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## Acculturation and interleukin (IL)-6 concentrations across pregnancy among Mexican-American women

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### Abstract

**Background.**—The process of acculturation (post-migration acquisition of host culture and/or loss of heritage culture) likely represents a key mediator of the observed post-migration decline in health that is evident among immigrant populations such as Mexican Americans. The observations that migrant health declines progressively as not only a function of length of stay in the U.S. but also across generations, and that this inter-generational decline in health is evident as early as at the time of birth itself, supports the concept of fetal programming of acculturation's effects. However, the underlying mechanisms remain to be elucidated. Inflammation during pregnancy represents a candidate pathway of particular interest for 2 reasons: it represents a key biological mediator of the psychosocial and/or behavioral sequelae of acculturation on health, and it represents a key pathway by which maternal states and conditions during pregnancy may influence fetal development and subsequent birth and child developmental and health outcomes. Therefore, the aim of this study was to examine the relationship between acculturation and inflammation across pregnancy in a population of Mexican-American women. Specifically, we tested the hypothesis that a higher level of acculturation is associated with higher circulating concentrations across pregnancy of the pro-inflammatory cytokine interleukin-6 (IL-6).

**Methods.**—75 pregnant first- or second-generation Mexican-American women constituted the study population. Acculturation was quantified using a commonly-used and previously validated measure – the Acculturation Rating Scale for Mexican Americans (ARSMA). Maternal blood samples were collected during early, mid and late pregnancy for analysis of circulating IL-6 concentrations.

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**Results.**—Hierarchical linear models indicated a significantly and positive main effect of acculturation on IL-6 concentrations across pregnancy after adjusting for key covariates including gestational age(s) at blood sampling, socioeconomic status, pre-pregnancy BMI, and presence of obstetric risk conditions.

**Conclusions.**—Maternal inflammation during pregnancy may represent a biological pathway of interest in the context of the inter-generational effects of acculturation from a mother to her as-yet-unborn child.

### Keywords

Acculturation; inflammation; Interleukin-6; pregnancy

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## 1. Introduction

International migrants — persons living in a country other than where they were born — represent a large ( $\approx 244$  million people) and rapidly growing ( $\approx 41\%$  increase from 2000 till 2015) global population (UN Department of Economics and Social Affairs, 2015). Epidemiological findings suggest that immigrants from lower to higher income countries exhibit a health advantage upon arrival that appears to decline over the length of their stay in the host nation (Argeseanu Cunningham et al., 2008). This health decline is believed to emerge as a biological consequence of some of migration's unfavorable social, psychological and behavioral sequelae. In this context, the concept of acculturation (post-migration acquisition of the host culture and/or loss of the heritage culture) (Berry, 2005), and the pathways by which acculturation may impact health (*via* acculturative stress, declining social ties, and adoption of unhealthy behaviors), is commonly invoked as an explanation. Measures of acculturation or its proxies, such as nativity, length of stay in the U.S., and language preference, have been associated with several physical and mental health outcomes, most frequently demonstrated in studies of Mexican immigrants to the U.S. (Fox et al., 2015; Lara et al., 2005; O'Brien et al., 2014). These outcomes include higher body mass index (BMI) (Ruiz et al., 2007), hypertension (Espino and Maldonado, 1990), diabetes (O'Brien et al., 2014; Ortiz et al., 2015; Stern et al., 1992; West et al., 2002), cardiovascular disease (Sundquist and Winkleby, 1999), poorer overall physical health (Riosmena et al., 2013), and depression (Castillo et al., 2015).

The unfavorable health effects of migration and acculturation-related processes on health may not be restricted to only the life span of the index individual, but also may affect the development and health of the next generation of their offspring via the process of fetal/developmental programming, thereby establishing an intergenerational cascade of perpetuation (Fox et al., 2015). The observation that these health disparities are evident as early as at the time of birth itself suggests that this process may start as early as during the offspring's period of intrauterine life, well before she/he is directly exposed to conditions in the host country. Consistent with this notion are findings that link various dimensions or proxy measures of maternal acculturation with adverse birth outcomes, including low birth weight, preterm birth, and reduced infant survival (D'Anna-Hernandez et al., 2012; Frisbie et al., 1998; Hummer et al., 1999; Powers, 2013; Ruiz et al., 2015, 2006; Singh and Yu,

1996; Wommack et al., 2013), all of which have important implications for long-term health and disease susceptibility.

How, specifically, might the effects of acculturation among pregnant women be transmitted to the fetus to program offspring physiology and disease risk in later life? The predominant, proximate pathway by which maternal states and conditions influence fetal development is ultimately biological in nature and involves maternal–placental–fetal gestational physiology. Several previously-published studies have shown that inflammation during pregnancy is related to stress (for a review see (Entringer et al., 2011)), pregnancy complications such as gestational hypertension (Sharma et al., 2018), adverse birth outcomes such as preterm birth and low birth weight (Denson et al., 2016; Goepfert et al., 2001; Hansen-Pupp et al., 2008; Kassal et al., 2005; Sorokin et al., 2010), and suboptimal child developmental and mental health outcomes (e.g., (Brown and Derkits, 2010; Ellman et al., 2010). Based on the considerations that the majority of acculturation’s disease-related sequelae have a pro-inflammatory component (e.g., obesity, diabetes, stress experience, depression (Entringer et al., 2011; Vega et al., 2009)) we propose that maternal inflammation may represent a pathway of particular interest in this context.

Some preliminary evidence in Hispanic pregnant women does suggest that acculturation is related to pro- and anti-inflammatory markers (interleukin-1 receptor antagonist (Ruiz et al., 2007); interleukin-10 (Wommack et al., 2013)), however these studies were cross-sectional in nature, and did not account for possible effects of key confounders. The aim of the present study was to examine whether maternal acculturation is a determinant of inflammation during pregnancy and thereby address the broader premise that it may represent a biological mechanism underlying the intergenerational transmission of health disparities. We specifically examined the prospective association between maternal acculturation and pro-inflammatory state across gestation in a low-risk sample of Mexican-American women. We selected circulating IL-6 as an indicator of pro-inflammatory state because this cytokine is among the most robust markers of inflammation and inflammatory states in pregnancy (e.g., obesity, infection, depression and psychosocial stress). These in turn have been found to alter offspring disease susceptibility in later life (Burns et al., 2003; Kubicki et al., 2005; Li et al., 2016; Madan et al., 2009). We quantified maternal IL-6 concentrations serially in early, mid and late gestation to capture the entire course of pregnancy. We also assessed and accounted for the possible effects of key covariates including maternal socioeconomic status, current body mass index, and obstetric complications. Socioeconomic status (SES) is a particularly important variable in this context because it has been argued that SES and ACC are interconnected factors as their effects on health and health behavior appear to be linked (Fitzgerald, 2010). However, several studies have suggested that the effects of acculturation on health persist across generations despite improvements in socioeconomic conditions (Coutinho et al., 1997; Foster et al., 2000; Jasienska, 2009). We therefore examined whether the effect of acculturation on inflammation is independent of the effect of SES, and additionally, if low SES potentiates the effect of acculturation on inflammation (effect modification).

## 2. Methods

### 2.1 Participants

The study population comprised 75 pregnant Mexican-American women with singleton intrauterine pregnancies who participated in a prospective cohort study at the University of California, Irvine, Development, Health and Disease Research Program. Exclusion criteria were uterine anomalies, use of antenatal systemic corticosteroids, antenatal administration of glucocorticoids, or illicit drug use. The study protocol incorporated three serial visits during early (T1, 9-17 weeks), mid (T2, 18-24 weeks) and late (T3, 29-35 weeks) gestation. The study was approved by the UC Irvine Institutional Review Board, and all participants provided written, informed consent. The socio-demographic, biophysical and obstetric characteristics of the study population are depicted in Table 1.

### 2.2 Measures

**Acculturation (ACC).**—At T1, participants completed the 20-item Acculturation Rating Scale for Mexican Americans (ARSMA) (Cuellar et al., 1980). ARSMA is among the most reliable, valid and commonly-used measures of acculturation. It comprises the factors language use and preference, ethnic identity, cultural heritage and ethnic behaviors, and ethnic interaction. ARSMA is a linear measure of ACC (i.e., based on the assumption that ACC can be measured on a continuum). The item response format differentiates five levels of acculturation: (1) Very Mexican, (2) Mexican-Oriented Bicultural, (3) True Bicultural, (4) Anglo-Oriented Bicultural, and (5) Very Anglicized. The total score is a mean score computed by dividing the sum of all item values by the number of items. Thus higher values reflect higher levels of acculturation.

**Interleukin (IL)-6.**—Maternal antecubital venous blood was collected at each of the three study visits at morning time between 7:30 and 9:00 am. Serum was used to quantify IL-6 concentrations using a commercial high sensitivity ELISA (eBioscience) with a sensitivity of 0.03 pg/ml. The intra- and inter-assay coefficients of variability for IL-6 measurements were 10% and 14% respectively. There were no significant outliers.

**SES.**—Total family income was used as an indicator of maternal SES. It was assessed at T1 by maternal report on a 5-point scale (Table 1).

**Obstetric complications.**—A dichotomous variable “obstetric complications” was created to indicate whether participants exhibited none (“0”) or any (“1”) obstetric risk condition during pregnancy, such as hypertension, gestational diabetes, severe infections, vaginal bleeding, and anemia.

We also considered other possible confounders such as smoking and alcohol consumption during pregnancy. However, their prevalence was very low prevalence in our sample (see Table 1), and the results of our statistical models do not change when excluding these participants from our analyses.

## 2.3 Data Analysis

Hierarchical linear models (HLM) (e.g. (Jeffrey D. Long, 2012)) with random intercepts and fixed slopes that account for the longitudinal data structure were used to quantify the effects of ACC and income on IL-6. Repeatedly measured IL-6 was the outcome variable, and the intra-class correlation of IL-6 [ICC=0.4275] suggested that 42.75% of the overall variance was between-person variance. The main predictors were the level-2 variables ACC, income, and an interaction term between ACC and income. HLMs were built successively: In the first model (M1), ACC and income were added to the model, and in the second model (M2) the interaction term between ACC and income was added to test effect modification by socioeconomic status. All metric predictors were grand-mean centered so that their mean became 0. Covariates included in M1 and M2 were gestational weeks at assessment of IL-6, mean maternal pregnancy BMI, and obstetric complications. HLM analyses were run in R using the lmer-function of the lme4-package. Pseudo-R<sup>2</sup> – a measure of explained variance – was derived by the r2glmm-package in R, and it refers to the respective model in comparison to an unconditional model that does not include the respective variable or interaction term of interest.

## 3. Results

First inspection of the data indicated that the main predictors were normally distributed, ACC score:  $M = 2.88$ ,  $SD = 0.53$ ,  $Min = 1.60$ ,  $Max = 4.00$ , income:  $M = 2.75$ ,  $SD = 1.09$ ,  $Min = 1$ ,  $Max = 5$ . 2<sup>nd</sup>-generation participants had a significantly higher ACC mean score ( $M_{2nd\ gen} = 3.01$ ,  $SD_{2nd\ gen} = 0.41$ ) compared to 1<sup>st</sup>-generation participants ( $M_{1st\ gen} = 2.55$ ,  $SD_{1st\ gen} = 0.64$ ),  $t(70) = -3.67$ ,  $p < .001$ ,  $d = 0.86$ , indicating validity of the scale. There were significant positive intercorrelations between mean IL-6 concentrations at all three assessment time points (see Table 1) (T1- & T2-IL-6:  $r = 0.68$ ,  $p < .001$ ; T1- & T3-IL-6:  $r = 0.57$ ,  $p < .001$ ; T2- & T3-IL-6:  $r = 0.44$ ,  $p < .001$ ). The mean IL-6 concentrations significantly increased from 0.77 pg/ml at T1 to 1.11 pg/ml at T3 (medium-sized effect based on a repeated-measure ANOVA ( $F(1.658, 94.530) = 11.957$ ,  $p < .001$ ,  $\eta^2 = 0.19$ ). When controlled for obstetric risks, mean pregnancy BMI, and income, the partial correlation between mean IL-6 concentrations and the ACC score was  $r = 0.31$ ,  $p < .05$ .

1<sup>st</sup> and 2<sup>nd</sup> generation did not significantly differ in the covariates of interest, including income,  $t(65) = 0.64$ ,  $p = .523$ ,  $d = 0.16$ , mean pregnancy BMI,  $t(72) = 0.91$ ,  $p = .368$ ,  $d = 0.26$ , and incidence of obstetric risks,  $\chi^2(1, N = 75) = 1.34$ ,  $p = .335$ .

The results of model M1 suggested a significant positive main effect of ACC on maternal IL-6 ( $b_{ACC} = 0.24$ ,  $t(58) = 2.53$ ,  $p = .014$ ), indicating that each unit increase in ACC was associated with a 0.26 pg/ml increase in maternal IL-6 concentration (Figure 1). ACC accounted for approximately 3% of the IL-6 variance across pregnancy (Pseudo-R<sup>2</sup> = 3.11%,  $p < 0.05$ ). There was no significant main effect of income on IL-6 ( $b_{income} = -0.07$ ,  $t(58) = -1.50$ ,  $p = .139$ , Pseudo-R<sup>2</sup><sub>income</sub> = 1.98%,  $p = .131$ ). In model M2, an interaction term between ACC and income was added which was not significant, indicating that the effect of ACC on IL-6 was not moderated by income ( $b_{ACC*income} = -.09$ ,  $t(58) = -0.89$ ,  $p = .377$ , Pseudo-R<sup>2</sup><sub>ACC\*income</sub> = 0.54%,  $p = 0.312$ ). Excluding women with OB risk factors ( $N = 15$ ) from the statistical analyses did not change the size or direction of the reported effects.

## 4. Discussion

In the present study, maternal acculturation was positively associated with IL-6 concentrations across pregnancy in a cohort of Mexican-American women. This association was independent of, and not moderated by, maternal SES and other potential confounders. Thus, acculturation appears to represent a migration-related factor that makes an independent contribution to variation in pro-inflammatory state during pregnancy, thereby providing evidence in support of the premise that this pathway may contribute to the fetal programming of health disparities in Mexican-American immigrants. Our result is consistent with the findings of other studies showing a relationship between acculturation and biological stress markers during pregnancy in Hispanic women (D'Anna-Hernandez et al., 2012; Hummer et al., 1999; Powers, 2013; Ruiz et al., 2015, 2012, 2007, 2006; Wommack et al., 2013). As outlined above, migrant health declines progressively as not only a function of length of stay in the U.S. but also across generations, and this inter-generational decline in health is evident as early as at the time of birth itself. Therefore, our finding that maternal acculturation is linked to inflammation during pregnancy provides support for a key aspect of the larger framework to explain not only the emergence, but also the transmission of health disparities from one generation to the next.

The prevailing paradigms suggest that the impact of acculturation on health is mediated by its behavioral, psychological, and biological sequelae. It is well-documented that among Hispanics higher levels of acculturation are associated with behaviors that promote a pro-inflammatory state, such as a less favorable nutrition that promotes adiposity and diabetes, and substance abuse (including smoking, alcohol and drug use) (Lara et al., 2005). Thus, alterations in IL-6 concentrations could represent a mediating pathway between acculturation and subsequent birth and offspring health outcomes. The mean IL-6 concentrations are all within a normal range of a non-clinical sample, however, we have recently shown that variation of IL-6 concentrations within this range across pregnancy are significantly and prospectively related to newborn brain development and infant child behavior at 2 yrs age (Graham et al., 2018; Rudolph et al., 2018), thus supporting the potential clinical significance of our current findings.

Limitations of our study include the following: Our results are based on a low-risk normative population. Additional analysis of the role of ACC in the link between IL-6 and pregnancy and birth outcomes were restricted due to small sample size. Thus, future studies that include longer child follow-ups are warranted to address the impact of ACC-related inflammation during pregnancy on offspring health status. Future studies should also address the effect of stress experience, anxiety, and depression in the context of the association between acculturation and inflammation during pregnancy.

To conclude, higher levels of maternal acculturation were significantly associated with higher concentrations of IL-6 during pregnancy. This finding provides support for a key part of the overall pathway in the context of the intergenerational transmission of maternal acculturation's effect on offspring health. Questions remain regarding the exact mechanisms underlying this effect and the nature of potential interactions with other biological and environmental processes. Nevertheless, the current finding represents an important advance

because it adds evidence in humans to support a role for acculturation in the trans-generational transmission of health disparities in migrant populations.

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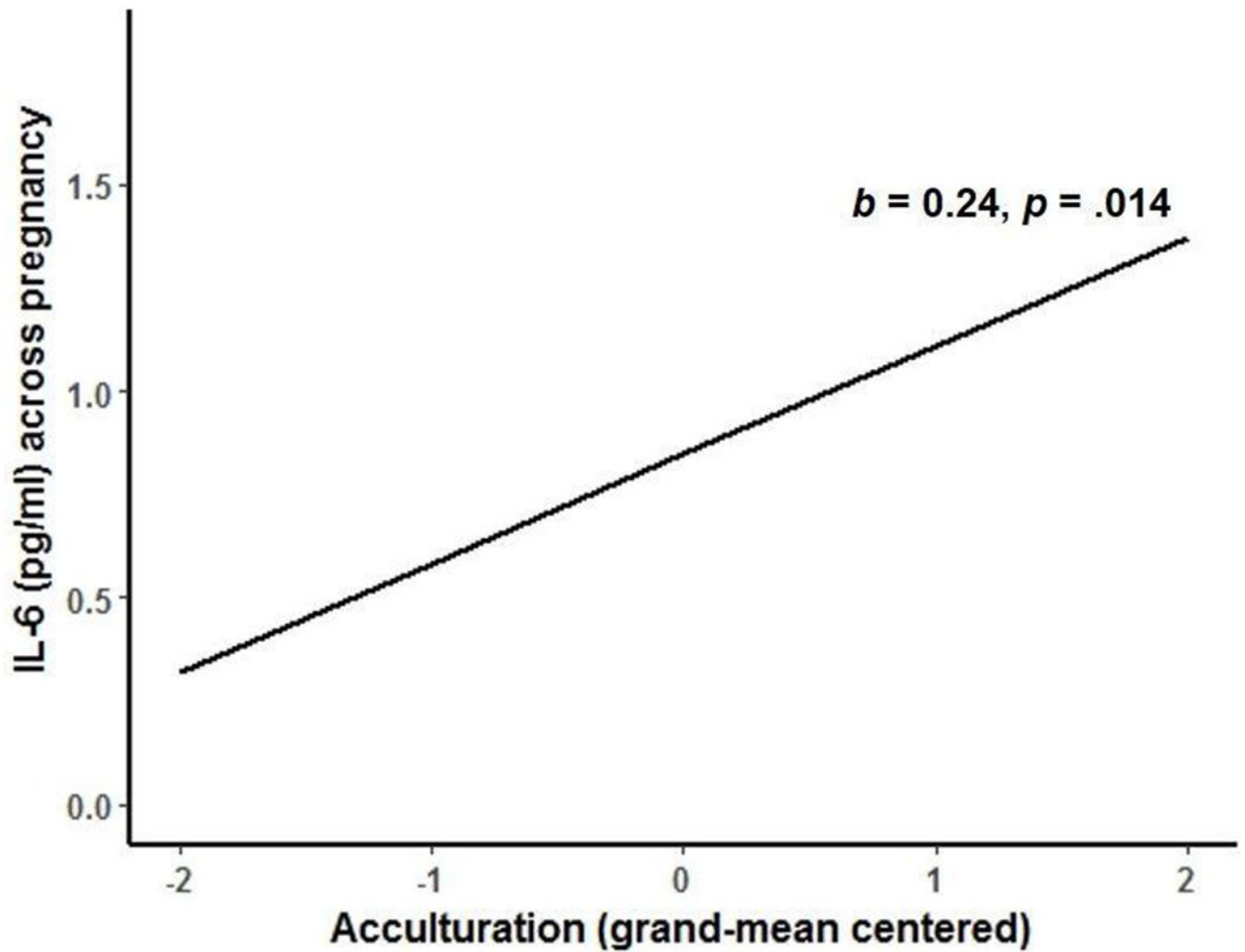


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### Highlights

- Acculturation predicted interleukin-6 among pregnant Mexican-American women.
- Acculturation predicted interleukin-6 after adjusting for socio-economic status.
- Socio-economic status was not related to interleukin-6.



**Figure 1.**

Association between ACC and IL-6 as predicted by model M1

*Note.* Figure 1 illustrates the main effect of ACC on IL-6 when all other covariates of the model are 0 (i.e., mean income, gestational week, and BMI, and absence of OB risk during pregnancy).

**Table 1.**

## Maternal characteristics.

<b>N = 75 pregnant Mexican-American women</b>		
	<b>frequency</b>	<b>mean <math>\pm</math> SD, range</b>
<b>Sociodemographic</b>		
Age at T1 (years)		26.06 $\pm$ 5.67, 18-39
<u>Income</u>		
Below \$15,000	9 (13.40%)	
\$15,000 - \$29,999	20 (29.90%)	
\$30,000 - \$49,999	20 (29.90%)	
\$50,000 - \$100,000	15 (22.40%)	
Over \$100,000	3 (4.50%)	
<u>Education</u>		
Primary, Elementary, or Middle School	5 (6.70%)	
High School or GED	28 (37.30%)	
Technical or Vocational School	13 (17.30%)	
Some College, but no degree	21 (28.00%)	
Associates Degree	2 (2.70%)	
Bachelors Degree	5 (6.70%)	
Certificate	1 (1.30%)	
<u>Generation status</u>		
1 <sup>st</sup> generation immigrants	21 (28%)	
2 <sup>nd</sup> generation immigrants	54 (72%)	
<b>Physiological</b>		
<u>IL-6 (pg/ml)</u>		
at T1		0.77 $\pm$ 0.38, 0.13-1.66
at T2		0.93 $\pm$ 0.58, 0.03-2.79
at T3		1.11 $\pm$ 0.61, 0.00-2.85
mean pregnancy		0.94 $\pm$ 0.43, 0.17-2.06
<u>BMI</u>		
Pre-pregnancy		26.25 $\pm$ 5.46, 17.41-48.07
Mean pregnancy		28.20 $\pm$ 4.89, 19.11-48.97
at T1		27.35 $\pm$ 5.04, 17.09-47.53
at T2		27.94 $\pm$ 5.00, 19.35-49.07
at T3		29.65 $\pm$ 5.04, 20.89-50.33
<b>Prevalence of obstetric risk conditions</b>		
hypertension	3 (4.00 %)	
gestational diabetes	5 (6.70 %)	
severe infections	6 (8.00 %)	
anemia	4 (5.30 %)	
smoking	2 (2.60%)	
alcohol consumption	1 (1.30)	