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Association of pica with cortisol and inflammation among Latina pregnant women

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Abstract

Pica, the urge to consume items generally not considered food, such as dirt, raw starch, and ice, are particularly common among pregnant women. However, the biology of pica in pregnancy is not well understood. Therefore, this study aimed to assess how pica relates to endocrine stress and immune biomarkers in a cohort of pregnant Latina women in Southern California. Thirty-four women completed a structured pica questionnaire. Maternal urinary cortisol and plasma cytokine levels were measured between 21 and 31 weeks' gestation. Associations between pica during pregnancy and biomarkers were assessed using linear regression models adjusting for gestational age. Twelve (35.3%) of the pregnant women reported pica (geophagy and amylophagy) during pregnancy. In multivariate models, those who engaged in pica had higher levels of cortisol (β: 0.37, 95% CI: 0.01, 0.073) and lower levels of IL-1β (β: −0.06, 95% CI: −0.11, −0.02), IL-8 (β: −0.30, 95% CI: −0.56, −0.05), IL-21 (β: −0.35, 95% CI: −0.63, −0.08), and type-1 inflammation composite (β: −0.29, 95% CI: −0.44, −0.14) than women who did not engage in pica. These results suggest that biological stress and immune response differ for women with pica compared to those without. This study suggests novel physiological covariates of pica during pregnancy. Further research is needed to better understand the mechanisms and temporality underlying the observed associations between pica and endocrine and immune biomarkers.

1 | INTRODUCTION

Pica is the craving and purposive consumption of non-food substances. The three types of pica most commonly reported include the consumption of earth, clay, chalk, mud, or soil (geophagy); raw starch (amylophagy); and ice or freezer frost (pagophagy) (Young, 2010). Additionally, numerous substances have been reported as being consumed by individuals with pica, including paper, ash, pencil lead, coffee grounds, and soap (Lacey, 1990; Young, 2011).

Pica is an enigmatic behavior found worldwide, most commonly seen in pregnant women (Horner et al., 1991). In a recent meta-analysis comparing studies conducted in various global regions, the aggregate prevalence of pica during pregnancy was shown to be 45% in Africa, 23% in North or South America, and 18% in Eurasia (Fawcett et al., 2016). In the United States, the prevalence is in the

20%–70% range in most studies among pregnant women (Young, 2011). This considerable variability in reported prevalence is due to the absence of a definitive pica definition, resulting in the use of diverse definitions across different studies, along with frequent underreporting among affected individuals, and the strong cultural and social influence on its detection. Furthermore, variations in prevalence appear to be associated with different demographic groups. Pica has been reported by pregnant women from all race/ethnic groups, but in the United States, a higher proportion of racially/ethnically minoritized women self-reported experiencing pica than white women (Bakhireva et al., 2012; Edwards et al., 1994; Simpson et al., 2000). For instance, African American pregnant women were twice as likely to engage in pica compared with pregnant women who were not African American (Fawcett et al., 2016), highlighting race/ethnicity as an important predictor of pica during pregnancy. This relationship between pica and categories of race can be explained through the lens of social determinants of health. Race is a socially constructed category that can impact the lived experiences of people and in turn, biological factors of health (Gravlee, 2009). Despite Hispanics/Latinos being the largest ethnic minority group in the United States, accounting for 19% of the total population, our understanding of pica among this group is limited.

Various possible etiological explanations of pica have been proposed, including cultural expectations, a response to psychosocial stress, hunger, gastrointestinal distress, micronutrient deficiency, and protection from toxins and pathogens (Young, 2010). Most studies that have measured biomarkers have focused on indicators of micronutrient deficiency, especially iron and zinc (Miao et al., 2015). There are, however, a number of non-nutrition-related biological pathways that could be involved in pica among pregnant women. Specifically, stress warrants further investigation in understanding the underlying mechanisms of pica.

If pica behaviors are linked to psychological distress, then the steroid hormone cortisol could be elevated among those who engage in it, given its role in the hypothalamic–pituitary–adrenal (HPA) stress response (Young, 2011). Pica behaviors might serve as a compensatory mechanism to manage or neutralize stressors, but they may not fully eliminate the source of stress. In some cases, the stressors may persist or recur, leading to continued cortisol release even if pica provides some relief. We anticipate that women whose stress is severe or long-term enough to elicit pica, a potentially costly coping behavioral adaptation, would exhibit cortisol levels above their less-stressed, non-pica peers. The greater incidence of pica among minoritized communities also suggests a potential association with psychological distress, given the disproportionate hardships faced by these communities. The independent associations between pica and psychological distress as well as minoritized women is supported by the established literature of the ill-effects of racial discrimination and structural social inequalities on the adverse health experiences of women (Carter et al., 2019; Paradies et al., 2015; Williams, 2018). Therefore, we hypothesize that pica will be positively associated with cortisol levels.

During pregnancy, increasing cortisol levels are normative and necessary for fetal organ development and for preparing the fetus for extrauterine life (Amiel-Tison & Pettigrew, 1991; Challis et al., 2001). Cortisol also promotes an immunosuppressive state during pregnancy, which is important in both the inflammatory process of implantation and the antirejection process that protects the fetus from the maternal immune system (Mastorakos & Ilias, 2003). However, excessive or prolonged cortisol secretion may negatively influence the mother and fetus. Studies have indicated that high cortisol levels have been associated with pregnancy complications such as prenatal depression and preterm delivery (Bandoli et al., 2018; Field & Diego, 2008) and can detrimentally affect fetal brain development (Amiel-Tison & Pettigrew, 1991). High maternal cortisol levels in early pregnancy have been associated with lower mental development scores in infants (Davis & Sandman, 2010) and childhood affective problems in girls (Buss et al., 2012).

Additionally, pica substances have been suggested as causes of various sicknesses, including anemia, heavy metal poisoning, parasites, and alimentary canal damage (Young, 2011). For these reasons, most medical professionals consider pica a pathological behavior (Reid, 1992). Further research from a much more biomedical point of view is needed to explore its purported negative health consequences. In contrast, potential positive health effects of pica have also been observed, such as preventing harmful chemicals or pathogens from entering the bloodstream (Young, 2010). To further explore the potential involvement of pathogenic or toxic exposures as second biological pathway in pica, we conducted a comprehensive analysis of a wide array of pro-inflammatory cytokines. Previous studies on pica have not extensively investigated cytokines, but based on previous suggestions regarding the potential harmful consequences of pica (Young, 2011), we hypothesized that pica would be associated with elevated levels of pro-inflammatory cytokines.

Dynamic changes in cytokines are involved in the maintenance of pregnancy, labor, and delivery. During normal pregnancy, there is a pro-inflammatory response to support embryo implantation and placental

development in the first trimester. Pro-inflammatory cytokines help create an environment that facilitates tissue remodeling and immune tolerance to the developing fetus. After placental implantation, the pregnant woman's immune system generally shifts away from pro-inflammatory responses to favor more anti-inflammatory responses, but immunosuppression is not total (Wang et al., 2020). Pregnancy is characterized by a decrease in T-helper-cell type (Th) 1 cytokines and an increase in Th2 cytokines, which promotes fetal tolerance by decreasing Th1 and Th17 cytokines. In the third trimester, cytokine concentrations tend to stabilize, with a balance between pro-inflammatory and anti-inflammatory cytokines. The maternal immune system remains vigilant against infections while not overreacting to the developing fetus. Given that pregnancy is a state of unique immunoregulation, perturbation towards excessive pro- or anti-inflammatory status could have deleterious consequences (Wang et al., 2020).

The intricate regulation of cytokines is influenced by various factors that can trigger inflammatory responses. As mentioned earlier, implantation and placental development can stimulate inflammatory cytokine release during early pregnancy. Another crucial factor is the presence of pathogenic microorganisms. In response to microbial invasion, the maternal immune system may release pro-inflammatory cytokines as part of its defense mechanisms. In the case of pica, we hypothesized that pregnant women who engage in pica may face increased susceptibility to pathogens and toxins, potentially elevating pro-inflammatory cytokines.

Hormonal changes also play a role in cytokine regulation during pregnancy. For instance, the hormone progesterone, which is essential for maintaining pregnancy, can have immunomodulatory effects (AbdulHussain et al., 2020). It tends to suppress pro-inflammatory responses and promote immune tolerance, particularly during the later stages of pregnancy. On the other hand, estrogen, which increases during pregnancy, can stimulate the production of pro-inflammatory cytokines. Furthermore, pregnancy health complications such as gestational diabetes mellitus (GDM) can influence the balance of pro- and anti-inflammatory cytokines during pregnancy. Women experiencing GDM have increased levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and C-reactive protein, compared to those without GDM (Lekva et al., 2016).

A greater understanding of how pica could relate to endocrine and immune physiology in pregnancy is needed, especially among vulnerable populations in which the prevalence of pica tends to be higher. Therefore, the aim of this study was to explore the association between pica and cortisol and immune biomarkers among a cohort of Latina women. Our observational study results can be evaluated as consistent or inconsistent with various hypotheses. We specifically sought to investigate the following hypotheses:

> **Hypothesis 1.** Pica behaviors will be associated with elevated cortisol levels due to their link with psychological distress.

> **Hypothesis 2.** Consuming non-food pica substances may be linked to increased pro-inflammatory cytokine levels, potentially indicating susceptibility to pathogenic or toxic exposures during pregnancy.

2 | METHODS

2.1 | Study population

Participants come from the Mothers' Cultural Experiences (MCE) study. Data for this analysis derive from MCE Wave 2, a cohort of women living in Southern California who self-identify as Latina, Hispanic, Chicana, Mexicana, or Latin American, were recruited between 2018 and 2020 at prenatal clinics at Olive View-UCLA Medical Center in Sylmar, Venice Family Clinic in Santa Monica, and UCLA West Medical in Los Angeles (NIH DK105110 and DK125524). In this manuscript, we use the term "Latina" because this was preferred by our study cohort, acknowledging that this term encompasses a diverse group. To be eligible to enroll, women had to be at least 18 years old, English or Spanish speaking, and ≤16 weeks pregnant. At two different prenatal stages, participants were asked to fill out a survey either in English or Spanish in the morning. The survey consisted of questions related to their demographic information such as age, education, country of birth, and marital status as well as other questions related to culture, identity, health, stressors, and relationships. Pre-pregnancy height and weight of the mothers were used to calculate their pre-pregnancy BMI (BMI = weight (k)/height $(m)^2$). Full details of the study design have been published previously (Fox, 2021, 2022; Fox & Wiley, 2022).

Data for this study come from the second prenatal assessment, when MCE Wave 2 participants were 21–31 weeks' gestation. From the initial cohort of 107 pregnant women enrolled at the first prenatal timepoint, $n = 59$ of these participants completed the second prenatal assessment. The participant attrition between the first and second timepoints was largely due to the onset of the COVID-19 pandemic, which resulted in a sudden halt to in-person research in keeping with university ethics

regulations. Of the $n = 59$ women who completed the second prenatal assessment, $n = 34$ participants completed the non-food pregnancy cravings questionnaires and therefore were included in this analysis. The missingness for $n = 25$ cases is because the non-food cravings questionnaires were added to the ongoing MCE Wave 2 study after those participants had already completed their second prenatal assessment. Other data collected during the second prenatal assessment included social relationships, health, pregnancy and fertility, home and living arrangements, culture and experiences, and food insecurity; participants also provided saliva, urine, and blood samples.

Participants provided written, informed consent after full study procedures were described. All protocols were approved by the Institutional Review Boards of participating institutions with appropriate reliances. Procedures comply with the tenets of the Declaration of Helsinki. Data are not publicly available because participants did not consent to share individual-level data publicly.

2.2 | Pica behavior assessment

Pica behavior was captured using a previously published questionnaire (Lin et al., 2015; Roy et al., 2018) used in other Latina or Mexican populations. The questionnaire inquires about 22 non-food items: chalkboard chalk, paper, ash, more than three cups of ice, unripe mango, freezer frost, bean stones, raw flour, corn starch, magnesium chloride/carbonate, pencil lead, brick, adobe, holy/blessed earth, raw potatoes, sand, clay, coffee grounds, eggshells, soap, pottery, and mothballs. Participants were asked how many times they consumed each item on purpose during pregnancy, as well as during their entire lifetime, with Likert scales of four ordinal options: never, a few times (once or twice), sometimes (three to ten times), and often (more than ten times). Pica was dichotomized into "no" if they answered never and "yes" if they answered a few times or greater. We refer to any endorsement of any pica questionnaire items during pregnancy and lifetime as "pica" for brevity.

2.3 | Cortisol and cytokine measures

Cortisol was measured from clean-catch urine samples. Urine was kept at refrigerator temperature and then transported in a hard-sided refrigerator-temperature cooler to the UCLA Biological Anthropology of Motherhood Lab. The specimen was vortexed, aliquoted, and frozen at −80°C. Cortisol was quantified using the enzyme-linked immunosorbent assay (ELISA) method according to kit manufacturer instructions (Cortisol ELISA Kit, Arbor Assays, Ann Arbor, MI). Specific gravity was measured for each urine sample using a refractometer (USG-Chek Digital Handheld Refractometer, Reichert, Inc., Depew, NY). Cortisol concentrations were corrected for specific gravity (SG) using the formula:

$$\text{SG} - \text{corrected concentration} = \text{raw cortisol concentration} \times \frac{\text{SG}_{\text{target}} - 1}{\text{SG}_{\text{sample}} - 1}$$

(Miller et al., 2004).

Urinary cortisol levels integrate across several hours of diurnal and pulsatile fluctuations. Therefore, urinary measures of cortisol are less noisy than measures from other matrices such as saliva and plasma (Sarkar et al., 2013). Also, by conducting our sample collection only during mornings, we measure a similar segment of the diurnal pattern for all participants.

Cytokines were measured from nonfasting morning blood samples. Blood used for cytokine assays was collected by antecubital venipuncture into EDTA-treated tubes and kept at refrigerator temperature until plasma extraction within a few hours, and the plasma aliquots were frozen at −80°C until assay. A multiplex assay was used to measure concentrations of the cytokines (Meso Scale Discovery, Meso Scale Diagnostics LLC, Rockville, MD). The minimum detectable amount for cytokines were as follows: IL-1β 0.04 pg/mL, IL-2 0.05 pg/mL, IL-12 0.05 pg/mL, IFN-γ 0.15 pg/mL, TNF-α 0.10 pg/mL, IL-8 0.03 pg/mL, and IL-21 0.35 pg/mL.

2.4 | Statistical analysis

All biomarkers were analyzed as continuous variables, with cortisol measured in ng/mL and cytokines measured in pg/mL. Cytokine composite scores were computed as the sum of the standardized value (z-score) of each cytokine. Th1 composite included IL-1β, IL-2, IL-12, IFN-γ, and TNF-α; Th2 composite included IL-4, IL-10, and IL13; and Th17 composite included IL-17, IL-21, and IL22. Prior to analysis, all the biomarkers, including composite scores, were natural log-transformed to reduce skew. Independent t-tests were used to analyze mean differences between pica and non-pica groups for continuous biomarker variables. Linear regression was used to estimate associations between the biomarkers and pica. Models were adjusted for gestational age (weeks). $p < 0.05$ was considered statistically significant and presented in the results. All statistical analyses were conducted using R, version 4.2.1.

3 | RESULTS

The final analytic cohort of 34 pregnant women was between the ages of 20 and 42 (Table 1). A substantial portion of women was US-born (44.1%), had education equivalent to graduating high school (70.6%), and employed (67.6%). Most women were married (52.9%) and cohabitating with the baby's father (79.4%), and on average 25 weeks' gestation. The mean pre-pregnancy BMI was 30 kg/m^2 (SD: 6.00), indicating that most women were overweight before becoming pregnant.

TABLE 1 Descriptive statistic of study population.

	All (n = 34)
Pica during pregnancy (%)	
No	22 (64.7%)
Yes	12 (35.3%)
Pica during lifetime (%)	
No	10 (29.4%)
Yes	24 (70.6%)
Age (years)	
Mean (SD)	30.7 (5.9)
Median [Min, Max]	30.3 [20.1, 41.8]
Country of birth (%)	
US	15 (44.1%)
Mexico	9 (26.5%)
Other[a]	10 (29.4%)
Education (%)	
Less than high school	4 (11.8%)
High school or equivalent	24 (70.6%)
Any college or beyond	6 (17.6%)
Work status (%)	
Employed	23 (67.6%)
Unemployed	11 (32.4%)
Marital status (%)	
Single	16 (47.1%)
Married	18 (52.9%)
Cohabitating with baby's father (%)	
No	7 (20.6%)
Yes	27 (79.4%)
Pre-pregnancy BMI (kg/m^2)	
Mean (SD)	29.9 (6.0)
Median [Min, Max]	29.0 [18.0, 49.1]
Gestational age (weeks)	
Mean (SD)	24.5 (2.8)
Median [Min, Max]	24.4 [20.6, 31.4]
Parity (%)	
Nulliparous	14 (41.2%)
Primiparous	8 (23.5%)
Multiparous	12 (35.3%)
Number of children	
Mean (SD)	1.2 (1.4)
Median [Min, Max]	1.0 [0.0, 5.0]
Number of pregnancy complications	
Mean (SD)	1.6 (1.2)
Median [Min, Max]	2.0 [0.0, 4.0]
Self-reported health (%)	
Very good	4 (11.8%)
Good	23 (67.6%)
Fair	6 (17.6%)
Poor	1 (2.9%)
Gestational diabetes (%)	
No	27 (79.4%)
Yes	7 (20.6%)
Preeclampsia (%)	
No	32 (94.1%)
Yes	2 (5.9%)
Preterm (%)	
No	27 (79.4%)
Yes	7 (20.6%)
Food insecure[b] (%)	
No	30 (88.2%)
Yes	4 (11.8%)

Abbreviations: BMI, body mass index; SD, standard deviation.
[a]Other includes El Salvador and Guatemala.
[b]Food insecure is measured using a published 2-item screen, where a positive response on either item was considered an indication of food insecurity (Hager et al., 2010).

About 41% were nulliparous women and 79% did not go on to deliver preterm. A small number of women were food insecure (11.8%). Twenty-four women (70.6%) reported ever engaging in pica and 12 women (35.3%) reported pica during pregnancy. There were a few notable differences between sociodemographic characteristics of women with pica during pregnancy and those without pica (Table S1). Women with pica during pregnancy were slightly younger and had fewer children on average compared to those without pica during pregnancy.

All women who reported pica during pregnancy had a history of engaging in pica prior to pregnancy; none of them initiated pica during pregnancy (Figure 1). For

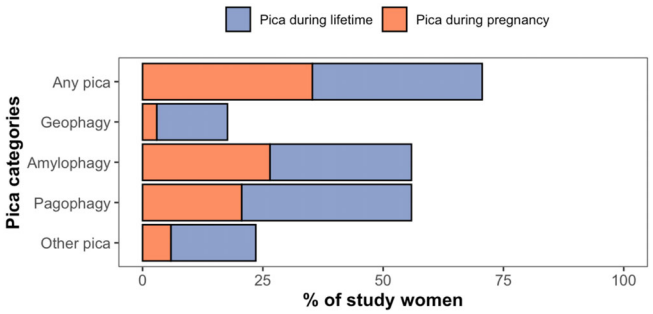

FIGURE 1 Prevalence of pica among pregnant Latina women ($n = 34$). Pica categories are not mutually exclusive. Geophagy includes holy earth, sand, clay, pottery, bean stones, brick, adobe, and magnesium chloride. Amylophgy includes raw flour, corn starch, raw potatoes, unripe mango. Pagophagy includes ice and freezer frost. Other pica includes chalkboard chalk, paper, ash, pencil lead, coffee grounds, eggshells, soap, mothballs.

geophagy, 17.6% of women had ever consumed earth materials, and 2.9% had done so during pregnancy. For amylophagy, 55.9% of women reported ever consuming raw starches, and 26.5% had done so during pregnancy. 55.9% of women reported consuming pagophagic items prior to pregnancy and 20.6% of them continued to do so during pregnancy. Other pica items were reported to have ever been consumed by 23.5% of women, and 5.9% during pregnancy.

Consistent with our first hypothesis, in the independent *t*-test analyses, the average cortisol concentrations were higher in women with pica during pregnancy compared to women without pica during pregnancy ($p = 0.037$) (Figure 2). Counter to our second hypothesis, women with pica had lower average concentrations of cytokines IL-1β ($p = 0.006$), IL-8 ($p = 0.019$), IL-21 ($p = 0.012$), and Th1 composite ($p < 0.001$) compared to women without pica during pregnancy.

To further investigate the associations between pica behaviors and biomarkers, we ran separate multiple linear regression analyses with log-transformed biomarkers as outcome variables and pica as predictor, adjusted for gestational age. The multiple linear regression analyses confirmed the findings from the independent *t*-test analyses. Specifically, women with pica during pregnancy had an average 45% higher levels of cortisol-adjusted-for specific-gravity, and an average 6%, 26%, 30%, and 25% lower levels of cytokines IL-1β, IL-8, IL-21, and Th1 composite, respectively, compared to those with non-pica during pregnancy (Table 2).

4 | DISCUSSION

In this first study to examine the association between prenatal biomarkers of stress and inflammation and pica, we made several noteworthy findings. First, the prevalence of pica during pregnancy among Latina women in Southern California was high; 35.3% of women engaged in pica during pregnancy, while 70.6% had ever engaged in pica. This is consistent with previous studies among Latina pregnant women (Roy et al., 2018; Simpson et al., 2000). Women reported consuming amylophagic (26.5%) and pagophagic (20.6%) items during pregnancy. The substances consumed were similar to those reported being consumed among other Latina populations, for example, holy earth, adobe, bean stones, magnesium carbonate, ice, and unripe mangoes (Bakhireva et al., 2012; Bruhn & Pangborn, 1971; Roy et al., 2018; Simpson et al., 2000). Roughly half of women who reported engaging in pica during pregnancy consumed multiple substances, and 70.8% reporting poly-pica during lifetime.

Within the context of our study, we developed a conceptual framework to understand the potential relationships between pica and maternal stress and immune markers (Figure 3). Our hypotheses directed our investigation into this complex relationship. Firstly, we hypothesized that pica behavior may be linked to maternal stress, specifically as a potential coping mechanism. This hypothesis led us to explore whether women engaging in pica might exhibit higher cortisol levels during pregnancy. By examining cortisol levels, we aimed to tap into a biologically relevant pathway associated with pica and its potential impact on maternal health. Secondly, we considered the hypothesis that women who engage in pica might be more susceptible to the harmful effects of these foreign substances, which could trigger immune responses, including the production of pro-inflammatory cytokines. As a result, we expected to observe a positive association between pica and pro-inflammatory cytokines. When cortisol and cytokine dysregulation coincide, they could potentially have detrimental effects on fetal development and contribute to pregnancy complications, such as preterm birth.

Our study findings support the first hypothesis, indicating that pica behavior is potentially associated with elevated maternal stress levels, as indicated by the higher cortisol levels observed in pregnant women who engaged in pica. Pica can be a symptom of stress, emotional upset, and obsessive-compulsive disorder (Edwards et al., 1994; Stein et al., 1996). This could explain why, in our study, women with pica had higher levels of cortisol, which plays an important role in the hormonal response to stress, suggesting that women with pica may have been subject to higher stress levels than women without pica but that this situation was soothed by the pica behavior. Future research is needed with larger cohorts to assess statistical mediation.

However, our results do not align with the second hypothesis, suggesting that the ingestion of non-

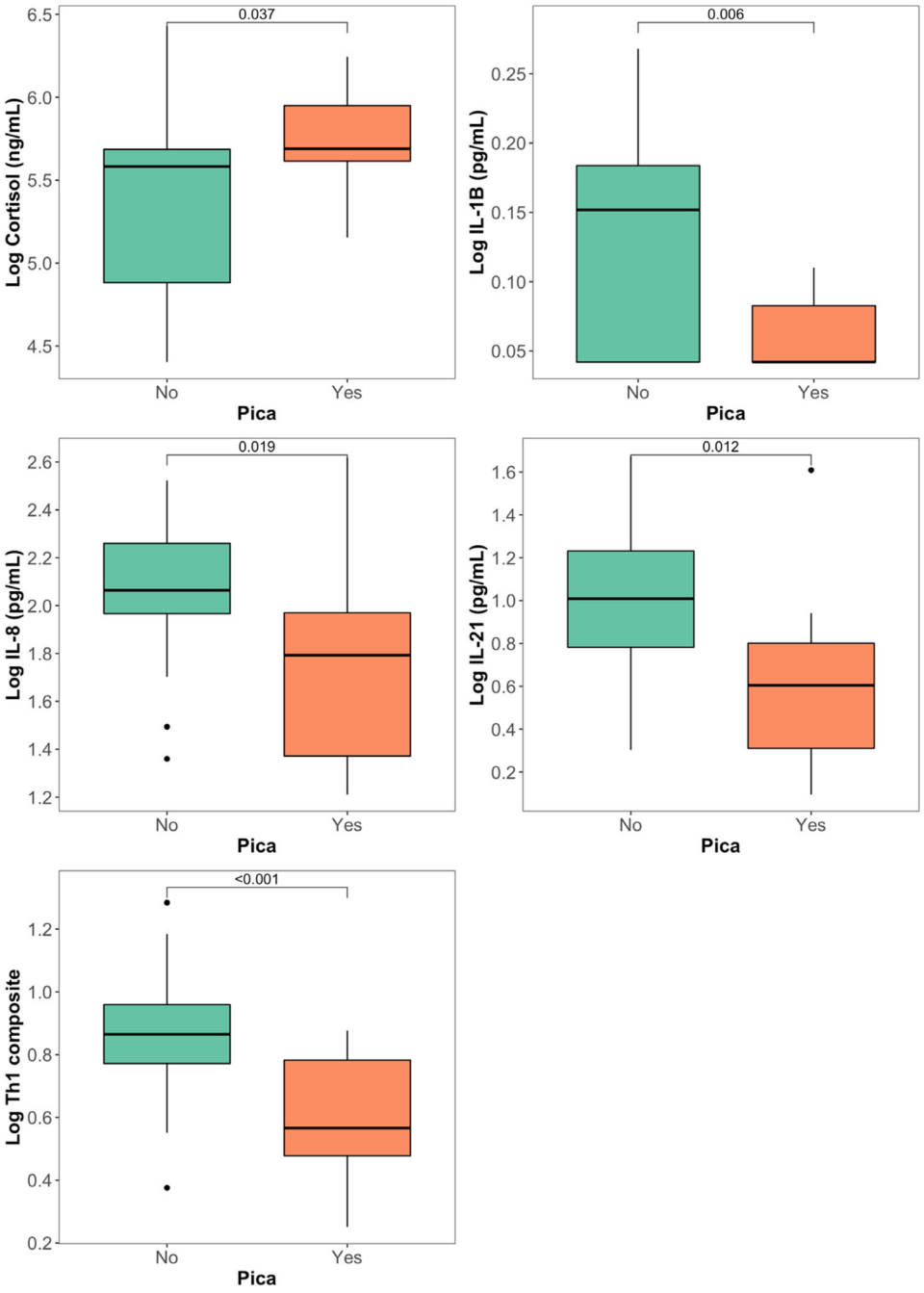

FIGURE 2 Boxplots of stress and immune biomarker levels in pregnant Latina women by pica status during pregnancy ($n = 34$). Differences were calculated using independent *t*-tests over log-transformed biomarker values. *p* values from the *t*-tests are written above the boxplots.

TABLE 2 Associations between maternal stress and immune markers and pica during pregnancy.

Biomarkers	Estimate[a] (95% CI)	*p* value
Cortisol (ng/mL)	0.37 (0.01, 0.73)	0.044
IL-1β (pg/mL)	−0.06 (−0.11, −0.02)	0.008
IL-8 (pg/mL)	−0.30 (−0.56, −0.05)	0.021
IL-21 (pg/mL)	−0.35 (−0.63, −0.08)	0.014
Th1 composite	−0.29 (−0.44, −0.14)	0.001

[a]Multivariable linear regression models with log-transformed biomarkers as outcome variables and pica as predictor. Adjusted for gestational age.

nutritive substances in pica does not appear to lead to increases in pro-inflammatory cytokines. Although our findings related to cytokines were unexpected, they may still make sense based on what we know about the immune system during pregnancy. In the second and third trimesters, there is a shift toward a more anti-inflammatory immune response, which involves the release of fewer pro-inflammatory cytokines and more anti-inflammatory mediators (Mor & Cardenas, 2010; Schminkey & Groer, 2014). Our study found that pregnant women with pica had lower levels of certain pro-inflammatory cytokines compared to those without pica

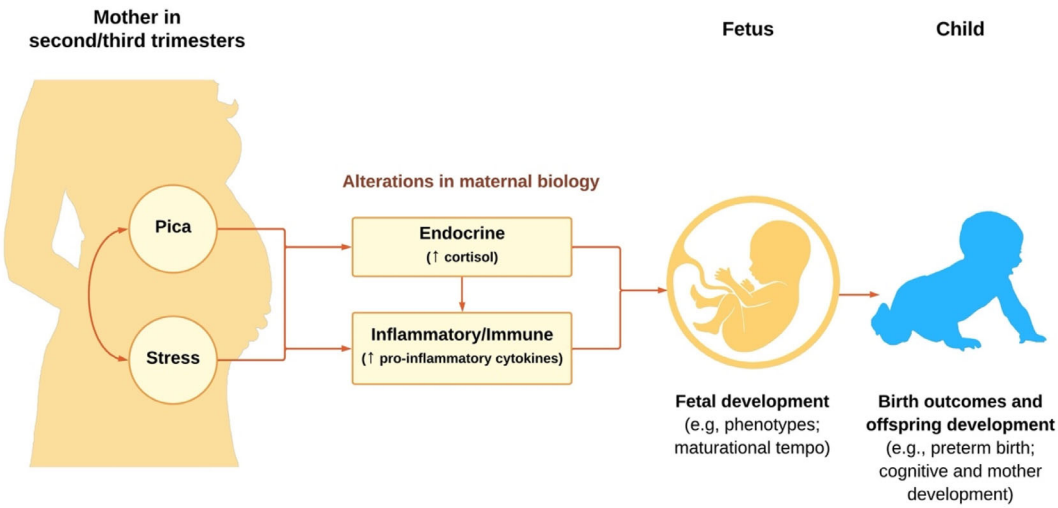

FIGURE 3 Conceptual framework on effects of pica on maternal stress and immune markers.

at a time point that includes late-second and early-third trimesters.

Additionally, pica has been associated with both positive and negative health conditions. An intriguing observation from our study is that the lower pro-inflammatory cytokine levels among pregnant women with pica align with the potential etiological explanation that pica substances offer protection from harmful chemicals and pathogens, particularly during pregnancy when susceptibility to toxins and pathogens is a concern (Young, 2010). Pica substances can strengthen the intestinal mucosal layer by coating the surface of the endothelium, potentially reducing the permeability of the gut wall and preventing the entry of toxins and pathogens into the bloodstream. This aligns with the observed decrease in pro-inflammatory cytokines, as fewer harmful agents entering the bloodstream would result in a reduced need for an inflammatory response. Moreover, pica substances can adsorb pathogens and toxins within the gut lumen, rendering them unabsorbable by gut. This mechanism may lead to a reduction in pro-inflammatory cytokine production, as fewer harmful agents would reach systemic circulation. Especially, amylophagic behavior, the most common form of pica during pregnancy observed in our sample, has been shown to be effective in this respect, as raw starch can absorb poisons and pathogens causing gastrointestinal distress (Ofoefule & Okonta, 1999).

Our overall results are consistent with the idea that cortisol has anti-inflammatory effects and reduces the production of pro-inflammatory cytokines by binding to glucocorticoid receptors (Anacker et al., 2011). When cortisol binds to these receptors, it can suppress the transcription of genes involved in the production of pro-inflammatory cytokines, leading to a decrease in their production. This mechanism is one way in which cortisol can exert its anti-inflammatory effects.

Because cortisol is associated with immunosuppression in pregnancy, it was unlikely that both our hypotheses would have been, simultaneously, true, that pica would be correlated with both higher cortisol and higher inflammation; therefore, our study may distinguish between these two possibilities. These two physiological states tend not to co-exist, although some studies have found no correlation between maternal prenatal cortisol and inflammation (Nazzari et al., 2020; Szpunar et al., 2021) and both have been associated with prenatal mood disorders (Christian et al., 2009; Haeri et al., 2013; Osborne et al., 2019; Schweizer-Schubert et al., 2021).

Another study of pregnant women between 16 and 26 weeks' gestation found a similar pattern, with increasing depressive symptom scores being associated with lower levels of pro-inflammatory cytokines (IL-1β, IL-7, and TNF-α), after adjusting for gestational age at blood draw (Shelton et al., 2015). The plasma cortisol levels were also inversely correlated with the levels of these pro-inflammatory cytokines, suggesting that cortisol may potentially play a role in the decreased levels of these cytokines (Shelton et al., 2015). Thus, pica-associated greater cortisol would manifest with less inflammation, which could be merely a side-effect of the more functional relationship between pica and cortisol. Future intervention studies are needed to disentangle these causal relationships.

While this study is limited by a small sample size and cross-sectional design, we observed significant associations between pica behavior and endocrine and immune markers. It is important to note that our findings may not

be generalizable to other populations due to the wide variability in pica behavior, but the prevalence of pica resembled that observed in other Latina populations (Roy et al., 2018; Simpson et al., 2000). Self-reporting non-food pregnancy cravings questionnaires are subject to recall bias due to the dependence on long-term memory and errors in estimating frequencies and underreporting due to social desirability. A substantial number of participants were lost to follow-up between the first and second study visits due to the onset of the COVID-19 pandemic before all participants had completed their second visits; therefore, we do not suspect bias in sampling. Moreover, those who did not complete the second study visit had mostly similar demographic and clinical characteristics, except they were more likely to be unemployed and not born in the US. Given the available sample types in this cohort, the optimal matrix for the assessment of cortisol was urine, because it integrates levels across several hours (Sarkar et al., 2013). Our morning urine collections were not taken immediately at wake up, but other studies of prenatal maternal urinary cortisol use the same type of mid-morning prenatal clinical visit samples as we did (Diego et al., 2009; Field et al., 2004, 2006, 2009; Luiza et al., 2015; Rouse & Goodman, 2014). Furthermore, pregnant women urinate throughout the night frequently (Brown, 1978), undermining the superiority of waking samples in this population.

Further research is needed to better understand the mechanisms and temporality underlying the observed associations between pica and endocrine and immune biomarkers. Future studies should consider larger sample sizes, longitudinal designs, more comprehensive assessment methods, and statistical analyses incorporating multiple comparison corrections to address these limitations and provide a more robust and causal understanding of the relationship between pica and these physiological markers. Moreover, it is important to consider maternal pre-pregnancy and pregnancy health in future studies. While our study has provided insights into the associations of pica behavior with cortisol and cytokine levels during pregnancy, various health-related factors, including conditions like GDM, may play a role in shaping these relationships. We refrained from including these health factors in our models due to the exploratory nature of this pilot study, which seeks to investigate correlations between pica behavior and biomarkers. To gain a more comprehensive understanding, we hope our findings will prompt future, larger studies that delve into the biomedical and psycho-behavioral processes that account for any observed correlations.

In conclusion, among a small cohort of Latina pregnant women in Southern California, we found that those who had eaten amylophagic and pagophagic items during pregnancy had higher cortisol levels and lower pro-inflammatory cytokine levels between 21 and 31 weeks' gestation. This suggests that pica during pregnancy could, potentially, be caused by or cause alterations to maternal HPA and/or immune function. A comprehensive study of the underlying physiological mechanisms of pica is needed to both fully characterize the role of pica in pregnancy and to develop strategies for supporting maternal-fetal health.

AUTHOR CONTRIBUTIONS

Dayoon Kwon: Conceptualization, Data curation, Formal analysis, Visualization, Writing—original draft, Writing—review & editing. **Delaney A. Knorr**: Data curation, Investigation, Project administration, Writing—review & editing. **Kyle S. Wiley**: Data curation, Investigation, Writing—review & editing. **Sera L. Young**: Conceptualization, Supervision, Writing—review & editing; **Molly M. Fox**: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are not publicly available because participants did not consent to sharing individual-level data publicly.

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