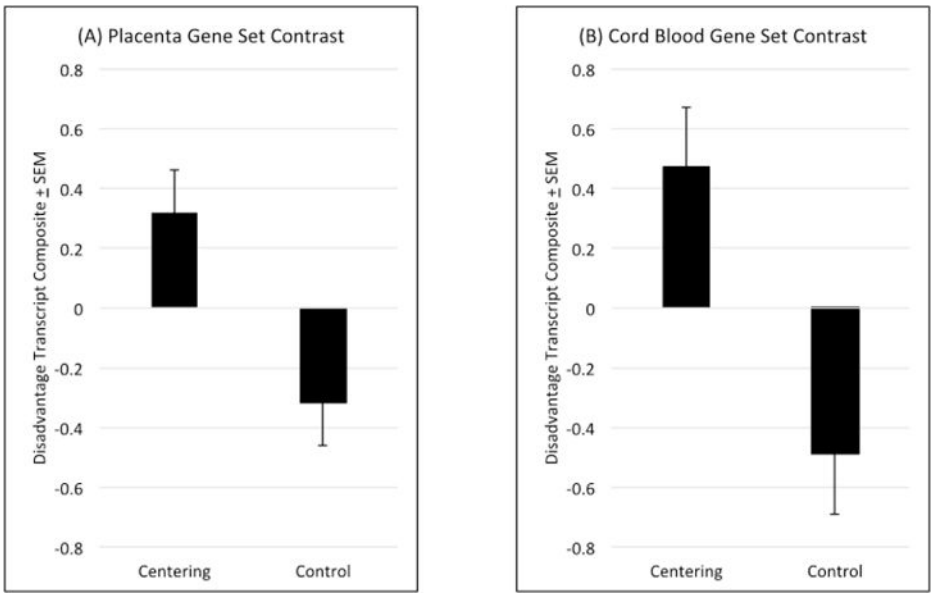

Figure 3. CenteringPregnancy Intervention

Relative to comparison subjects, women who participated in the intervention displayed higher expression of transcripts that were down-regulated in concert with disadvantage in Study 1. These patterns were apparent in both (A) biopsies of the placenta's chorionic villous layer and (B) bulk cord blood cells (i.e., un-separated) from newborns.

Table 1

Characteristics of Study 1 analytic sample (N = 79).

Characteristic	Mean (SD) or N (%)
Age, years	30.72 (5.30)
Racial/ethnic group, White (non-Latina)	43 (54.43%)
Racial/ethnic group, Black (non-Latina)	20 (25.31%)
Racial/ethnic group, Latina (any race)	12 (15.19%)
Pre-pregnancy body mass index (BMI)	27.35 (6.94)
Normal weight (BMI ≤ 24.99)	39 (49.40)
Overweight (BMI 25.00 – 29.99)	18 (22.80)
Obese (BMI ≥ 30.00)	22 (27.80)
Nulliparous	35 (44.30%)
Pre-eclampsia	7 (8.86%)
Diabetes	9 (11.39%)
Caesarean delivery	22 (27.85%)
Gestational age at delivery, weeks	39.20 (1.13)
Fetal sex, female	36 (45.60)
Disadvantage composite (0–3)	0.90 (1.18)
Disadvantage score = 0	45 (57.00)
Disadvantage score = 1	11 (13.90)
Disadvantage score = 2	9 (11.40)
Disadvantage score = 3 or more	14 (17.70)

Table 2

Characteristics of Study 2 sample according to intervention status (N=40).

	Centering Group Mean (SD) or N (%)	Comparison Group Mean (SD) or N (%)	Difference (p value)
Age, years	24.80 (4.36)	28.45 (6.19)	.04
Racial/ethnic group, White	9 (45.0 %)	10 (50.0 %)	.75
Racial/ethnic group, Black	4 (20.0 %)	4 (20.0 %)	.99
Racial/ethnic group, Latina	7 (35.0 %)	5 (25.0%)	.49
Pre-pregnancy BMI	30.51 (6.25)	28.66 (6.01)	.35
Nulliparous	6 (30.0 %)	5 (25.0 %)	.72
Pre-eclampsia	0 (0.0 %)	2 (10.0%)	.15
Diabetes	0 (0.0 %)	2 (10.0%)	.15
Caesarean delivery	6 (30.0 %)	5 (25.0 %)	.72
Gestational age, weeks	39.57 (1.05)	39.01 (1.37)	.16
Fetal sex, female	11 (55.0 %)	8 (40.0 %)	.34
Didn’t complete high school	6 (30.0 %)	8 (40.0 %)	.51
High school diploma, but no Bachelor’s degree	14 (70.0 %)	10 (50.0%)	.74