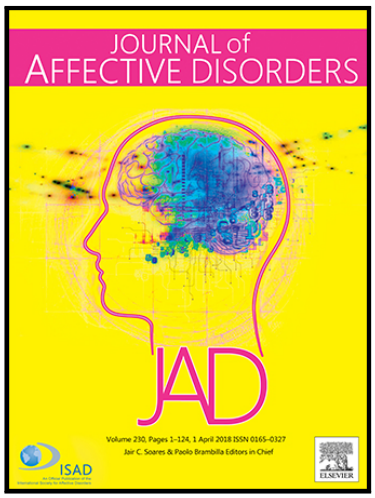

Biopsychosocial Correlates of Psychological Distress in Latina Mothers

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Highlights

- Everyday discrimination was most consistently and strongly associated with increased psychological distress across prenatal and postpartum visits
- Acculturative stress and mood associations were more pronounced postnatally
- Acculturation correlated with the overall depression and anxiety scores
- There were postnatal associations between economic hardship and psychological distress
- *NR3C1* methylation effects the associations between psychological and psychosocial distress.

Biopsychosocial Correlates of Psychological Distress in Latina Mothers

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Biosocial Correlates of Psychological Distress

Abstract

Background

Few studies have explored the relationship between psychological, psychosocial and biological factors among Latinas. An integrated understanding of how these factors associate with psychological distress is necessary for development of culturally relevant screening tools and interventions. This study aim was to examine the relationships among (a) psychological distress symptoms, (b) psychosocial factors (discrimination, acculturation, acculturative stress, economic hardship), and (c) biological (DNA methylation of stress-related genes) factors among Latinas during pregnancy and postpartum period.

Methods

A sample of 150 pregnant Latinas completed the Inventory of Depression and Anxiety Symptoms II (IDAS-II), psychosocial questionnaires (discrimination, acculturation, acculturative stress, economic hardship) before (24-32 weeks) and after gestation (4-6 weeks postpartum). Blood sample was collected at 24-32 weeks' gestation. Correlations were determined between psychosocial and biological measures on psychological distress measures. Multivariable linear regression models were conducted to assess the linear relationship between IDAS and stressors.

Results

Several correlations among psychosocial measures and gene methylation factors and IDAS-II variables were identified. Among the psychosocial measures, everyday discrimination was the most strongly and consistently associated with IDAS-II. DNA methylation of *NR3C1* affects the associations between psychological and psychosocial distress.

Limitations

We only assessed DNA methylation during pregnancy and focused on four HPA-related genes. Longitudinal assessment of DNA methylation and genome-wide analysis can provide a better picture of the role of methylation in psychological distress.

Conclusions

This work may assist clinicians and policy makers in effectively recognizing and preventing maternal mental health disparities based on discrimination and other psychosocial stressors in at-risk groups.

Keywords: Latinas; psychological distress; prenatal; postpartum; biomarkers; DNA methylation

Introduction

Latinas in the United States (U.S.) face a heightened risk for poor mental health as approximately one third experience a psychiatric disorder during their lifespan (Alegría et al., 2007). They also have the highest fertility rate and are the largest and fastest growing ethnic minority group in the US (Krogstad and Lopez, 2014; Passel and Rohal, 2015). This compounds their mental health risk as women often experience elevated psychological distress, such as depressive and anxiety symptoms during the perinatal period (Holditch-Davis et al., 2015), which, in turn, can precipitate functional impairments and diagnosable psychopathology (O'Hara and Wisner, 2014).

In fact, psychological distress in pregnancy is highly prevalent in Latinas and well highlighted across the literature (Dunkel-Schetter et al., 2016; Dunkel-Schetter and Tanner, 2012; Guardino and Schetter, 2014; Kuo et al., 2004; Liu and Tronick, 2013; Lucero et al., 2012; Ramos et al., 2019; Zayas et al., 2003). For example, the prevalence of postpartum depression among Latinas has been estimated as 30-43%, which is three times higher than the general US population (Lucero et al., 2012). Moreover, this health disparity is exacerbated by the fact that Latinas are less likely to be insured and utilize health care services compared to Non-Latina-White and Asian women (Alcalá et al., 2016). Latinas may face other barriers in accessing mental health care, such as cultural and linguistic barriers and fear of stigmatization (Lara-Cinisomo et al., 2018; Maxwell et al., 2019; Nadeem et al., 2007; Sentell et al., 2007).

Given these health disparities, research has identified risk factors that contribute to Latina's experience of psychological distress (Ayón, 2015). Higher levels of acculturation (i.e., the process of adapting to host country values, practices, and beliefs and/or losing cultural heritage) (Berry, 1997; Schwartz et al., 2010) in Latina mothers has been associated with higher

levels of prenatal (Ruiz et al., 2007) and postpartum (Alhasanat and Giurgescu, 2017) depressive symptoms and worsened prenatal neuroendocrine and immune profiles associated with chronic stress (D'Anna-Hernandez et al., 2012; Ruiz et al., 2006; Scholaske et al., 2018; Wommack et al., 2013). In fact, acculturative-related processes have been implicated in the postmigration intergenerational transmission of health disparities in Latinas (Fox et al., 2015). However, acculturation per se does not assess maternal perceptions of stress and has not always yielded significant findings in perinatal mental health research, potentially due to inconsistencies in the operationalism and measurement of acculturation (Beck, 2006). Furthermore, the psychosocial stress pathways (acculturative stress, discrimination, economic hardship) by which acculturation may be associated with maternal mental health and biological profiles have been unclear.

Acculturative stress (i.e., psychosocial stress resulting from adapting to the host culture) and perceived discrimination have been suggested as salient interrelated culture-specific stressors (Berry, 1997; Schwartz et al., 2010). Acculturative stress has been associated with increased prenatal depressive and anxiety symptoms in a sample of predominantly Mexican-born mothers (D'Anna-Hernandez et al., 2015; Preciado and D'Anna-Hernandez, 2017). However, in a sample with proportionately more US-born Latina mothers, perceived discrimination was the strongest predictor of prenatal depressive symptoms (Walker et al., 2012). Some research suggests that perceived discrimination levels increase with greater time living in the US (Viruell-Fuentes, 2007), potentially due to increased exposure to the hierarchal racial structure and stigmatization in the US (Viruell-Fuentes et al., 2012). Few studies have examined the relationship between these culture-specific stressors and biological pathways although acculturative-related process may be differentially biologically embedded across life stages and physiological systems (Fox et al., 2017). For instance, discrimination during pregnancy has been linked to epigenetic alteration

of stress-regulatory genes implicated in increased vulnerability to stress-induced disorders (Santos et al., 2018).

Economic hardship, a universal stressor, is both a well-established risk factor for prenatal depression (Lancaster et al., 2010) and a culturally relevant stressor, considering that 26% of Latino families live in poverty (U.S. Census Bureau, 2017). Some research suggests that lower income heightens the relationship between acculturative stress and psychological distress in immigrant Latinas (Bekteshi and van Hook, 2015), whereas other research suggests that the relationship between adverse prenatal immune profiles and acculturation is not moderated by income (Scholaske et al., 2018). As such, the extent to which economic hardship in Latinas may be associated with prenatal depressive and anxiety symptoms and biological profiles in relation to other psychosocial stressors remains less understood.

The risk of psychological distress has been hypothesized to have a substantial biologic etiology component related to exposure to chronic or prolonged stress (Yim et al., 2015). Research suggests chronic stress has a disproportionate impact on ethnic minority mothers placing them at increased risk for cumulative physiologic dysregulation (O'Campo et al., 2016). Furthermore, increased incidence of depression may exacerbate this process as the stress response is dysregulated in women with depression (Glynn et al., 2013; Jolley et al., 2007), including Latinas (Lara-Cinisomo et al., 2017). Although there is some debate regarding the pathways through which chronic stress and psychological distress are related to adverse health outcomes and health disparities, multiple potential neuroendocrine mechanisms have been implicated including epigenetic factors (Beijers et al., 2014).

Epigenetic alterations, such as via DNA methylation (DNAm), allow the modification of gene expression pathways in response to environmental stimuli without changing the DNA

sequence. The epigenetic regulation of genes related to the stress response signaling in the hypothalamic-pituitary-axis (HPA) is one key mechanism thought to allow control of stress reactivity programming in response to environmental stressors (Murgatroyd and Nephew, 2013; Murgatroyd et al., 2015). For example, we have previously shown that discrimination Latina mothers negatively associated with DNAm within two stress-response-associated genes: the glucocorticoid receptor (*NR3C1*) and the glucocorticoid binding protein (*FKBP5*) (Santos et al., 2018). There is further evidence that these environmentally induced epigenetic changes associate with long-term changes in stress-responses, behavior and HPA activity. For example, DNA methylation at key specific CpG sites within *NR3C1* exon 1-F promoter has been associated with exposure to stress in a number of studies, supported by a meta-analysis (Palma-Gudiel et al., 2015) while a further meta-analysis supported links between *NR3C1* DNAm correlating early life stress with major depression. A recent study finding an association with increased DNAm of *NR3C1* and blunted cortisol reactivity to stress in major depression (Bakusic et al., 2020) highlights the possible mechanisms. Stress exposure has also been associated with DNAm within specific CpG loci in intron 7 of *FKBP5*, that associate with higher cortisol levels, and prolonged recovery following exposure to stress (Zannas et al., 2016).

Alterations in HPA activity following exposure to stress is known to involve neuroplasticity. Activity of Brain derived neurotrophic factor (*BDNF*) is related to impaired neurocognitive function, altered sensitivity to stress, and numerous stress-related disorders (Notaras and van den Buuse, 2020). DNAm at *BDNF* is known to regulate activity of BDNF (Martinowich et al., 2003) and that *BDNF* DNAm is influenced by various environmental and lifestyle factors; for example, we have previously shown that an association with discrimination in Latina mothers with *BDNF* DNAm (Santos et al., 2018). An extensive review of cross-

sectional studies supported that methylation of the *BDNF* gene is higher in depressed patients than in controls (Chen et al., 2017) while longitudinal studies also suggest that *BDNF* DNAm is a risk factor for depression in later life (e.g., (Kang et al., 2015)).

The oxytocin (OXT) system, addition to its role in the regulation of complex social behaviors, also influences the physiological stress response and responses to psychosocial stress (Kumsta et al., 2013). Studies have shown DNAm to regulate OXT receptor (*OXTR*) (Kusui et al., 2001) and that DNAm relates to individual differences in various behavioral problems such as acute psychosocial stress (Unternaehrer et al., 2012) while further studies have found *OXTR* DNAm associations with social stress-related disorders such as social anxiety (Ziegler et al., 2015) and postpartum depression (Kimmel et al., 2016). Importantly, the respective associations and roles of these biological factors with perinatal psychological distress in Latinas are unknown.

While there have been recent calls for the integration of psychosocial and biological factors to understand psychological distress risk (Nephew et al., 2019; Yim et al., 2015), few studies have explored the relationship between psychological distress and relevant psychosocial and biological factors among Latinas. An integrated understanding of how these factors associate with psychological distress is necessary for development of culturally relevant screening tools and interventions. The purpose of this study was to examine the relationships among (a) psychological distress symptoms, (b) psychosocial factors (discrimination, acculturation, acculturative stress, economic hardship), and (c) biological (DNAm of stress-related genes) factors among Latinas during pregnancy (24-32 weeks) and the postpartum period (4-6 weeks). We hypothesize that psychological distress will be strongly associated with psychosocial stress, and that DNA methylation will distinguish women with chronic levels of biological stress.

Methods

Participants

A sample of healthy pregnant Latinas living in North Carolina (*n*=150) were enrolled in the study between May 2016-March 2017. Eligibility criteria were (1) 18-45 years old, (2), Spanish or English speaking, (3) carrying a singleton pregnancy (i.e., not pregnant with twins or multiples), (4) available for follow up at 6 weeks postpartum. Exclusion criteria were (1) currently experiencing severe depressive symptoms as determined by psychiatric interview, (2) history of bipolar or psychotic disorder, (3) receiving psychotherapy, (4) history of substance abuse in the past two years, (5) fetal anomaly, or (6) life threatening conditions. These exclusion criteria were implemented to avoid potential confounding variables and to control for severe mood symptoms with the onset before the time frame of the study. Interviews were conducted in English or Spanish based upon participant preference by a trained research assistant. Data were collected during a prenatal visit at 24-32 weeks' gestation and 4-6 weeks postpartum; these times will be referred to as prenatal and postnatal visit, respectively. The measures included in this study had validated versions in English and Spanish. The Institutional Review Board of North Carolina at Chapel Hill approved this study (#15-3027).

Psychological Distress

In order to comprehensively assess psychological distress, defined as maladaptive psychological functioning in the face of stressful life events (Ridner, 2004), the Inventory of Depression and Anxiety Symptoms II (IDAS-II) was used at the prenatal and postnatal visits (Watson et al., 2012). This 99-item self-report measure assesses a broad range of psychological distress symptoms across mood and anxiety domains including specific feelings, sensations, problems, and experiences felt within the past two weeks. The 99 items are divided into 19

individual scales that assess multiple psychological domains including depression (general depression, dysphoria, lassitude, insomnia, suicidality, appetite loss, appetite gain), anxiety (panic, social anxiety, claustrophobia, traumatic intrusions, and traumatic avoidance), anger (ill temper), positive mood (well-being), obsessive compulsive (checking, ordering, and cleaning), and bipolar (mania and euphoria). The IDAS-II uses a 1-5 Likert scale with higher scores indicating more severe symptoms. IDAS-II scores can be used for each dimension or as a total; in both cases higher scores means increased distress. The IDAS-II cronbach's alpha for item consistency was > 0.78 for both the prenatal and postpartum visits.

Psychosocial Stressor Assessments

Acculturation

During the prenatal visit, the 24-item Bidimensional Acculturation Scale (BAS) was used to measure acculturation (Marin and Gamba, 1996). The BAS assesses the degree to which individuals participate in the cultural domains of both the original and the culture of contact. The BAS includes items related to both Hispanic and Non-Hispanic cultural domains and includes three subscales, language use (6 questions), language proficiency (12 questions), and electronic media (6 questions). The BAS asks participants to report the frequency with which they experience events or their ability to use technology on a 1-4 Likert scale, with higher scores indicating higher frequency or better ability (1=Almost Never to 4=Very Well). (Marin and Gamba, 1996). An overall acculturation score that included both the Hispanic and Non-Hispanic domains was used in this study.

Acculturative Stress

At the prenatal and postnatal visits, the 9-item Acculturative Stress Scale was used to assess subjects' experience with the acculturation process (Gil et al., 1994); how well one adapts

to the changes that are occurring, some of which are not under one's control. Respondents report the frequency of certain emotions and experiences regarding acculturation to the US in the past year on a Likert scale of 1-5 (1=Not at All to 5=Almost Always). Sample questions include "How often do you feel that you would rather be more American if you had a choice?" and "How often do you feel uncomfortable having to choose between non-Hispanic/Latino and Hispanic/Latino ways of doing things?". The sum of the responses was averaged, resulting in a score range of 1-5, with a higher score indicating a greater degree of acculturative stress.

Discrimination

At the prenatal and postnatal visits, the 9-item Everyday Discrimination Scale (EDS) was utilized to measure routine day to day experiences of discrimination. The EDS is a common measure of the subjective experience of discrimination (Campo-Arias et al., 2015; Park et al., 2018; Williams et al., 1997). The EDS asks participants to rate the frequency in which they experience discrimination related events in their daily life on a 0-5 Likert scale (0=Never to 5=Almost Every day), with higher scores indicating higher frequency of perceived discriminatory events. Sample questions include: "In your day-to-day life, how often do any of the following things happen to you?... (1) "you are treated with less courtesy than other people are", "people act as if they are afraid of you." A mean score was taken from the 9 items to get a score from 0-5, with 0 indicating less frequent discrimination and 5 indicating higher frequency discrimination.

The EDS does not prompt individuals to think about race which can impact prejudice related cues on responses (Deitch et al., 2003). Therefore, in addition to rating the frequency of the discriminatory events, participants were then asked for their perception regarding the main reason for these experiences, which includes specific rationales including ethnicity, gender, race,

age, religion, height or weight, physical appearance, sexual orientation, education, income level, or other type of discrimination.

Economic Hardship

At the prenatal and postnatal visits, the 6-item Economic Hardship Measure was utilized to assess financial strain (Ayala et al., 2014; Zilanawala and Pilkauskas, 2012). This measure asks participants (yes or no) if they had experienced the following situations within the last year. Sample questions include: (1) "was there a time in the past year when the individual or household was without a telephone", (2) "were you unable to pay a full gas or electricity bill." A sum score from 0-6 was calculated based on the participant's self-response, with higher scores indicating higher economic strain.

Biological Assessments at Prenatal Visit

DNA Methylation

As previously described (Santos et al., 2018), a 6mL blood sample was collected prenatally followed by self-report measures in order to reduce potential variability in the stress response. The initial blood sample was drawn from a peripheral vein into a chilled EDTA-vacutainer, immediately placed on ice, and processed. The buffy coat was separated by centrifugation, frozen on dry ice, and stored at -80^{0}C at the University of North Carolina Biobehavioral lab for DNA extraction. DNA extraction was conducted with the QIAamp DNA Blood Mini Kit into individual cryovials and stored at -80^{0}C. The extracted DNA was transported on dry ice to Manchester University for DNA methylation analysis. DNA methylation levels were determined by bisulphite pyrosequencing. This process included treating 1 µg of DNA with EpiTect Bisulfite Kit (Qiagen) and candidate gene regions containing specific CpG loci within the *FKBP5* intron 7 (Paquette et al., 2014), *BDNF* untranslated exon IV

(Perroud et al., 2013), *NR3C1* exon 1F (Murgatroyd et al., 2015), and *OXTR* intron 1 (Bell et al., 2015) and then amplified using the PyroMark PCR kit. See **Supplemental Table I** for primer sequences, locations of regions, and PCR conditions. We focused only on specific CpG sites supported by previous literature to maintain statistical power and minimize effects of multiple testing. The single stranded biotinylated product was purified by mixing 10 µl of amplification mixture, 2 µl of streptavidin sepharose HP (Amersham Biosciences), and 40 µl of binding buffer. The sepharose beads containing the immobilized biotinylated product were purified, washed, and denatured in a 0.2mol/l NaOH solution and washed again using Pyrosequencing Vacuum Prep Tool (Qiagen). The biotinylated DNA was resuspended in a 12 µl annealing buffer containing 0.3µmol/l pyrosequencing primer and quantified by pyrosequencing using the PSQ 24MA system with the PyroMark Q24 Advanced CpG Reagents (Qiagen). The percentage methylation for each of the CpG sties was calculated using Pyro Q-CpG software (Qiagen). The average of the three separate assays were used for analysis.

Statistical Analysis

We assessed correlations with non-parametric Spearman rank correlation and tested for dependence between variables with Spearman rank order test. We elected to use a non-parametric estimation of correlation since the underlying distributions for the variables compared are not approximately Gaussian but are at least ordinal. We corrected P-value for multiple testing burden using the Benjamini-Hochberg procedure at a false discovery rate of 0.05. We also conducted multivariable linear regression to assess the linear relationship between IDAS total measurements during the prenatal and postnatal visits and stressors, controlling for gestational age, mother's age in years, mother's education level, ethnicity, and the infant's sex. We tested the

relationship between the IDAS and stressor measures using Wald-type tests, correcting for multiple comparisons with a more conservative Bonferroni correction.

Results

Our sample included 150 healthy pregnant Latinas with a mean age of 27.6 (SD=6.31) years. Most of the women (64.7%) were low income earning less than $25,000/year of total income, and had a low level of education, with 79.4% having a high school education or less. Most of the sample was non married and living with a partner (40%). Regarding nativity status, 78.7% of the women were born outside of the U.S. and the average years spent living in the US was 10.7 years (SD=6.27). The sex of the baby was almost equally divided with 48.9% male and 51.1% female newborns. The IDAS-II total score reflecting psychological distress was 142.5 (SD=27.02) at the prenatal visit (24-32 weeks' gestation) and 135.6 (SD=6.71) at the postnatal visit (4-6 weeks postpartum). Please see **Table I** for full demographic statistics.

Association Between IDAS-II and Psychosocial Stress Measures

Several positive associations were identified between IDAS-II sub-scales and the psychosocial stress measures, suggesting that increase in psychosocial stress is linked to increase in severity of depression and anxiety symptoms. The strength of the associations and statistical significance is displayed in **Figure I** (additional numeric details is provided in **Supplemental Table II**). Below we highlight specific associations for each of the psychosocial stress measures analyzed.

Acculturation

Acculturation, which was only measured during the prenatal visit, was positively associated with the overall IDAS-II score (r=.22) as well as seven subscales with a range

between *r*=.19 (lassitude) and *r*=.27 (appetite gain). The next strongest associations observed included general depression (*r* = .27) and checking (*r* = .22). These correlations suggest that increased acculturation is associated with worse psychological distress during pregnancy.

Acculturative Stress

Acculturative stress, which was measured at both gestation and the postnatal period, was only associated with IDAS-II scores in the postpartum period. Significant associations were observed with IDAS-II total (*r*=.28) and 12 subscales, with correlations ranging between *r*=.19 (traumatic intrusions) and *r*=.29 (checking), suggesting that increase acculturative stress is associated with postnatal psychological distress.

Everyday Discrimination and Ethnic Discrimination

Everyday discrimination had the strongest associations with IDAS-II total score during gestation (*r*=.37) and the postpartum (*r*=.39). Across the two time points we observed 13 and 15 significant associations among with the IDAS-II subscales at prenatal and postnatal, respectively. Of the subscales, 11 were consistently associated across the two time points (**Figure I**, **Supplemental Table II**), including general depression (gestation, *r*=.28; postpartum, *r*=.38), traumatic intrusions (gestation, *r*=.20; postpartum, *r*=.37), and ill-temper (gestation, *r*=.21; postpartum, *r*=.32). Experiencing ethnic discrimination was also associated with some aspects of the IDAS-II across both time points, such as total IDAS score (gestation, *r*=.25; postpartum, *r*=.21) and appetite loss (gestation, *r*=.28; postpartum, *r*=.19).

Economic Hardship

During the prenatal visit economic hardship was significantly associated with one IDAS-II subscale, traumatic intrusions (*r*=.20). The relationship between economic hardship and the IDAS-II was more evident during the postpartum visit, with a range of associations from *r*=.19

(traumatic avoidance) to *r*=.27 (traumatic intrusions) for individual subscales during the postnatal visit. Of note, traumatic intrusion was significantly associated with the economic hardship measure over time with a higher association at the postnatal visit (**Figure I**, **Supplemental Table II**).

Adjusted Associations Between IDAS-II and Psychosocial Stressors

For the statistically significant correlations described above, we conduct follow-up analysis to evaluate the effects of the psychological stressors on IDAS-II scores while adjusting for a priori selected set of covariates, which included gestational age, mother's age in years, mother's education level, ethnicity, and the infant's gender. Our results indicate that everyday discrimination is linked to increased risk of psychological distress as assessed by IDAS-II both during pregnancy (b=10.50, p= 1.04E-05) and the postpartum period (b=10.74, p = 4.11E-06), while economic hardship and acculturative stress only showed significant relationship in the postpartum period (**Table II**).

Biological Measures and IDAS-II Associations

We tested the correlation between prenatal markers of DNA methylation of four stress-related genes (*FKBP5*, *BDNF*, *NR3C1*, and *OXTR*) and pre- and postpartum IDAS-II scores. We identified weak positive correlations during gestation, and mostly negative correlations in the postpartum period (**Supplemental Figure 1)**. However, these associations did not show statistical significance after adjusting for multiple testing (**Supplemental Tables III-IV**). In linear regression models with covariates (gestational age, mother's age in years, mother's education level, ethnicity, and the infant's gender) we also did not observe a significant relationship between DNA methylation and IDAS-II (**Table III**)

In a post-hoc analysis, we explored the effects of biological levels of chronic stress, defined by top quartile of methylation of the glucocorticoid receptor gene (*NR3C1*), on the correlation between IDAS-II and psychosocial stress. In a stratified analysis for high and low methylation levels of *NR3C1*, women with hypermethylation of *NR3C1* exhibited strong associations between everyday discrimination and psychological distress (IDAS-II) both during pregnancy and in the postpartum period. For women with hypomethylation of *NR3C1*, we observed moderate associations between everyday discrimination and psychological distress, especially in the postpartum period (**Figure 2**).

Discussion

The objective of the current study was to evaluate the correlations between dimensions of psychological distress symptoms as measured by the IDAS-II symptom subscales and biopsychosocial factors in Latinas from pregnancy to the early postpartum period. The results characterize several associations between both psychosocial and psychological measures, and evidence that the strength of their association might vary by chronicity of biological stress as measured by methylation of *NR3C1*. These data may allow policy makers and activists to increase awareness of the adverse effects of discrimination and clinicians to more effectively recognize those at risk for discrimination stress related illness and recommend additional social support and care to their standard pre and postnatal medical care.

Psychosocial Measures

The IDAS-II measure assesses psychological distress symptomology across multiple domains including depressive, anxiety, anger, positive mood, obsessive-compulsive, and bipolar symptomatology. This analysis explored the correlation between the IDAS-II symptom subscales and multiple psychosocial measures including everyday discrimination, acculturation,

acculturative stress, and economic hardship. The psychosocial measure that had the strongest and most frequent associations with psychological distress symptoms was everyday discrimination. Additionally, everyday discrimination was the most consistent psychosocial measure between the two time points with the highest number of associations (prenatal visit=13 significant subscales, postnatal visit=15 significant subscales) and the highest magnitude of association (postnatal visit; general depression r=0.389). The magnitude of the associations increased over time with the majority of the subscales including general depression, dysphoria, lassitude, suicidality, ill temper, claustrophobia, traumatic intrusions, checking, and ordering having increased magnitudes and appetite loss, mania, traumatic avoidance, and cleaning having decreased magnitudes.

Everyday discrimination was the strongest psychosocial variable associated with prenatal depression symptoms among pregnant Latina women, and exposure to discrimination has also been identified as a substantial risk factor for postpartum depression in low-income, diverse samples (Incollingo Rodriguez et al., 2019; Walker et al., 2012), and particularly among populations with low levels of education (Stepanikova and Kukla, 2017), similar to the current study. The association between psychological distress and discrimination was moderate and consistent across the prenatal and postnatal visit, indicating the significant need for interventions that address discrimination-related stressors.

This need is greater than ever considering how today's social climate may magnify everyday discrimination. This is especially relevant to the current study where the data were collected in the peri- presidential election period of 2016. Namely, there is rapidly accumulating evidence of associations between the election of Donald Trump and adverse changes in the health of Latinos. For example, the 2016 presidential election has been correlated with an

increase in preterm births in US Latinas (Gemmill et al., 2019). This dovetails with a previous study of election-associated preterm birth in New York City, where the post-election increase was greatest among foreign born Hispanic women (Krieger et al., 2018). Furthermore, exposure to restrictive immigration policies has been associated with lower birth weights in the children of Latina migrants (Torche and Sirois, 2018). Similarly, in a study of racial disparities containing 420 young pregnant women (62% Latina), it was found that birth weights were lower in those who rated highly on the everyday discrimination scale (Earnshaw et al., 2013). These studies indicate that exposure to sociopolitical-related stress can have adverse health effects.

Acculturative stress had the next highest result of significantly associated IDAS-2 subscales. These associations were more pronounced during the postpartum visit with 12 significant subscales. This is a dramatic difference in the relevance of the associations with psychological distress during the postpartum visit comparatively to the prenatal visit. Although acculturative stress has adverse effects on maternal depressive symptoms during the prepartum period as well (D'Anna-Hernandez et al., 2015), the current data suggests that the postpartum period may be more susceptible to acculturative stressors than the prenatal period when psychological distress symptoms are concerned. However, this trend is likely not coincidental. Relationships between acculturative stress and IDAS-II variables may be more significant/robust postnatally due to increased exposure and/or sensitivity to this form of stress in the postpartum period. For instance, with the arrival of their child, mothers face a precipitous increase in critical responsibilities and disruption to daily routines. This is accompanied by substantial changes in behaviorally relevant endocrine patterns, in tandem, these result in increased stress. In addition to reporting greater levels of stress, mothers also can experience decreased social support postpartum compared to prepartum (De Caroli and Sagone, 2014). All these factors likely

combine to strengthen the relationship between acculturative stress and psychological distress postpartum. It is also important to note that perceived stress interacts with socioeconomic disadvantage to contribute to deficits in the response to infant cues, such as cry (Kim et al., 2016). Enhanced maternal sensitivity to infant cues during the postpartum period, which is likely to pertain to social stimuli in general, is critical to the expression of maternal care (Goldstein et al., 1996; Kim et al., 2016; Shin et al., 2006; Smith and Pederson, 1988), so the present results suggest that acculturative stress may have adverse effects on maternal care and associated neurodevelopmental outcomes of infants. While further study is needed, an increased focus on reducing exposure to and/or perceptions of acculturative stress while ensuring adequate social support during the postpartum period may have beneficial effects on both maternal and infant outcomes. Future studies should also evaluate the specific aspects of acculturative stress that becomes salient in the postpartum period, and the mechanisms underlying these associations.

Acculturative stress in the postpartum period may have been heightened by discrimination; these interrelated and highly correlated experiences (Torres et al., 2012) may interact separately, additively, or synergistically with symptoms of depression and anxiety during the postmigration process of acculturation. For instance, acculturative stress, which is heightened not only by discrimination but by language barriers and family separation, may have been a more salient stressor for the foreign-born (compared to US-born) Latinas in our sample who face the innate challenges of navigating a new country (Smart and Smart, 1995). Discrimination, however, may undermine mental health across generations regardless of nativity or documentation status (Finch et al., 2000; García, 2017). In fact, Latinas with darker skin may experience greater levels of discrimination than their lighter skinned counterparts (Pew Research

Center, 2019), suggesting that racialization processes in the US may further impede acculturation "into a society that may never fully accept them (or their children)" (Schwartz et al., 2010).

Although acculturation was only measured at the prenatal visit, because of the unlikely chance of it varying from the prenatal to the postnatal period, there were eight significant associations with IDAS-II measures, which was not in concordance with the results from acculturative stressor data at postnatal visit suggesting that acculturation and acculturative stress may different implications with regards to psychological distress. Similar to discrimination and acculturative stress, overall acculturation is linked strongly to depressive and obsessive-compulsive symptoms in the current study, further supporting the involvement of ethnic-related stress in maternal mental illness, particularly the role of long-term acculturation as well as acute levels of stress.

Economic hardship had the least number of significant associations with psychological distress symptomology. Economic hardship had a stronger relationship to IDAS subscales during the postpartum period, as compared to the prenatal period, suggesting increased levels of depressive and obsessive-compulsive symptoms. These results support population-based reports of the associations between economic stress and postpartum depression (Chang et al., 2016), and point to a specific role of traumatic intrusions in the adverse effects of economic factors on maternal depression. Traumatic intrusions have been identified as a key factor in the adverse impacts of traumatic birth related post-traumatic stress disorder (Fenech and Thomson, 2014).

There are also concerning implications for potential adverse effects of economic stress on maternal responsivity to infant stimuli (Kim et al., 2016). While maternal behavioral factors were not assessed in the current study, traumatic intrusions may mediate the adverse effects of traumatic birth on breastfeeding (Beck and Watson, 2008). Economic stress could exacerbate the

maladaptive effects of birth related post-traumatic stress disorder (or traumatic events in general) on mother and child. Furthermore, social support is an established protective factor in the etiology of postpartum depression (Manuel et al., 2012), and economic stress may increase the risk of postpartum depression through decreased social support (Gjesfjeld et al., 2010), as both greater income and social support are related to decreased depression in low income pregnant women (Ritter et al., 2000). The increased consideration of economic factors may result in more accurate identification of at-risk mothers and lead to enhanced prevention and/or treatment of trauma and/or depressive symptomology.

Across all of the psychosocial measures, the most consistent associations of psychological distress were with depressive and anxiety symptomology. Discrimination was uniquely associated with obsessive-compulsive and bipolar symptomology suggesting a more global impact across psychological distress domains, while the acculturative and economic measures were correlated with the depressive, traumatic stress, and anxiety domains. Our study significantly contributes to the literature by identifying the differences in association between psychosocial stressors and the specific domain of psychological distress symptomology.

Biologic Measures

Overall, the biological measures showed a weaker correlation compared to the psychosocial measures, indicating a more complex and/or indirect connection between epigenetic regulation and psychological distress symptomology. We observed that both hypermethylation and hypomethylation of the *NR3C1* resulted in significant associations between IDAS and psychosocial stressors. Much of the research on *NR3C1* methylation and maternal wellbeing is focused on the effects of maternal wellbeing on methylation in offspring (Hompes et al., 2013; Mansell et al., 2016). However, there is evidence that exposure to prenatal

stress differentially affects HPA related methylation in both mother and child (Kertes et al., 2016). The adverse effects of discrimination on the HPA axis may behaviorally manifest in decreased emotional wellbeing. Our data indicate that associations between discrimination exposure and psychological distress are present in Latina mothers exhibiting both hyper and hypo-methylation *NR3C1* states. This suggests an inverted U-shaped curve for the relationship between the glucocorticoid receptor activity (and perhaps overall HPA function) and ethnic stress-induced psychological symptomology. Epigenetic changes in the *NR3C1* gene are strongly linked to exposure to social stressors, though most of this work is focused on early life stress (Turecki and Meaney, 2016). The current *NR3C1* hypomethylation data are similar to studies of HPA-related epigenetic changes and post-traumatic stress disorder, where racism has been identified as a form of traumatic stress (Carter, 2007) and decreased *NR3C1* DNAm is observed in veterans with post-traumatic stress (Yehuda et al., 2015) as well as patients with major depressive disorder (Na et al., 2014). Hypomethylation and accompanying increased *NR3C1* expression may mediate the lower basal cortisol pathological responses to stressful stimuli in those suffering from PTSD, depression, and/or chronic discrimination, including maternal populations (Szpunar and Parry, 2018; Wahbeh and Oken, 2013). Ethnic discrimination has been specifically linked to post-traumatic stress symptoms in adolescent Mexican Americans (Flores et al., 2010), and the general prevalence of post-traumatic stress in Latinos is high compared to European American populations (Marshall et al., 2009). Hypermethylation of the *NR3C1* has also been associated with depression (Bakusic et al., 2020; Farrell et al., 2018) (though these correlations can be site specific) (Bustamante et al., 2016), and a recent systematic review of *NR3C1* DNAm underscores the particular complexity of the links between this epigenetic system and psychosocial stress/psychopathology (Turecki and Meaney, 2016), perhaps due to an

inverted U-shaped relationship as has been reported with peripheral cortisol and depression (Bremmer et al., 2007). Critical factors to consider improving our understanding of the role of *NR3C1* DNAm in the etiology of social stress related illness would be to understand the possible role of generational effects of maternal mental health on child stress-responses and the possible role of the epigenetic programming of stress-regulatory genes on mediating this.

Strengths and Limitations

Strengths of the current study include a comprehensive psychosocial assessment which includes multiple factors implicated in maternal mental health, a moderately large sample size, and pre and postpartum sampling. We only assessed DNA methylation during pregnancy in four HPA-related genes and used pyrosequencing, which can only analyze short segments of DNA (300-500 nucleotides) and involves a risk of sequencing errors. Longitudinal assessment of DNA methylation and genome-wide analysis can provide a broader picture of the role of methylation in psychological distress. Additional time points could have provided a broader view of effects of the factors explored in this study. For example, additional data on life history of exposure to social stress and psychiatric family history would have been valuable. Given the robust relationships between maternal mental health, parenting, and offspring health, related studies on the effects of discrimination on parenting and offspring outcomes are warranted.

Conclusion

Using a biopsychosocial approach to assess maternal psychological distress, the present study identified and characterized multiple correlational links with psychosocial stressors (discrimination, acculturation, acculturative stress, economic hardship) and epigenetic markers. This work may assist clinicians and policy makers in effectively recognizing and preventing maternal mental health disparities based on racial and ethnic discrimination in at-risk groups through public health campaigns to increase awareness of the adverse effects of discrimination and other psychosocial stressors on maternal mental health. Early intervention should focus on reducing exposure to and/or perceptions of acculturative stress and discrimination by ensuring adequate social support, potentially through culturally relevant community support groups both pre and postnatally. Peer support groups, for instance, may mitigate symptoms of depression precipitated by sociocultural stressors (Page-Reeves et al., 2019). With the increasingly contentious political climate in the US and proliferation of overt acts of racism and discrimination, ensuring these groups receive proper care is paramount.

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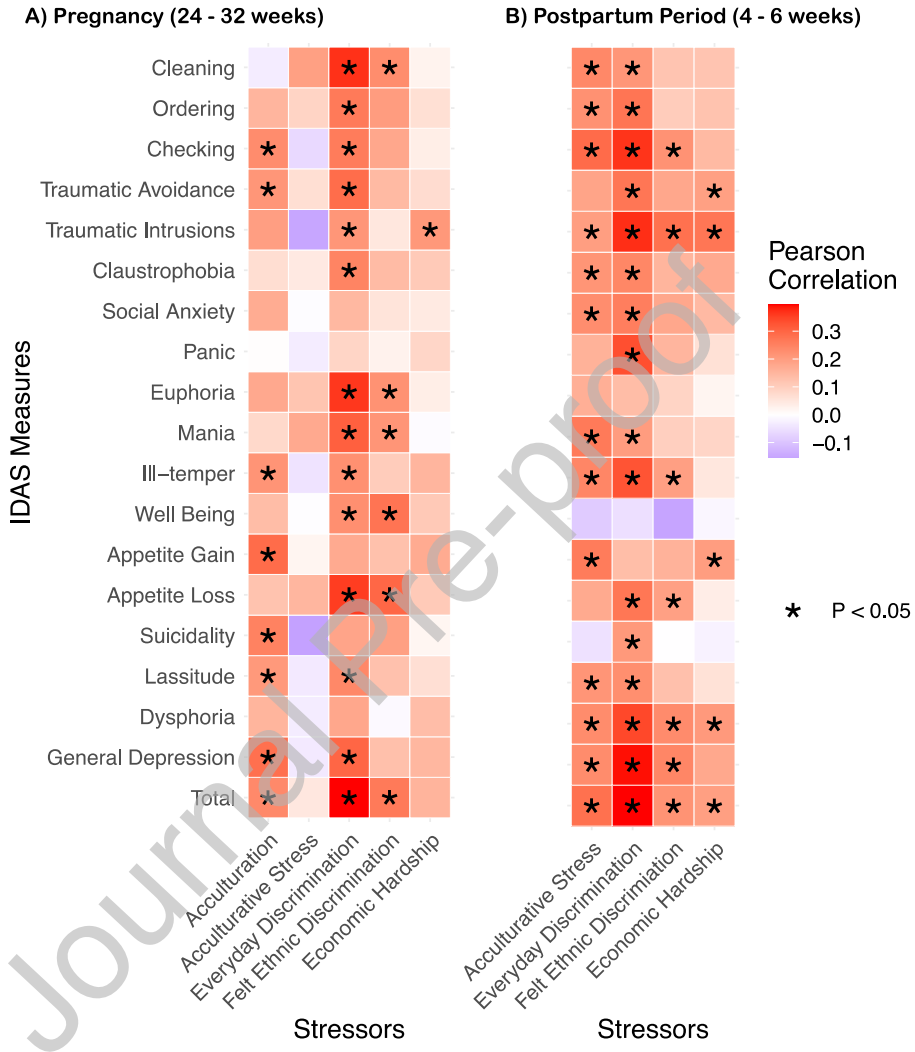
Biosocial Correlates of Psychological Distress

Figure I. Heatmap showing the associations among IDAS-II subscales and psychosocial stressors



Biosocial Correlates of Psychological Distress

Figure II. Heatmap showing the associations among IDAS-II subscales and stratified levels of *NR3C1* methylation

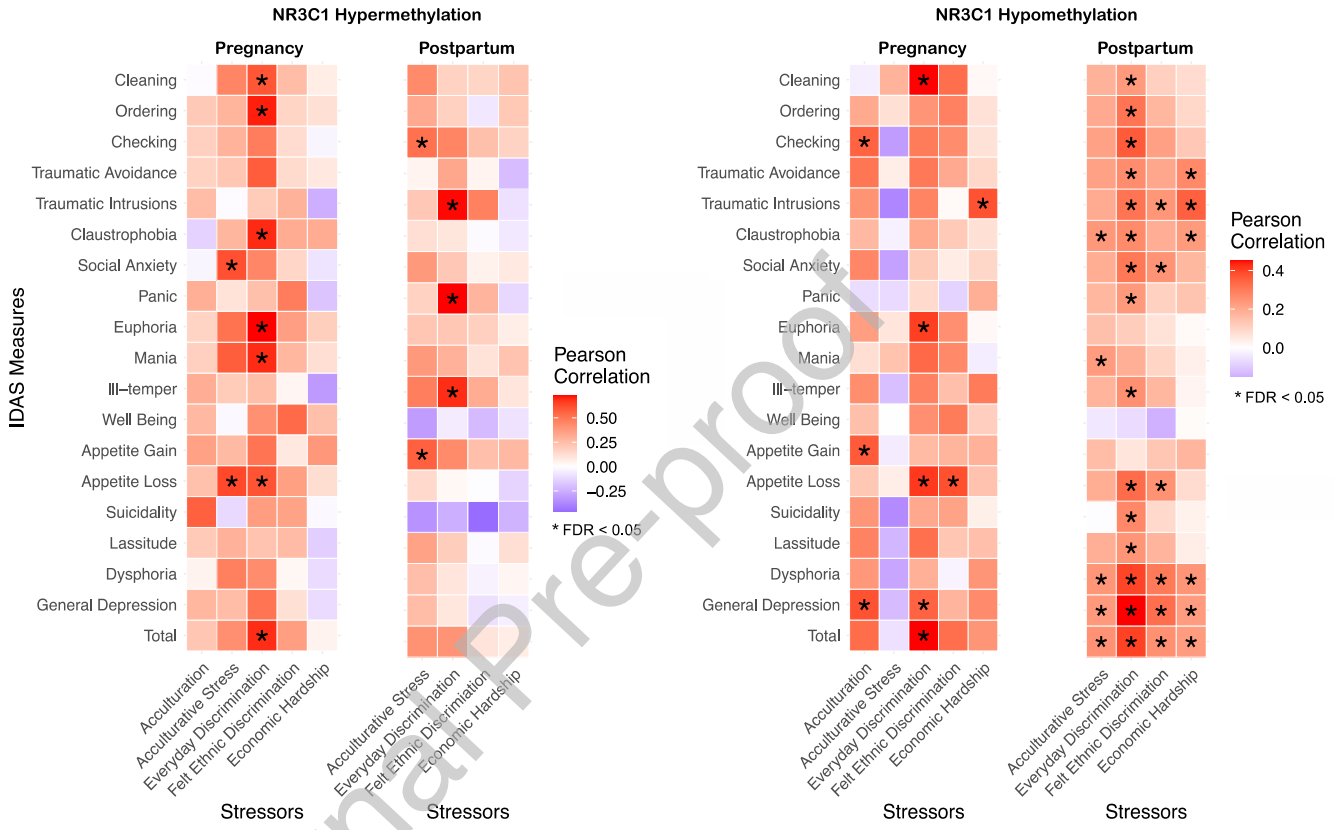


Table I. Demographic and clinical characteristics of the sample

Characteristics	**Cohort (N= 148)**
Mean Age in years (SD)	27,7 (6,3)
Ethnicity/Cultural background	
- Non-US born	84,5%
- US born	15,5%
Country of Origin for Non-US born	
- Mexico	75,0%
- El Salvador	8,3%
- Dominican Republic	8,3%
- Honduras	4,2%
- Peru	4,2%
Years living in US	
- Mean (SD)	10.7 (6.27)
- Median (Range)	11 (30)
Marital status:	
- Married	34,5%
- Living with partner	39,9%
- Single/divorced/widowed	25,7%
Income (yearly)	
- <15.000	39,9%
- 15.000 – 19.999	23,0%
- 20.000 – 24.999	16,9%
- 25.000 – 29.999	10,8%
- >30.000	9,4%
Sex of the infant	
- Male	51,1%
- Female	48,9%
IDAS Total Mean Score (SD) at T1	142,8 (27,0)
IDAS Total Mean Score (SD) at T2	135,8 (26,9)

Table II. Linear regression results of the effects of psychosocial stressors on IDAS-II

	Pregnancy (24-32 weeks)			Postpartum Period (4-6 weeks)		
Covariates[1]	**Beta**	**SE**	**P-value***	**Beta**	**SE**	**P-value***
Acculturation	3.41	2.59	0.191	-	-	-
Acculturative Stress	2.53	2.36	0.286	8.43	2.33	**< 0.001**
Everyday Discrimination	10.50	2.28	**< 0.001**	10.74	2.23	**4.1134E-06**
Felt Ethnic Discrimination	7.11	2.27	**0.002**	5.90	2.42	0.016
Economic Hardship	5.93	2.36	0.013	7.19	2.41	**0.003**

[1]All models were adjusted for gestational age, mother's age in years, mother's education level, ethnicity, and the infant's gender

* FDR adjusted, bolded p-values represent significant results

Table III. Linear regression results of the effects of DNA methylation on IDAS-II

	IDAS-II at Pregnancy (24-32 weeks)			IDAS-II at Postpartum Period (4-6 weeks)		
Covariates[1]	**Beta**	**SE**	**P-value***	**Beta**	**SE**	**P-value***
OXTR	0.016	0.024	0.496	0.004	0.022	0.873
NR3C1	-0.002	0.003	0.611	-0.002	0.003	0.644
FKBP5	-0.002	0.007	0.816	-0.004	0.006	0.539
BDNF	0.001	0.003	0.811	-2.3E-05	0.003	0.995

[1]All models were adjusted for gestational age, mother's age in years, mother's education level, ethnicity, and the infant's gender

* FDR adjusted