Association of Viral Exposures and Parity with CRP Among

Childbearing Age Mexican American Women

BY

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THESIS

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This thesis is dedicated to my husband, Scott, my daughters, Juliet and Eve, my mother, Anna, and my brother, Igor. Your love and support sustain and motivate me.

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
CMV	Cytomegalovirus
CRP	C-reactive Protein
CVD	Cardiovascular Disease
ELISA	Enzyme-linked Immunoabsorbent Assay
FSSM	Food Security Survey Module
HbA1c	Hemoglobin A1c
HBV	Hepatitis B Virus
HDL	High Density Lipoprotein
hsCRP	High Sensitivity C-reactive Protein
HSV-1	Herpes Simplex Virus Type 1
HSV-2	Herpes Simplex Virus Type 2
MA	Mexican American
MEC	Mobile Examination Center
NHANES	National Health and Nutrition Examination Survey
OR	Odds Ratio
U.S.	United States

SUMMARY

In two cross-sectional analyses, the associations of parity status and viral exposure burden with C-reactive protein (CRP) were examined in a nationally representative sample of non-pregnant Mexican American (MA) women of childbearing age, after accounting for socioeconomic, lifestyle, and health-related factors. The role of acculturation and other factors in modifying the association of parity status and viral exposure burden with CRP was also investigated. Existing data from the National Health and Nutrition Examination Survey (NHANES 1999-2010) were used.

In the first analysis, a history of live birth within one year, compared to nulliparity, was significantly associated with elevated CRP among MA women with low level of acculturation. In the same group, a history of live birth more than one year ago was associated, albeit statistically non-significantly, with a two-fold risk of elevated CRP. Parity status was not associated with an increased risk of elevated CRP among MA women with moderate and high levels of acculturation. Measured socioeconomic, lifestyle, and health related variables, with the exception of waist circumference, had limited effect on the observed associations.

In the second analysis, among Mexico-born women, those with high viral exposure burden, compared to seronegative status, had a two-fold, albeit statistically non-significant, increased risk of elevated CRP. Among U.S.-born women, viral exposure burden was not associated with an increased risk of elevated CRP. Among MA women with borderline high and high serum total cholesterol levels, women with at least one viral exposure had a significantly increased risk of elevated CRP, compared to seronegative women.

Mexico-born women and low acculturated MA women with histories of live birth and viral exposures appear to be at an increased risk of elevated CRP. Results suggest that increased clinical attention should be given to the postpartum inflammatory status of recent MA immigrant women and offer preliminary evidence to support more consistent lipid screening and viral exposure evaluation among MA immigrant women.

I. INTRODUCTION

A. **Background**

Chronic systemic inflammation is a maladaptive inflammatory response, which is associated with sustained physiological activity of immune mediators, disruption of normal biological pathways, and eventual development of chronic disease (Bastard et al., 1999; Hotamisligil, 2006; Pankow et al., 2001; Pepys & Hirschfield, 2003; Petersen & Pedersen, 2005). Currently, the causes of chronic systemic inflammation are not completely understood, however, it is generally agreed that such causes are multi-factorial (Egger & Dixon, 2010; Lopez-Jaramillo, Lahera, & Lopez-Lopez, 2011; Prescott, 2013). C-reactive protein (CRP), a liver-produced acute phase protein, is a well-established marker of chronic systemic inflammation (Black, Kushner, & Samols, 2004; Jialal, Devaraj, & Venugopal, 2004). A substantial body of research has shown a link between elevations in CRP and chronic conditions, such as atherosclerosis (Eisenhardt, Habersberger, & Peter, 2009), diabetes (Greenfield & Campbell, 2006; Wang et al., 2013), incident coronary heart disease and ischemic stroke (Emerging Risk Factors Collaboration et al., 2010), depression (D.E. Ford & Erlinger, 2004), and cognitive decline (Komulainen et al., 2007). In addition, there is accumulating evidence that exposure to maternal systemic inflammation in utero may contribute to the development of childhood metabolic diseases through fetal programming mechanisms (Heerwagen, Miller, Barbour, & Friedman, 2010; Schmatz, Madan, Marino, & Davis, 2010; Segovia, Vickers, Gray, & Reynolds, 2014).

Mexican Americans (MAs) are a demographically young and fast growing population, and also one of the largest racial/ethnic groups in the United States (U.S.) (Ennis et al., 2011;

Passel et al., 2012). MA women of childbearing age currently have the highest birth rate compared with females from other major U.S. ethnic/racial groups (Pew Research Center, 2011), and, therefore, contribute a significant share of all U.S. births. During childbearing years, MA women exhibit one of highest levels of CRP among similarly aged non-Hispanic White and Black women in the U.S. (Danner, Kasl, Abramson, & Vaccarino, 2003; E. S. Ford, Giles, Mokdad, & Myers, 2004; Ramos & Olden, 2008) and experience the greatest lifetime increases in inflammation-linked metabolic conditions, such as diabetes (Schneiderman et al., 2014) and metabolic syndrome (Heiss et al., 2014; Mozumdar & Liguori, 2011). A similar elevated inflammation risk is also observed among MA children and adolescents, who currently exhibit the highest levels of CRP among their U.S. age counterparts (J. B. Dowd, Zajacova, & Aiello, 2010; E. S. Ford et al., 2003; Lande, Pearson, Vermilion, Auinger, & Fernandez, 2008). Given the shared environmental history and the possibility of intergenerational transmission of inflammation risk, a better understanding of risk factors for maternal inflammation is essential for the prevention of chronic diseases in the MA population.

Traditional risk factors, such as obesity, diabetes and hypercholesterolemia, do not fully explain CRP elevations among MA women (E. S. Ford et al., 2003; E. S. Ford et al., 2004) and studies examining the role of other factors in inflammation among MA women are limited. Since the rise in inflammation- linked conditions among MA females coincides with childbearing years, any prominent physiological, lifestyle, and environmental exposures during this period may be shaping their inflammation risk. Among MA women of childbearing age, prominent and previously unexamined exposures include high fertility, high infectious exposure burden, and migration/acculturation.

A history of pregnancy with a live birth, defined as parity ("Parity," n.d.), may be an independent risk factor of systemic inflammation. Growing evidence links inflammation with

reproductive functions, including ovulatory cycle, labor, and birth (Jabbour, Sales, Catalano, & Norman, 2009) and shows that pregnancy is naturally accompanied by increases in inflammation and CRP (Belo et al., 2005; Kuzawa, Adair, Borja, & McDade, 2013; E. M. Miller, 2009). Several studies among young and middle-aged women have linked parity with greater risk for inflammation-linked conditions, including metabolic syndrome (E. Gunderson et al., 2009; Skilton, Serusclat, Begg, Moulin, & Bonnet, 2009; Skilton et al., 2010) and cardiovascular disease (CVD) (Skilton et al., 2009; Skilton et al., 2010). Studies that examine the association between parity and CRP among MA women are lacking.

There is also increasing evidence that viral infections contribute to systemic inflammation because infection-mediated tissue injury or other processes may lead to the disruption of normal immune regulatory mechanisms (Elenkov, Iezzoni, Daly, Harris, & Chrousos, 2005; Karin, Lawrence, & Nizet, 2006). A history of exposure to persistent viruses, such as cytomegalovirus (CMV), Herpes Simplex virus (HSV), and Hepatitis B virus (HBV), has been associated with elevated CRP, atherosclerosis, and CVD (Espinola-Klein et al., 2002; Ishizaka et al., 2002; Mendy, Vieira, & Gasana, 2013; Roivainen et al., 2000; Simanek, Dowd, & Aiello, 2009; J. Zhu et al., 2000b). According to NHANES data, MA adults have higher prevalence of select persistent viral infections, such as CMV and HSV type 1, than White and African-American adults (Zajacova, Dowd, & Aiello, 2009). The association of exposure to persistent viral infections with CRP among MA women of childbearing age remains unexplored even though many risk factors that are associated with differential outcomes of viral infections, including low socioeconomic level (J. Dowd, Hann, Blythe, Moore, & Aiello, 2008; J. Dowd & Aiello, 2009; Stowe et al., 2010) and lipid abnormalities (Khoretonenko, Leskov, Jennings, Yurochko, & Stokes, 2010; Ludewig, Krebs, & Scandella, 2004; Maekawa et al., 2011), are

highly prevalent in MA women of childbearing age (Daviglus et al., 2012; Kieffer et al., 2013; Ruiz, Dolbier, & Fleschler, 2006).

In contrast to the majority of their White and Black American counterparts, many MA women of childbearing age undergo significant social and lifestyle transitions related to immigration to the U.S. The average age at immigration to the U.S. for MAs is 21 years (Holguin et al., 2005) and more than 50% of all births among MAs are to immigrant mothers (Pew Research Center, 2011). Implications of these transitions for inflammation status among MA women of childbearing age remain unexamined. In prior studies of MA and Hispanic adults, acculturation level has been shown to be significantly associated with CRP levels, with U.S.-born MAs exhibiting higher levels of CRP than Mexico-born MAs (Crimmins, Kim, Alley, Karlamangla, & Seeman, 2007; Rodriguez, Peralta, Green, & Lopez, 2012). Based on the studies of composite cardiovascular, metabolic, and inflammatory biomarker measures, longer length of residence in the U.S. is associated with increased biological risks among Mexican-born MA adults (Crimmins et al., 2007; Kaestner, Pearson, Keene, & Geronimus, 2009; Peek et al., 2010). Therefore, the role of acculturation in modifying the association of parity and viral exposure burden with CRP also needs to be examined.

B. **Purpose of the Study**

The overall purpose of this thesis was to examine the associations of two prevalent but understudied risk factors among MA women, parity and viral exposure burden, with the systemic inflammatory marker, CRP. To achieve this goal, we conducted two separate analyses. The aims of the first analysis were to: (1) examine the association of parity status with CRP, after accounting for socioeconomic, lifestyle, and health-related risk factors; and (2) examine whether

acculturation modifies the association of parity with CRP. The aims of the second analysis were to: (1) examine the association of viral exposure burden with CRP, after accounting for socioeconomic, reproductive, and health-related variables; (2) examine whether reproductive (parity status, history of birth control pill use), country of birth, and total cholesterol factors modify the association of viral exposure burden with CRP among MA women of childbearing age.

II. PARITY IS ASSOCIATED WITH ELEVATED C-REACTIVE PROTEIN AMONG LOW ACCULTURATED MEXICAN AMERICAN WOMEN OF CHILDBEARING AGE

A. Introduction

There is growing recognition that physiological stresses of pregnancy, including significant increases in dyslipidemia, insulin resistance, immune function changes, and complex hemodynamic adaptations (Denison, Roberts, Barr, & Norman, 2010; Sacks & Redman, 1999; Schmaltz, Madan, Marino, & Davis, 2010), may unveil or potentiate health vulnerabilities in women (Catalano, 2010; Kaaja & Greer, 2005). Increasing emphasis has been placed on the identification and treatment of women at risk from childbearing-related health complications, such as infections, gestational diabetes and hypertension, before, between, and after births, to prevent the development of chronic diseases (Lu et al., 2006; Pina, 2011; Rich-Edwards, Fraser, Lawlor, & Catov, 2014). There is accumulating evidence that exposure to maternal inflammation in utero may contribute to the development of childhood obesity and diabetes through fetal programming mechanisms (Heerwagen et al., 2010; Schmatz et al., 2010; Segovia et al., 2014). In addition, elevated inflammation profile, as measured by a systemic inflammatory marker CRP, significantly raises women's risk for CVD, diabetes, and cognitive decline (Kuo et al., 2005; Ridker, 2009; Wang et al., 2013). In this context, the association of history of pregnancy with a live birth, defined as parity ("Parity," n.d.), with CRP among women of childbearing age needs examination. Further, the relationship of parity with CRP in Hispanic women is understudied.

Mexican American (MA) women of childbearing age currently have higher birth rates than females from other major U.S. ethnic/racial groups (Pew Research Center, 2011) and

exhibit one of the highest levels of CRP among similarly aged women in the U.S. (Danner et al., 2003; E. S. Ford et al., 2004; Ramos & Olden, 2008). During childbearing years, MA women experience the greatest lifetime increases in inflammation-linked metabolic conditions, such as diabetes (Schneiderman et al., 2014) and metabolic syndrome (Heiss et al., 2014; Mozumdar & Liguori, 2011). In contrast to the majority of their White and Black American counterparts, many MA women of childbearing age undergo significant social and lifestyle transitions related to immigration to the U.S. The average age at immigration to the U.S. for MAs is 21 years (Holguin et al., 2005) and more than 50% of all births among MAs are to immigrant mothers (Pew Research Center, 2011). Implications of these transitions for inflammation status among MA women of childbearing age remain unexamined.

1. Parity and inflammation

Accumulating evidence supports a physiological link between pregnancy and inflammation. Inflammatory pathways regulate normal reproductive processes, including labor and birth (Jabbour et al., 2009), and pregnancy is associated with a natural upregulation of CRP levels compared to the non-pregnancy state (Belo et al., 2005; Kuzawa et al., 2013; E. M. Miller, 2009). Prospective studies have shown that parity is independently associated with metabolic syndrome (E. Gunderson et al., 2009) and carotid atherosclerosis (Skilton et al., 2009; Skilton et al., 2010) among young and middle-aged women. Experimental evidence shows that the restoration of normal immune function following a pregnancy takes place over one year following delivery (Watanabe et al., 1997). Existing epidemiological data on CRP levels in the postpartum period show that, in uncomplicated pregnancies, CRP levels are normal (< 3.0 mg/L) within weeks of delivery (Christian & Porter, 2014; M. E. Groer, Jevitt, & Ji, 2015; Kew et al., 2014; Winzer et al., 2004). Given the possibility of significant social and lifestyle transitions

during the first year after childbirth among some MA women, as well as biological significance of this period for the resolution of pregnancy-associated immune changes, a close examination of MA women in the first year after childbirth is needed.

2. Parity and inflammation: potential pathways for the association

A better understanding of factors that explain parity-CRP association will help in designing appropriate prevention strategies. First, parity may contribute to CRP elevations through its well-documented association with short- and long-term weight gain (Rooney, Schauberger, & Mathiason, 2005) and increases in abdominal obesity (E. P. Gunderson et al., 2008; Lassek & Gaulin, 2006). Adiposity, especially abdominal, is a significant determinant of CRP among women (Berrahmoune et al., 2008; Khera et al., 2009; Thorand et al., 2006) because adipose tissue generates CRP precursors, IL-6 and TNF-alpha (Bastard et al., 1999; Yudkin, Stehouwer, Emeis, & Coppack, 1999). Some researchers have proposed that in the setting of obese pregnancy the concurrent stimulation of inflammation by adipose and placental sources may lead to an "over-taxing" and dysregulation of the inflammatory regulatory mechanisms (Catalano, 2010; Power & Schulkin, 2012; Rebholz et al., 2012). Persistent post-partum CRP elevations in the weeks following birth have been observed in obesity-complicated pregnancies (Christian & Porter, 2014). A significant proportion of Hispanic and MA women experience parity-associated weight gain (Davis, Zyzanski, Olson, Stange, & Horwitz, 2009).

Second, the association of parity with CRP may be explained by socioeconomic and lifestyle aspects of childbearing. Previous prospective and cross-sectional studies found that the associations of parity with traditional coronary heart disease risk factors (Hardy, Lawlor, Black, Wadsworth, & Kuh, 2007) and coronary heart disease (Lawlor et al., 2003) among middle-aged and older women were significantly reduced after the adjustment for behavioral and

socioeconomic factors. MA women are more likely to be in low socioeconomic groups (Morales, Lara, Kington, Valdez, & Escarce, 2002). Significant acculturation-related variations in dietary (Batis, Hernandez-Barrera, Barquera, Rivera, & Popkin, 2011; Duffey, Gordon-Larsen, Ayala, & Popkin, 2008), smoking (Wilkinson et al., 2005), physical activity (Crespo, Smit, Carter-Pokras, & Andersen, 2001; Evenson, Sarmiento, & Ayala, 2004), and breastfeeding behaviors (Ahluwalia, D'Angelo, Morrow, & McDonald, 2012; Gibson-Davis & Brooks-Gunn, 2006; Gill, 2009; Harley, Stamm, & Eskenazi, 2007) in this population have been also reported. Low socioeconomic status has been shown to account for increased inflammation risk among Mexico-born MA adults, when compared to White adults (Crimmins et al., 2007). CRP elevations have also been linked to high fat and low fiber dietary patterns (Heidemann et al., 2005; Lopez-Garcia et al., 2004), chronic stress (Coussons-Read, Okun, & Nettles,2007; Gallo, Jimenez, Shivpuri, Espinoza de los Monteros, & Mills, 2011; Johnson, Abbasi, & Master, 2013), and poor oral health (Horton et al., 2008; Pitiphat et al., 2006) among women. Lastly, breastfeeding is associated with high energy demands and increased body fat utilization (Dufour & Sauther, 2002; Zafon, 2007) and may be related to CRP though its influence on weight regulation (Stuebe et al., 2010).

3. The role of acculturation

Prior literature shows that acculturation modifies inflammation levels among Hispanic and MA adults. In a study based on NHANES, Hispanic adults aged 20 years and older who predominantly used Spanish language had significantly lower CRP levels, compared with individuals who predominantly used English language (Rodriguez et al., 2012). In another NHANES study of adults 40 years and older, Mexico-born MAs had significantly lower inflammatory marker levels compared to U.S.-born MAs (Crimmins et al., 2007). Longer

duration of residence in the U.S. has been linked with a less favorable biological marker profile among Mexico-born adults (Kaestner et al., 2009; Peek et al., 2010).

Given the temporal overlap between acculturation and childbearing, the role of acculturation as a potential modifier of the association between parity and CRP among MA women of childbearing age needs examination. Acculturation may modify CRP levels in MA women through its association with such inflammation-linked risk factors as stress (Johnson et al., 2013) and lifestyle changes (Bazzano, He, Muntner, Vupputuri, & Whelton, 2003; Heidemann et al., 2005; Lopez-Garcia et al., 2004). Acculturation has been associated with stress and negative environmental exposures among Latino immigrants (D'Alonzo, Johnson, & Fanfan, 2012). As mentioned previously, a significant patterning in lifestyle behaviors by acculturation level among MA women is observed (Ahluwalia et al., 2012; Batis et al., 2011; Crespo et al., 2001; Duffey, Gordon-Larsen et al., 2008; Evenson et al., 2004). Lastly, multiparity, which has been associated with greater cardiovascular risk (Humphries et al., 2001; Skilton et al., 2009), is more common among Mexico-born MA women compared to U.S.-born MA women (Parrado & Morgan, 2008).

Prior research suggests that parity may be associated with CRP among MA women of childbearing age, however, no previous study has examined this association. A better understanding of this relationship may promote early identification and prevention of chronic diseases among MA women and their offspring. Therefore, the aims of this study were to: (1) examine the association of parity status with CRP, after accounting for socioeconomic, lifestyle, and health-related risk factors; and (2) examine whether acculturation modifies the association of parity with CRP.

B. Methods

1. Study population

Data from the NHANES (1999-2006) were used. NHANES uses a complex multistage sampling design to collect socio-demographic, behavioral, dietary, laboratory, physical, and health-related data from a nationally representative sample of civilian, non-institutionalized U.S. residents. NHANES interviews are conducted in participants' homes, while physical examination and laboratory measurements are performed by trained physicians and technicians in the Mobil Examination Centers (MEC). Additional information about NHANES MEC examination and laboratory procedures is available elsewhere (CDC, 2014; CDC, 2009). The current study included non-pregnant MA women ages 16 to 49 years who were examined at the NHANES MEC and for whom data on reproductive history were available. Pregnant women (N=349) were excluded because pregnancy is associated with adaptive CRP elevations and CRP levels vary over the course of pregnancy (Belo et al., 2005; E. M. Miller, 2009). An additional 46 participants who reported a previous pregnancy without a live birth were excluded because the data on the reasons and the timing of pregnancy termination were not available. A total of 1,420 of eligible participants had valid reproductive and CRP data. Sample sizes varied in bivariate analyses based on availability of data. The final logistic regression models were based on 1,243 participants for whom complete data on the main exposure, outcome, and covariate variables were available. This secondary data analysis study was determined as exempt by the University of Illinois at Chicago Institutional Board of Review.

2. Main Variables of Interest

a. Parity status

A parity status categorical variable was created based on the answers to two survey questions: (1) "Have you ever been pregnant?" and (2) "How many of your pregnancies/deliveries resulted in a live birth?" Participants were categorized as "parous" is they reported at least one live birth and "nulliparous" if they reported that they had never been pregnant. Parous women were further divided into two categories: "A history of live birth within one year" and "A history of live birth more than one year ago," based on the time since the last live birth. The time since the last live birth was the difference between the participant's age at the time of the MEC exam and the age of the last live birth, both measured in years. The age of the last birth was measured based on the answer to the survey question:"How old were you at the time of your last birth?" Multiparous women were defined as participants who reported a history of four or more live births, based on previously published evidence (Humphries et al., 2001; Skilton et al., 2009).

b. C-reactive protein

Serum high sensitivity CRP (hsCRP) levels were measured using latex-enhanced nephelometry technique. Details regarding CRP laboratory methods have been previously reported (CDC, 2011). A dichotomous CRP variable was created based on the current clinical guidelines (Pearson et al., 2003) . Low risk (< 9.5 mmol/L (<1.0 mg/L)) and average risk CRP (9.5-28.6 mmol/L (1.0-3.0 mg/L)) categories were combined into the normal category (≤ 28.6 mmol/L (≤3.00 mg/L)) and compared to the high risk category (28.7-95.2 mmol/L (3.01-10.00 mg/L)).

c. **Acculturation**

Similar to a previously published report (Kandula et al., 2008), an acculturation scale was constructed based on nativity status, duration of residence in the U.S., and predominant language use at home. First, nativity status and duration of residence in the U.S. were scored as: 3 (U.S. born), 2 (Mexico-born and duration of U.S. residence ≥20 years), 1 (Mexico-born and duration of U.S. residence 10–19 years), and 0 (Mexico-born and duration of U.S. residence < 10 years). Second, a predominant language use at home was scored as: 2 (English only), 1 (English and Spanish), 0 (Spanish only). The sum of two sub-scale scores yielded a total score (range 0-5), with lower scores indicating lower level of acculturation. Acculturation was further categorized as low (score 0-1), moderate (score 2-3) and high (score 4-5) levels.

3. **Covariates of Interest**

a. **Socioeconomic variables**

Age in years was used as a continuous variable. Educational level was categorized as: less than high school, high school or higher level. Access to health care was defined as a positive response to the question: "Is there a place that you usually go when you are sick or need advice about your health?" Similar to previously published methods (Bate, Dollard, & Cannon, 2010), household density was defined as the total number of persons in the household divided by the number of rooms in the house. It was categorized as "average" if a household had ≤1 person per room and "crowded" if a household had >1 person per room. Household food security for the last 12 months was assessed based on the 18-item U.S. Household Food Security Survey Module (FSSM) (Bickel, Nord, Price, Hamilton, & Cook, 2000) administered during the NHANES Household interview. Food security categories, as provided by the NHANES,

included: fully food secure, marginally food secure, low food security, and very low food security.

b. **Lifestyle variables**

Smoking status was operationalized as serum cotinine levels. Using previously published criteria (Benowitz, Bernert, Caraballo, Holiday, & Wang, 2009), participants were defined as non-smokers (serum cotinine <17.0 nmol/L (< 3.0 ng/mL)) and smokers (≥ 17.0 nmol/L (≥3.0 ng/mL)). Dietary data came from the first 24-hour dietary recall interview at the MEC, which was performed across all examined NHANES data cycles. Additional details on dietary data collection methods can be found elsewhere (CDC, 2013a). Diet was assessed using two variables; daily total intake of total fat (in grams) and daily total intake of fiber (in grams), which were used in the analysis as continuous variables. Physical activity was defined as the sum of activity minutes per week from three activity domains (household/yard, transportation, and leisure-time). Activity minutes were categorized as: "Does not meet guideline recommendations" and "Meets or exceeds guideline recommendations", according to the national physical activity guidelines (U.S. Department of Health and Human Services, 2008). History of birth control pill use was determined by the response to the question: "Have you ever taken birth control pills for any reason?" (Yes/No).

c. **Health-related variables**

Participants' waist circumference was measured by trained examiners using standard NHANES protocols (CDC, 2005). Consistent with gender-specific Centers for Disease Control and Prevention (CDC) guidelines (CDC, 2015), waist circumference was categorized as low risk (≤88 cm) and high risk (>88 cm). Total cholesterol and high density lipoprotein cholesterol (HDL-cholesterol) were measured in serum. According to the National

Cholesterol Education Program criteria (U.S. Department of Health and Human Services [U.S. DHHS], 2001), total cholesterol was characterized as normal (< 5.18 mmol/L (<200 mg/dL)) and elevated (≥ 5.18 mmol/L (≥200 mg/dL)) and HDL-cholesterol as normal (≥1.30 mmol/L (≥50 mg/dL)) and low (< 1.30 mmol/L (<50 mg/dL)). Participants were categorized as having normal Hemoglobin A1c (HgA1c) levels (<5.7%) and levels indicative of pre-diabetes/diabetes (≥5.7%), according to the published professional guidelines (American Diabetes Association, 2014). The pre-diabetes and diabetes categories were combined in the analysis because of small cell sizes. A history of high blood pressure diagnosis was measured based on the response to the questions: "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" (Yes/No). Perceived oral health status was assessed by the answer to the question: "How would you describe the condition of your mouth and teeth?" Categorical responses included: very good, good, fair, poor. Perceived oral health status was only examined in a subsample of NHANES 1999-2002 participants, because of inconsistencies in measurement across examined NHANES surveys. An ordinal variable was created to describe recent illness status during the past 30 days, based on the participants' responses to three questions assessing the experience of (1) head or chest cold; (2) stomach or intestinal illness; and (3) flu, pneumonia or ear infection during the past 30 days. The variable responses ranged from 0 (no recent illness) to 3 (a history of 3 recent illnesses). Similar to prior published reports (Zajacova et al., 2009; J. Zhu et al., 2000b), viral exposure burden was defined as the sum of seropositive status scores (1=positive, 0=negative) for three viral pathogens, Herpes Simplex virus type1, Herpes Simplex virus type 2, and Hepatitis B virus. Participants were defined as "seronegative", if they had negative tests for all three viral agents, or "seropositive", if they were seropositive for at least one viral infection. Viral infection burden was further categorized as "low" if the participant was

seropositive for one infection and "high" if the participant was seropositive for two or three infections. The analysis of viral exposure was limited to participants ages 18 -49 years for whom data on viral exposures are publically available. Detailed information on the NHANES procedures on specimen collection and laboratory analysis can be found elsewhere (CDC, 2009).

d. **Current breastfeeding status**

Current breastfeeding status was assessed among women who had a live birth one year ago or less. It was measured based on the answer to the question, "Are you now breastfeeding a child?" (Yes/No).

4. **Statistical Analysis**

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). Chi-squared statistics were used to examine the bivariate associations of parity and CRP status with categorical socioeconomic, lifestyle, and health-related variables. Linear regression was used to examine the bivariate associations of continuous variables (age, number of pregnancies resulting in live birth, total fat and fiber intake) with parity and CRP status. Binary logistic regression was used to examine the association of parity with CRP, after adjustment for socioeconomic (age, educational levels, access to healthcare, household density, household food security), lifestyle (smoking status, physical activity, total fat intake, total fiber intake, a history of birth control pill use), and health-related factors (waist circumference, total cholesterol, HDL-cholesterol, HgA1c status, a history of high blood pressure diagnosis). These variables were included in the final models because they are considered important covariates based on the literature. To examine whether acculturation modifies the association of parity with CRP, we entered a parity by acculturation product term in the final logistic regression model.

Variables with data restrictions (viral exposure status, breastfeeding status) or inconsistent data across the surveys (perceived oral health), as well as recent acute illness status, were examined in sub-analyses. Binary logistic regression was used to examine whether the association of parity status with CRP was additionally explained by these variables, after adjustment for socioeconomic, lifestyle, and health-related factors. Because of the limited sample size, linear regression was used to examine whether current breastfeeding status is associated with mean CRP levels among women with a history of live birth within the past year, after adjustment for age and waist circumference. CRP values were log transformed because of positive skewness of CRP data. In addition, two sensitivity analyses were performed. Since the association of parity status with CRP by multiparity levels could not be examined because of the limited sample size, we re-examined this association after excluding women with four or more births (n=60). In the second sensitivity analysis, we excluded participants with CRP >95.24 mmol/L (>10.0 mg/L) (n=137), which may be indicative of an ongoing acute infection or a condition (Gabay & Kushner, 1999; Pearson et al., 2003).

All crude and adjusted multiple logistic regression analyses were restricted to participants with complete data on all the variables used in the logistic regression models. All sub-population statistics were calculated in domain analysis and all variance estimates were adjusted based on sample weights provided by NHANES. We used combined 8-year interview, MEC exam, and dietary sample weights, which were constructed using NHANES-provided guidelines (CDC, 2013b). Additional information of NHANES analytical guidelines is available elsewhere (Johnson et al., 2013).

C. **Results**

Of the participants for whom reproductive history data were available, 8.2 % had a live birth within one year, 65.8 % had a live birth more than one year ago, and 26.0% were nulliparous. The characteristics of women by parity status are listed in Table I. Parity was associated with an increased prevalence of elevated CRP ($p<0.001$). Women who had a live birth within one year had a higher prevalence of elevated CRP compared to the women who had a live birth more than one year ago and nulliparous women (53.8% vs. 46.9% vs. 31.5%, $p<0.001$). Compared to nulliparous women, parous women were more likely to have lower educational levels and acculturation levels, low or very low household food security, and were more likely to live in crowded households. Parous women were also more likely to be physically inactive and have a history of birth control pill use. Compared to nulliparous women, parous women were more likely to have high risk waist circumference, abnormal total cholesterol, HgA1c consistent with pre-diabetes/diabetes status, a history of high blood pressure diagnosis, poor oral health, and a history of viral exposure. The mean number of pregnancies resulting in live births was greater among women with a history of live birth more than one year ago compared to women with a history of birth within one year ($p=0.035$). Among women with a history of birth within one year, 44.5% were currently breastfeeding (not tabulated).

TABLE I

PARTICIPANT CHARACTERISTICS BY PARITY STATUS

Variable	n	Parous, ≤1 year %	Parous, > 1 yr %	Nulliparous %	P-value[a]
	Categorical variables				
CRP	1,420				
Normal		46.2	53.1	68.5	<0.001
Elevated		53.8	46.9	31.5	
Educational Level	1,442				0.006
Less Than High School		54.4	53.3	43.2	
High School and Higher		45.6	46.7	56.8	
Access to Health Care	1,474				0.831
Yes		75.1	73.7	71.9	
No		24.9	26.3	28.1	
Household Density	1,474				0.007
Average		58.9	72.2	77.5	
Crowded		41.1	27.8	22.5	
Household Food Security	1,417				0.002
Fully Food Secure		45.4	57.1	70.7	
Marginally Secure		19.3	13.7	12.2	
Low Food Security		28.0	23.8	13.7	
Very Low Food Security		7.3	5.4	3.4	

(continued)

TABLE I (continued)

PARTICIPANT CHARACTERISTICS BY PARITY STATUS

Variable	n	Parous, ≤1 year %	Parous, > 1 yr %	Nulliparous %	P-value[a]
Acculturation Score	1,457				<0.001
0		31.9	24.6	14.9	
1		16.6	14.2	9.6	
2		6.6	13.5	6.4	
3		8.2	9.8	5.2	
4		19.5	21.4	32.6	
5		17.1	16.5	31.3	
Birth Control Pill Use	1,473				<0.001
Yes		68.0	66.9	29.7	
No		32.0	33.1	70.3	
Smoking Status	1,411				0.934
Non-smoker		87.7	86.1	86.4	
Smoker		12.3	13.9	13.6	
Physical Activity	1,474				<0.001
Below Recommended Level		67.8	54.8	40.7	
Meets or Exceeds Recommended Level		32.2	45.2	59.3	
Waist Circumference	1,453				<0.001
Low Risk		40.0	37.5	62.0	
High Risk		60.0	62.5	38.0	

(continued)

TABLE I (continued)

PARTICIPANT CHARACTERISTICS BY PARITY STATUS

Variable	n	Parous, ≤1 year %	Parous, > 1 yr %	Nulliparous %	P-value[a]
Hemoglobin A1c	1,427				<0.001
Normal		95.5	85.8	91.4	
Pre-diabetes/Diabetes		4.5	14.2	8.6	
Total Cholesterol	1,416				<0.001
Normal		64.8	65.3	81.0	
Elevated		35.2	34.7	19.0	
HDL Cholesterol	1,416				0.321
Normal		56.5	50.9	56.3	
Low		43.5	49.1	43.7	
History of High Blood Pressure Diagnosis	1,413				<0.001
Yes		6.6	12.8	5.1	
No		93.4	87.2	94.9	
Perceived Oral Health	841				<0.001
Very Good		8.4	12.4	21.0	
Good		35.0	27.8	44.4	
Fair		45.5	42.1	27.5	
Poor		11.1	17.7	7.1	

(continued)

TABLE I (continued)

PARTICIPANT CHARACTERISTICS BY PARITY STATUS

Variable	n	Parous, ≤1 year %	Parous, > 1 yr %	Nulliparous %	P-value[a]
Illness During the Past 30 Days	1,473				0.833
0		70.6	62.9	69.1	
1		23.8	25.3	24.6	
2		5.3	6.2	5.1	
3		0.3	0.6	1.3	
Viral Exposure Burden	1,114				<0.001
Seronegative		12.4	7.1	29.4	
Low		81.7	75.8	67.9	
High		5.8	17.1	2.7	
Continuous variables					
Age	1,474	27.5(0.7)	35.3(0.3)	23.4(0.5)	<0.001
Number of Live Births	852	2.3(0.1)	2.6(0.0)		0.035
Total Fat	1,439	73.5(6.1)	73.5(6.1)	71.2(2.3)	0.927
Fiber	1,439	16.8(1.4)	16.3(0.6)	14.4(0.6)	0.065

Note. Variable sample sizes vary because of data availability or data restriction.

[a] Based on the Rao-Scott Modified Chi-Square test for categorical variables and linear regression for continuous variables, treating parity status as independent variable and continuous variables as the outcome variable.

Table II. shows participants' characteristics by CRP status. Compared to women with normal CRP, women with elevated CRP were older and were more likely to have high risk waist circumference, HgA1c consistent with pre-diabetes/diabetes status, elevated total cholesterol, low HDL-cholesterol, and history of high blood pressure diagnosis. Women with elevated CRP also had higher acculturation levels and were more likely to report a history of birth control pill use, compared to women with normal CRP. CRP status was not significantly associated with educational level, access to health care, household density, household food security, perceived oral health, the mean total number of live births, smoking, physical activity, diet variables. Current breastfeeding status was not significantly associated with CRP status (not tabulated).

TABLE II

PARTICIPANT CHARACTERISTICS BY CRP STATUS

Variable	n	Normal %	Elevated %	P-value[a]
Categorical variables				
Educational Level	1,598			0.607
Less Than High School		49.9	57.1	
High School and Higher		50.1	48.9	
Access to Health Care	1,633			0.240
Yes		71.8	75.2	
No		28.2	24.8	
Household Density	1,633			0.605
Average		72.3	70.7	
Crowded		27.7	29.3	
Household Food Security	1,575			0.315
Fully Food Secure		62.0	56.3	
Marginally Secure		13.0	13.3	
Low Food Security		19.7	23.7	
Very Low Food Security		5.3	6.7	
Acculturation Score	1,616			0.008
0		23.8	20.0	
1		15.0	11.8	
2		8.8	14.9	
3		8.8	8.4	
4		21.4	27.1	
5		22.3	17.7	
Birth Control Pill Use	1,483			<0.001
Yes		52.9	64.0	
No		47.1	36.0	
Smoking Status	1,624			0.431
Non-smoker		86.4	87.8	
Smoker		13.6	12.2	
Physical Activity	1,633			0.502
Below Recommended Level		51.1	53.5	
Meets or Exceeds Recommended Level		48.9	46.5	
Waist Circumference	1,596			<0.001
Low Risk		61.1	21.6	
High Risk		38.9	78.4	

(continued)

TABLE II (continued)

PARTICIPANT CHARACTERISTICS BY CRP STATUS

		Normal	Elevated	
Variable	n	%	%	P-value[a]
Hemoglobin A1c	1,632			<0.001
Normal		94.0	80.6	
Pre-diabetes/Diabetes		6.0	19.4	
Total Cholesterol	1,627			0.038
Normal		72.3	65.8	
Elevated		27.7	34.2	
HDL Cholesterol	1.627			<0.001
Normal		60.0	45.5	
Low		40.0	54.5	
History of High Blood Pressure Diagnosis	1,591			0.003
Yes		8.4	14.3	
No		91.6	85.7	
Perceived Oral Health	923			0.144
Very Good		17.1	12.2	
Good		33.9	31.9	
Fair		34.0	43.2	
Poor		15.0	12.7	
Illness During the Past 30 Days	1,487			<0.001
0		72.5	62.1	
1		23.5	27.5	
2		3.5	9.4	
3		0.5	1.0	
Viral Exposure Burden	1,280			0.590
Seronegative		13.3	11.3	
Low		73.8	75.7	
High		12.9	13.0	
Continuous variables				
Age	1,630	30.6(0.4)	32.8(0.4)	<0.001
Number of Live Births	877	2.4(0.1)	2.5(0.1)	0.372
Total Fat	1,560	71.3(1.9)	72.4(3.0)	0.747
Fiber	1,560	15.5(0.4)	16.4(0.5)	0.126

Note. Variable sample sizes vary because of data availability or data restriction.
[a] Rao-Scott Modified Chi-Square for categorical and linear regression for continuous variables.

1. **The association of parity status with CRP with interaction assessment**

Compared to nulliparous women, a history of live birth within one year was associated with elevated CRP in an age-adjusted model, (OR =2.22, 95% CI 1.39-3.50). This association became attenuated after adjustment for socioeconomic, lifestyle, and health-related variables (OR=1.80, 95% CI 0.99-3.25). Similarly, compared to nulliparous women, a history of live birth more than one year ago was associated with elevated CRP in an age-adjusted model (OR=1.51 95% CI 1.01-2.27). This association was markedly attenuated and became non-significant after adjustment for socioeconomic, lifestyle, and health-related variables (OR=1.25 95% CI 0.77-2.05). When we entered the parity by acculturation product term in the final logistic regression model, we found a statistically significant interaction between parity and acculturation (P for interaction =0.045) (Table III). Therefore, we stratified our subsequent analysis by acculturation categories.

TABLE III

ASSOCIATION OF PARITY STATUS WITH CRP AMONG MEXICAN AMERICAN WOMEN[a]

	Crude		Adjusted		Adjusted	
Variable	OR	95% CI	OR	95% CI	OR	95% CI
Parity Status						
Live Birth Within One Year	2.22	[1.39, 3.50]	1.80	[0.99, 3.25]	--	--
Live Birth More Than One Year Ago	1.51	[1.01, 2.27]	1.25	[0.77, 2.05]	--	--
Nulliparous	1.00		1.00		--	--
Age	1.02	[1.01, 1.04]	0.99	[0.97, 1.01]	0.99	[0.97, 1.01]
Less Than High School Educational Level			1.01	[0.74, 1.38]	1.01	[0.74, 1.39]
No Access to Health Care			1.12	[0.77, 1.62]	1.08	[0.74, 1.60]
Crowded Household Density			1.03	[0.70, 1.52]	1.03	[0.70, 1.52]
Very Low Household Food Security (vs. Fully Secure)			0.78	[0.39, 1.54]	0.73	[0.36, 1.47]
Below Recommended Physical Activity Level			0.99	[0.72, 1.35]	0.99	[0.71, 1.36]
Smoker			1.38	[0.85, 2.25]	1.40	[0.86, 2.30]
Fiber			1.00	[0.99, 1.02]	1.00	[0.98, 1.02]
Total Fat			1.00	[0.99, 1.00]	1.00	[0.99, 1.00]
History of Birth Control Pill Use			1.44	[1.04, 1.99]	1.50	[1.07, 2.09]
Pre-diabetes/Diabetes HgA1c Level			2.47	[1.38, 4.41]	2.48	[1.37, 4.47]
Low HDL Cholesterol			1.67	[1.21, 2.24]	1.69	[1.26, 2.28]
Elevated Total Cholesterol			1.11	[0.79, 1.57]	1.11	[0.79, 1.50]
History of High Blood Pressure Diagnosis			0.96	[0.64, 1.44]	0.98	[0.65, 1.48]
High Risk Waist Circumference			4.81	[3.42, 6.67]	4.87	[3.48, 6.80]

(continued)

TABLE III (continued)

ASSOCIATION OF PARITY STATUS WITH CRP AMONG MEXICAN AMERICAN WOMEN[a]

	Crude		Adjusted		Adjusted	
Variable	OR	95% CI	OR	95% CI	OR	95% CI
Acculturation Level						
Low			0.81	[0.47, 1.38]	--	--
Moderate			1.11	[0.66, 1.86]	--	--
High			1.00			
Acculturation x Parity Status[b]				P interaction		0.045

Note. OR = odds ratio; CI = confidence interval.
[a] N=1,243. Analysis is based on the participants with complete data on all variables in the models.
[b] Stratified ORs are presented in Tables IV, V, and VI.

2. **The association of parity status with CRP: women with low acculturation level**

The results of logistic regression analyses for the low acculturation level are shown in Table IV. Compared to nulliparous women, a history of live birth within one year was associated with elevated CRP in an age-adjusted Model 1, (OR =6.32, 95% CI 2.91-13.71). This association became modestly attenuated after adjustment for socioeconomic variables (OR=5.88, 95% CI 2.56-13.50) (Model 2), remained largely unchanged after adjustment for lifestyle variables (OR =5.91, 95% CI 2.17-16.08) (Model 3), and strengthened after the further adjustment for health-related variables (OR=7.83, 95% CI 2.67-22.99) (Model 4). The association of a history of live birth within one year with elevated CRP was markedly attenuated but remained significant after the addition of waist circumference in the final Model 5, (OR=5.81, 95% CI 1.87-18.03).

Compared to nulliparous women, a history of live birth more than one year ago was associated with elevated CRP in an age-adjusted Model 1, (OR=3.35, 95% CI 1.59-7.07). This association became modestly attenuated after adjustment for socioeconomic variables (OR=2.66, 95% CI 1.20-5.92) (Model 2), largely unchanged after further adjustment for lifestyle variables (OR=2.64, 95% CI 1.10-6.34) (Model 3), and strengthened after further adjustment for health-related variables (OR =2.87, 95% CI 1.13-7.27) (Model 4). However, a history of live birth more than one year ago was no longer significantly associated with elevated CRP after the addition of waist circumference in the final Model 5, (OR 2.09, 95% CI 0.76-5.71).

In the fully adjusted logistic regression model, high risk waist circumference and HbA1c were independently associated with elevated CRP.

TABLE IV

ASSOCIATION OF PARITY STATUS WITH CRP AMONG WOMEN WITH LOW ACCULTURATION LEVEL[a]

`	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Live Birth ≤ 1 year	6.32	[2.91, 13.71]	5.88	[2.56, 13.50]	5.91	[2.17, 16.08]	7.83	[2.67, 22.99]	5.81	[1.87, 18.03]
Live Birth > 1 year	3.35	[1.59, 7.07]	2.66	[1.20, 5.92]	2.64	[1.10, 6.34]	2.87	[1.13, 7.27]	2.09	[0.76, 5.71]
Nulliparous	1.00		1.00		1.00		1.00		1.00	
Age	1.01	[0.98, 1.03]	1.01	[0.98, 1.04]	1.01	[0.98, 1.04]	1.00	[0.97, 1.04]	0.97	[0.95, 1.00]
< HS Education			1.40	[0.71, 2.79]	1.44	[0.70, 2.77]	1.38	[0.66, 2.88]	1.39	[0.62, 3.15]
No Access to HC			0.85	[0.48, 1.49]	0.85	[0.47, 1.54]	0.85	[0.48, 1.54]	0.86	[0.45, 1.66]
Crowded Density			0.95	[0.53, 1.69]	0.90	[0.46, 1.74]	1.05	[0.57, 1.94]	0.79	[0.41, 1.53]
Very Low Food Security			1.93	[0.77, 4.83]	2.02	[0.82, 4.99]	1.48	[0.63, 3.50]	1.75	[0.72, 4.24]
Below Recommended PA					0.93	[0.54, 1.60]	0.99	[0.56, 1.77]	0.88	[0.53, 1.47]
Smoker					0.70	[0.33, 1.51]	0.50	[0.22, 1.15]	0.59	[0.20, 1.78]
Fiber					1.01	[0.98, 1.03]	1.01	[0.98, 1.03]	1.01	[0.98, 1.04]
Total Fat					1.00	[0.99, 1.00]	1.00	[0.99, 1.00]	1.00	[0.99, 1.00]
Birth Control Pill Use					1.37	[0.88, 2.13]	1.39	[0.86, 2.25]	1.51	[0.84, 2.71]
Pre-/Diabetes HgA1c							4.81	[1.83, 12.35]	3.15	[1.16, 8.57]
Low HDL Cholesterol							2.28	[1.38, 3.77]	1.67	[0.96, 2.90]
Elevated TC							0.85	[0.52, 1.38]	0.92	[0.55, 1.52]
High BP Diagnosis							0.76	[0.26, 2.23]	0.63	[0.24, 1.71]
High Risk WC									5.74	[3.79, 8.68]

Note. OR = odds ratio; CI = confidence interval. HS = high school; HC = health care; PA = physical activity; TC = total cholesterol; BP = blood pressure; WC = waist circumference.

[a] N= 375. Analysis is based on the participants with complete data on all variables in the models.

3. **The association of parity status with CRP: women with moderate acculturation level**

The results of logistic regression analyses for the moderate acculturation level are shown in Table V. Compared to nulliparous women, a history of live birth more than one year ago was not associated with elevated CRP in an age-adjusted Model 1, (OR=1.57, 95% CI 0.33-7.51). This association remained non-significant in the fully adjusted Model 5, (OR=0.76, 95% CI 0.15-3.79). A history of live birth more than one year ago was not associated with CRP, in the age-adjusted (OR=1.99, 95% CI 0.75-5.25) (Model 1) and the fully adjusted model (OR=1.45, 95% CI 0.44-4.80) (Model 5).

In the fully adjusted logistic regression model, high risk waist and HbA1c, and a history of birth control pill use were independently associated with elevated CRP.

TABLE V

ASSOCIATION OF PARITY STATUS WITH CRP AMONG WOMEN WITH MODERATE ACCULTURATION LEVEL[a]

	Model 1		Model 2		Model 3		Model 4		Model 5	
Variable	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Live Birth ≤ 1 year	1.57	[0.33, 7.51]	1.18	[0.29, 4.78]	0.68	[0.13, 3.47]	0.80	[0.16, 3.97]	0.76	[0.15, 3.79]
Live Birth > 1 year	1.99	[0.75, 5.25]	1.77	[0.68, 4.63]	1.51	[0.54, 4.29]	1.76	[0.52, 5.96]	1.45	[0.44, 4.80]
Nulliparous	1.00		1.00		1.00		1.00		1.00	
Age	1.01	[0.96, 1.06]	1.01	[0.96, 1.06]	0.99	[0.94, 1.04]	0.97	[0.91, 1.02]	0.97	[0.91, 1.02]
< HS Education			1.52	[0.83, 2.79]	1.67	[0.88, 3.16]	1.56	[0.77, 3.17]	1.32	[0.61, 2.88]
No Access to HC			0.72	[0.35, 1.49]	0.82	[0.40, 1.71]	0.93	[0.36, 2.38]	1.01	[0.38, 2.72]
Crowded Density			0.96	[0.48, 1.91]	0.95	[0.48, 1.88]	0.78	[0.33, 1.85]	0.87	[0.36, 2.66]
Very Low Food Security			2.75	[0.42, 18.04]	4.17	[0.78, 27.28]	6.82	[1.13, 41.06]	5.50	[0.65, 46.51]
Below Recommended PA					0.72	[0.38, 1.38]	0.84	[0.40, 1.75]	0.79	[0.36, 1.71]
Smoker					0.88	[0.39, 1.96]	0.72	[0.27, 1.92]	0.65	[0.25, 1.70]
Fiber					0.99	[0.95, 1.03]	1.00	[0.96, 1.04]	0.99	[0.95, 1.04]
Total Fat					1.00	[0.99, 1.01]	1.00	[0.99, 1.01]	1.00	[0.99, 1.01]
Birth Control Pill Use					2.47	[1.04, 5.90]	2.75	[1.12, 6.79]	2.99	[1.21, 7.38]
Pre-/Diabetes HgA1c							5.33	[1.70, 16.79]	4.02	[1.21, 13.32]
Low HDL Cholesterol							2.82	[1.37, 5.79]	2.18	[0.91, 5.22]
Elevated TC							1.21	[0.60-2.44]	1.05	[0.47, 2.32]
High BP Diagnosis							2.18	[0.52-9.22]	1.91	[0.38, 9.75]
High Risk WC									2.81	[1.03, 7.70]

Note. OR = odds ratio; CI = confidence interval. HS = high school; HC = health care; PA = physical activity; TC = total cholesterol; BP = blood pressure; WC = waist circumference.

[a] N=234. Analysis is based on the participants with complete data on all variables in the models.

4. **The association of parity status with CRP: women with high acculturation level**

The results of logistic regression analyses for the high acculturation level are shown in Table VI. Compared to nulliparous women, a history of live birth more than one year ago was not associated with elevated CRP in an age-adjusted Model 1, (OR=1.59, 95% CI 0.88-2.81). This association remained non-significant in the fully adjusted Model 5 (OR=0.83, 95% CI 0.40-1.70). Similarly, a history of live birth more than one year ago was not associated with CRP, in the age-adjusted model (OR=1.19, 95% CI 0.73-1.92) (Model 1) and fully adjusted model (OR=1.12, 95% CI 0.97-1.04) (Model 5).

In the fully adjusted logistic regression model, high risk waist circumference was independently associated with elevated CRP.

TABLE VI

ASSOCIATION OF PARITY STATUS WITH CRP AMONG WOMEN WITH HIGH ACCULTURATION LEVEL[a]

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Live Birth ≤ 1 year	1.59	[0.88, 2.81]	1.45	[0.78, 2.67]	1.34	[0.73, 2.48]	1.17	[0.58, 2.38]	0.83	[0.40, 1.70]
Live Birth > 1 year	1.19	[0.73, 1.92]	1.13	[0.68, 1.89]	1.15	[0.71, 1.86]	1.17	[0.69, 2.00]	1.12	[0.60, 2.09]
Nulliparous	1.00		1.00		1.00		1.00		1.00	
Age	1.03	[1.01, 1.06]	1.04	[1.01, 1.06]	1.03	[1.01, 1.06]	1.02	[0.98, 1.04]	1.01	[0.97, 1.04]
< HS Education			0.84	[0.64, 1.11]	0.82	[0.62, 1.09]	0.75	[0.57, 1.00]	0.82	[0.59, 1.12]
No Access to HC			0.85	[0.54, 1.34]	0.83	[0.53, 1.31]	0.90	[0.59, 1.37]	1.03	[0.63, 1.68]
Crowded Density			1.37	[0.75, 2.51]	1.40	[0.76, 2.47]	1.41	[0.74, 2.71]	1.47	[0.70, 3.00]
Very Low Food Security			1.03	[0.30, 3.52]	1.07	[0.30, 3.78]	0.98	[0.25, 3.76]	0.57	[0.14, 2.26]
Below Recommended PA					1.30	[0.83, 2.05]	1.19	[0.74, 1.91]	1.15	[0.68, 1.97]
Smoker					1.02	[0.55, 1.90]	0.99	[0.51, 1.91]	0.99	[0.53, 1.85]
Fiber					1.00	[0.97, 1.03]	0.99	[0.96, 1.02]	1.00	[0.97, 1.02]
Total Fat					1.00	[1.00, 1.01]	1.00	[1.00, 1.01]	1.00	[0.90, 1.01]
Birth Control Pill Use					0.98	[0.62, 1.56]	1.10	[0.68, 1.77]	1.09	[0.66, 1.79]
Pre-/Diabetes HgA1c							2.40	[1.08, 5.33]	1.47	[0.66, 3.31]
Low HDL Cholesterol							2.34	[1.63, 3.35]	1.57	[0.98, 2.51]
Elevated TC							1.99	[1.08, 3.57]	1.62	[0.93, 2.83]
High BP Diagnosis							0.96	[0.46, 1.99]	0.92	[0.40, 2.11]
High Risk WC									6.04	[3.51, 10.2]

Note. OR = odds ratio; CI = confidence interval. HS = high school; HC = health care; PA = physical activity; TC = total cholesterol; BP = blood pressure; WC = waist circumference.

[a] N=634. Analysis is based on the participants with complete data on all variables in the models.

In the sub-analyses, additional adjustment for perceived oral health, viral exposure status, or recent acute illness status had no appreciable effect on the association between parity status and CRP. We found no difference in the mean CRP levels between currently breastfeeding and non-breastfeeding women with a history of live birth within one year. In the sensitivity analyses, the exclusion of multiparous women and participants with acute CRP levels did not change the results (not tabulated).

D. **Discussion**

Parity status was significantly associated with CRP among MA women of childbearing age with low level of acculturation. In this group, a history of live birth within one year was associated with a 5.81 increased odds of elevated CRP, compared to nulliparous women, after adjustment for age, socioeconomic, lifestyle, and health-related variables. A history of live birth more than one year ago was associated with a nearly three-fold risk of elevated CRP after adjustment for socioeconomic, lifestyle, and most health-related variables. This risk became attenuated and non-significant after adjustment for waist circumference. Among women with moderate and high acculturation level, parity status was not significantly associated with an increased risk of elevated CRP, regardless of time since last live birth.

To our knowledge, this is the first study to find a significant independent association between parity status and elevated CRP in a subpopulation of American women of childbearing age. Our results showing the association of parity with inflammatory risk among less acculturated recent mothers support our earlier hypothesis that a history of migration with acculturation may influence the relationship between parity and inflammation among MA women. Previous studies, which examined the association of parity with CRP, found no

significant association between these variables, however, were based on a small number of women of childbearing age (Clendenen et al., 2011) or a racially heterogeneous sample (Ramos & Olden, 2008).

Our study sought to examine a range of potential mechanisms that underlie the association of parity with elevated CRP. However, measured socioeconomic, lifestyle and health-related factors had limited explanatory power. Results suggest that excess inflammation risk among women with low acculturation level may be due to unmeasured factors, such as stress exposure and intra-pregnancy factors. The peripartum period is associated with psychological stress among populations of diverse women (Bener, Gerber, & Sheikh, 2012; Lara et al., 2015; Navarro et al., 2008) and there is substantial evidence linking psychological stress with elevated CRP (Coussons-Read et al., 2007; Johnson et al., 2013). According to qualitative reports, MA immigrant women report significant psychological stress related to loss of culturally valued family ties (Martinez-Schallmoser, MacMullen, & Telleen, 2005; Sanchez-Birkhead, Kennedy, Callister, & Miyamoto, 2011). Among recent immigrants, socioeconomic pressures on women to divide their time between work and childrearing, clash with the cultural norms in which Mexican mothers enjoy an elevated social status and communal support in their childrearing duties (Lagana, 2003). Experience of discrimination in society at large (Caplan, 2007) and within the healthcare setting (S. Guendelman, Thornton, Gould, & Hosang, 2006) by MA immigrants may serve as additional sources of psychological stress.

Unmeasured occurrence of gestational diabetes during pregnancy may also explain excess parity-associated inflammatory risk in the low acculturation group. Persistent CRP elevations in the weeks, months and years following births have been observed after gestational diabetes-complicated pregnancies (Di Benedetto et al., 2005; Di Cianni et al., 2007; Heitritter, Solomon, Mitchell, Skali-Ounis, & Seely, 2005; Winzer et al., 2004). Emerging evidence shows

that foreign-born MA women of childbearing age are at greater risk for gestational diabetes compared to U.S.-born MA women of similar age (Ramadhani et al., 2011; Savitz, Janevic, Engel, Kaufman, & Herring, 2008), and that living within an ethnic enclave is associated with greater risk of gestational diabetes among immigrant MA women (Janevic, Borrell, Savitz, Echeverria, & Rundle, 2014). Although the likelihood of significantly elevated CRP levels (>3.0 mg/L) in post-gestational diabetes pregnancies is higher among obese women (Di Benedetto et al., 2005; Di Cianni et al., 2007; Winzer et al., 2004) and we controlled for abdominal obesity in our analyses, residual effects from insulin resistance during pregnancy may remain. Prior evidence indicates a lack of consistent association between obesity and insulin resistance among childbearing age MA women (Marcinkevage et al., 2013) and MA adults (Lorenzo, Lee, & Haffner, 2012; Zhang, Wang, & Huang, 2009).

A previous study reported that immigration history and psychological stress jointly predicted greater susceptibility to insulin resistance among African-Caribbean immigrants without diabetes (Tull, Thurland, LaPorte, & Chambers, 2003). Since normal pregnancy is accompanied by a nearly 60% decrease in insulin resistance (Catalano, 2010), recent immigrant mothers with stress exposure during and after pregnancy may be more vulnerable to unsuccessful resolution of pregnancy-associated insulin resistance which resulting persistent inflammation. Although this hypothesis cannot be tested in this cross-sectional study, it warrants an examination in future research studies.

Women with a history of live birth within a year were more likely to live in crowded and food insecure households and had lower educational and physical activity levels, compared to nulliparous women. Socioeconomic variables had a modest effect on the parity-associated inflammatory risk among recent mothers. These results are consistent with earlier studies showing minimal influence of socio-economic factors on CRP and cardiometabolic biomarkers

among middle aged and older MA/Hispanic adults (Crimmins et al., 2007; Kershaw, Mezuk, Abdou, Rafferty, & Jackson, 2010; Khan, Sobal, & Martorell, 1997; Ranjit et al., 2007). The impact of lifestyle variables was greater among moderately acculturated recent mothers than in low acculturated recent mothers. Previously, weak associations between lifestyle factors and various cardio-metabolic risk factors were shown among Mexican American adults (Crimmins et al., 2007; Kaestner et al., 2009; Peek et al., 2010; Rodriguez et al., 2012) and Mexican American women (Dinwiddie, Zambrana, & Garza, 2014). Since lifestyle modification is one of the cornerstones of health risk prevention (Bauer, Briss, Goodman, & Bowman, 2014), variations in the contribution of lifestyle variables on the association between parity and CRP by acculturation levels require further exploration.

As expected, waist circumference accounted for a significant amount of risk in the association of parity with CRP and was the most significant independent predictor of CRP levels in our population. These results underscore the need for an increased public health focus on obesity prevention and weight control during childbearing years (Davis, Stange, & Horwitz, 2012). Previous reports have linked a positive history of breastfeeding with lower risk of postpartum weight retention (Stuebe et al., 2010), as well as reduced risk of subclinical cardiovascular changes (McClure, Catov, Ness, & Schwarz, 2012) among women of childbearing age. However, as shown in other studies (M. W. Groer et al., 2005; Kuzawa et al., 2013), we found that current breastfeeding status was not associated with mean CRP levels among women who had a live birth within one year.

Contrary to the results of previous studies showing that less acculturated MA adults have lower inflammatory marker levels than their more acculturated peers (Crimmins et al., 2007; Rodriguez et al., 2012), women with the low acculturation level were at greater risk of parity-associated inflammation compared to women with the moderate and high acculturation levels.

The study adds to the growing literature showing that lower acculturation is not always health protective among MA adults (Dinwiddie et al., 2014; Espinosa de Los Monteros, Gallo, Elder, & Talavera, 2008; Salinas, Abdelbary, Rentfro, Fisher-Hoch, & McCormick, 2014). Greater research on the health status of MA women immigrants is required, especially in light of the evidence that recent MA immigrants are still significantly more likely to have undiagnosed diabetes than U.S. born MAs (Barcellos, Goldman, & Smith, 2012) and immigrant MA women are less likely to be told about health risks by their healthcare providers than U.S.-born MA women (S. D. Guendelman, Ritterman-Weintraub, Fernald, & Kaufer-Horwitz, 2013). Although we accounted for the effect of poor perceived oral health, persistent inflammatory effects in women with low acculturation may still be related to poor dental health in this group. The true occurrence of dental disease may be underestimated in low income MA women of childbearing age because they tend to underutilize preventative dental care (Azofeifa, Yeung, Alverson, & Beltran-Aguilar, 2014). Periodontal disease is a significant risk factor for elevated CRP (Moutsopoulos & Madianos, 2006; Noack et al., 2001) and has been previously linked to gestational diabetes (Borgnakke, Ylostalo, Taylor, & Genco, 2013; Xiong, Buekens, Vastardis, & Pridjian, 2006) and chronic stress among MA adults (Borrell & Crawford, 2011).

A lack of data on pre-conception and intra-pregnancy CRP levels constitutes the main study limitation, because the temporal precedence of pregnancy and live birth before elevations in CRP levels cannot be established. Gestational diabetes status could not be assessed in this study, because these data were not available in the 1999-2006 NHANES survey cycles. Lastly, we could not fully account for potential illness-related or birth-related complications, all of which could have influenced CRP levels. The study has several strengths. First, the study adds new knowledge of early indicators of chronic disease in the MA population. Second, the study contributes to the current theoretical knowledge of acculturation by showing that the protective

health advantage of lower acculturation observed in biological health indicators does not extend to inflammation risk among MA women of childbearing age. Third, the study was based on a nationally representative sample of MA women of childbearing age in the U.S. which increases generalizability of our findings.

In conclusion, parity was associated with greater risk of elevated CRP among MA women of childbearing age with low level of acculturation, after accounting for multiple socioeconomic, lifestyle, and health-related variables. Results confirm that obesity is a significant determinant of elevated CRP levels among women. Longitudinal trends in CRP levels during the first year after childbirth and one year after delivery need to be examined in future studies. A potential interactive effect of psychological stress and gestational and post-gestational insulin resistance on inflammation status among recent MA immigrant women requires further study.

III. ASSOCIATION OF VIRAL EXPOSURE BURDEN WITH C-REACTIVE PROTEIN AMONG MEXICAN AMERICAN WOMEN OF CHILDBEARING AGE

A. Introduction

Mexican American (MA) population has the highest growth rate among racial/ethnic groups in the U.S. (Ennis et al., 2011; Passel et al., 2012). In 2008, MAs accounted for 10% of the general U.S. population but 16% of all U.S. births. In the last decade, new births have replaced immigration as the major determinant of U.S. population growth among MAs, largely because MA women currently have higher birth rates compared with non-Hispanic White, non-Hispanic Black, and other U.S. Hispanic women (Pew Research Center, 2011). Epidemiological studies indicate that MA women of childbearing age have among the highest levels of CRP, a marker of systemic inflammation, compared to similarly aged non-Hispanic White and Black women in the U.S. (Danner et al., 2003; E. S. Ford et al., 2004; Ramos & Olden, 2008). At least one third of MA women of childbearing age have been estimated to have abnormally elevated levels of CRP (Danner et al., 2003; Ramos & Olden, 2008), defined as greater than 3.0 mg/L. Therefore, this population is at increased risk for chronic conditions associated with inflammation, including CVD, diabetes, and cognitive decline (Kuo et al., 2005; Ridker, 2009; Wang et al., 2013). Importantly, their offspring are at an increased risk of diabetes and obesity from exposure to maternal inflammation in utero (Desai, Beall, & Ross, 2013; Gillman et al., 2008; Vrachnis et al., 2012). MA children and adolescents currently exhibit the highest levels of CRP among their American age-peers (J. B. Dowd et al., 2010; E. S. Ford et al., 2003; Lande et al., 2008) and MA/Hispanic youth are disproportionately affected by childhood obesity (Ogden, Carroll, Kit, &Flegal, 2014) and diabetes (Dabelea et al., 2014). Given the demographic importance of the population and the possibility of maternal transmission of inflammation risk,

research on factors associated with elevated CRP among MA women of childbearing age is necessary.

1. Infection, inflammation, and atherogenesis

There is growing recognition that exposure to infectious agents may play a role in the initiation and maintenance of atherosclerosis and chronic systemic inflammation (S. Epstein , Zhu, Najafi, & Burnett, 2009; Karin, Lawrence, & Nizet, 2006). In experimental animal studies, persistent viral infections with latency and re-activation have been implicated in promoting atherogenic changes (Castrillo et al., 2003; Lathe, Sapronova, & Kotelevtsev, 2014; Ludewig et al., 2004) and several epidemiological studies have shown that a history of cumulative exposure to several persistent viruses, such as CMV, HSV, and HBV, is associated with elevated CRP, atherosclerosis, and CVD (Espinola-Klein et al., 2002; Ishizaka et al., 2002; Mendy et al., 2013; Roivainen et al., 2000; Simanek et al., 2009; J. Zhu et al., 2000b).

Epidemiological evidence shows that young MAs are disproportionately affected by viral exposures and persistent viral infections (J. B. Dowd, Zajacova, & Aiello, 2009; Zajacova et al., 2009). In a national study, MAs were found to have 3-4 fold increased odds of high infectious exposure burden (based on seropositive status for CMV, HSV-1, Helicobacter pylori and HBV) compared to Whites, after controlling for socioeconomic status. In the same study, MA men and women ages 20-34 with low educational levels had higher infectious exposure burden than their White and African American counterparts (Zajacova et al., 2009). Gender disparities in viral exposure burden exist within the MA population. For example, MA women have been found to have a significantly higher seroprevalence for HSV-2, compared to MA men (Rubicz et al., 2011). Higher infectious exposure burden is also observed among Mexico-born compared to U.S. born adults (Schillinger et al., 2004; Wasley et al., 2010).

Evidence suggests that childbearing may modify the course of persistent viral infections among minority women. Robust cell-mediated immunity is necessary for an effective response to viral infections (Glaser & Kiecolt-Glaser, 2005; Ludewig et al., 2004). However, pregnancy (Sacks & Redman, 1999; Schmaltz et al., 2010) and psychological stress (Coussons-Read et al., 2007) are both associated with downregulation of cellular immunity. Increased occurrence of viral reactivation, as measured by increased levels of anti-viral antibodies, has been observed among pregnant or recently pregnant women with perceived psychological stress and experience of discrimination (Borders et al., 2010; Christian, Iams, Porter, & Glaser, 2012). Results of several studies show that minority women with low socioeconomic status tend to have higher viral activity, based on the levels of antibodies to persistent viral infections (J. Dowd et al., 2008; J. Dowd & Aiello, 2009; Stowe et al., 2010). Birth control pill use is common among childbearing age American women (Tinker, Broussard, Frey, & Gilboa, 2014) and there is some evidence that hormonal contraceptive use may interfere with immune response against viral infections (Marks et al., 2011).

Additionally, there is increasing evidence that viral infections and traditional lipid risk factors may jointly influence inflammation risk. Infections by various infectious agents have been shown to significantly compound hypercholesterolemia-related inflammation in animal models (Khoretonenko et al., 2010; Ludewig et al., 2004; Maekawa et al., 2011). Alarmingly, a near 2-fold increase in the prevalence of elevated total cholesterol occurs in women between ages 20 and 54 years (E. Ford, Mokdad, Giles, & Mensah, 2003).

2. Viral burden and inflammation in MA women of childbearing age

Many of the abovementioned factors linked to differential outcomes of viral infections converge in MA women of childbearing age. A significant proportion of MA women go through pregnancy and birth in the context of low socioeconomic status, inadequate access to healthcare (Crimmins et al., 2007; Morales et al., 2002), and recent migration to the U.S. (Holguin et al., 2005; Pew Research Center, 2011). Over 60% of Hispanic childbearing age women are reported to use birth control pills (Daniels & Mosher, 2013). One third of young to middle aged MA women (mean age 43.0 years) have hypercholesterolemia (Daviglus et al., 2012). Despite these trends, little is known about the association of viral exposure burden with CRP among MA women of childbearing age and how sociodemographic, reproductive, and health-related variables impact this association. Therefore, the aims of this study were to: (1) examine the association of cumulative viral exposure burden with CRP, after accounting for socioeconomic, reproductive, and health-related variables; (2) examine whether reproductive (parity status, history of birth control pill use), country of birth, and total cholesterol factors modify the association of viral exposure burden with CRP among MA women of childbearing age.

B. Methods

1. Study Population

Data from the National Health and Nutrition Examination Survey (NHANES 1999-2010) were used. NHANES uses a complex multistage sampling design to collect socio-demographic, behavioral, dietary, laboratory, physical, and health-related data from a nationally representative sample of civilian, non-institutionalized U.S. residents. NHANES trained professional staff conduct interviews in participants' homes and perform health and laboratory

measurements in MEC. Additional information about MEC examination (CDC, 2014), laboratory procedures (CDC, 2009), and analytic guidelines (Johnson et al., 2013) can be found elsewhere. The current study included non-pregnant MA women ages 18-49 years for whom data on infectious exposures to HSV-1, HSV-2, and HBV were available. Of a total 2,395 MA women ages 18-49 who participated in NHANES, 261 pregnant women were excluded from this analysis because pregnancy is associated with adaptive biological CRP elevations (Belo et al., 2005; E. M. Miller, 2009), which are beyond the scope of this study. We also excluded 33 women who reported a previous pregnancy without a live birth because the data on the reasons and the timing of pregnancy termination are not available. An additional 363 participants with CRP levels > 95.24 mmol/L (> 10.0 mg/L) were excluded since such high levels may represent acute infectious or immune-related conditions (Gabay & Kushner, 1999) and should not be evaluated for long-term CVD risk (Pearson et al., 2003). Lastly, 17 women who reported using lipid lowering statin medications were also excluded from the analysis. A total of 1,627 women had complete data on all examined viral exposures. This secondary analysis study was determined as exempt by the University of Illinois at Chicago Institutional Board of Review.

2. **Main Variables of Interest**

a. **Viral exposure burden**

Details on NHANES procedures on specimen collection and laboratory analysis have been previously described (CDC, 2009). Briefly, blood samples were obtained using standard phlebotomy methods. Seropositivity status for Hepatitis B infection was determined based on the presence of the total anti-Hepatitis B core antibody (anti-HBc), using the qualitative enzyme-linked immunosorbent assay (ELISA). Seropositivity for anti-HBc is a reliable indicator of current or past Hepatitis B infection. Seropositivity for HSV-1 and HSV-2 was determined by testing participants' sera for HSV-1 and HSV-2 antibodies, using solid-phase enzymatic

immunodot assay. Similar to previously published methods (Zajacova et al., 2009; J. Zhu et al., 2000b), cumulative viral exposure burden was defined as the sum of seropositive status scores (1=positive, 0=negative) for the three examined viral pathogens (range 0-3). Participants were defined as "seronegative", if they had negative tests for all three viral agents, or "seropositive", if they were seropositive for at least one viral infection. Viral infection burden was further categorized as "low" if the participant was seropositive for one infection and "high" if the participant was seropositive for two or three infections.

b. **C-reactive protein**

Serum high sensitivity CRP (hsCRP) levels were measured using latex-enhanced nephelometry technique. Details regarding CRP laboratory methods have been previously reported (CDC, 2011). A dichotomous CRP variable was created based on the current clinical guidelines (Pearson et al., 2003) . Low risk (< 9.5 mmol/L (<1.0 mg/L)) and average risk CRP (9.5-28.6 mmol/L (1.0-3.0 mg/L)) categories were combined into the normal category (≤ 28.6 mmol/L (≤3.00 mg/L)) and compared to the high risk category (28.7-95.2 mmol/L (3.01-10.00 mg/L)).

3. **Covariates of Interest**

a. **Reproductive variables**

History of birth control pill use was defined as a response to the question: "Have you ever taken birth control pills for any reason?" (Yes/No). Parity status was created based on answers to two survey questions: (1) "Have you ever been pregnant?" (2) "How many of your pregnancies/deliveries resulted in a live birth?" Participants were categorized as "parous" is they reported at least one live birth and "nulliparous" if they reported that they had never been pregnant. In the analyses with parity status, the ages of participants were 18-49 years in the 1999-2006 NHANES waves and 20-44 years in the 2007-2010 NHANES waves.

b. **Serum lipids**

Total cholesterol and high density lipoprotein cholesterol (HDL-cholesterol) were measured in serum. According to the National Cholesterol Education Program criteria (U.S. DHHS, 2001), total cholesterol was characterized as low (< 4.14 mmol/l (<160 mg/dL)), normal (4.14-5.17 mmol/l (160-199 mg/dL)), borderline high (5.18-6.21 mmol/L (200-239mg/dL)) and high (≥6.22 mmol/L (≥240 mg/dL)). Following the same gender-based criteria, HDL-cholesterol was defined as normal (≥1.30 mmol/L (≥50 mg/dL)) and low (< 1.30 mmol/L (<50 mg/dL)).

c. **Socioeconomic variables**

Age represented the participant's age at the time of the MEC exam, in years, and was used as a continuous variable. Annual household income was categorized as: less than $20,000, $20,000-$44,999 and ≥$45,000. Educational level was categorized as: less than high school, high school or higher level. Access to health care was defined as a positive response to the question: "Is there a place that you usually go when you are sick or need advice about your health?" Similar to previously published methods (Bate et al., 2010), household density was defined as the total number of persons in the household divided by the number of rooms in the house and was categorized as "average" if a household had ≤1 person per room and "crowded" if a household had >1 person per room. Country of birth was measured based on the answer to the questions: "In what country were you born?" (U.S.-born and Mexico-born). Duration of residence in the U.S. was categorized as: less than 5 years, 5 years to less than 10years, 10 years to less than 20 years, 20 years or longer.

d. **Lifestyle variables**

Smoking history was operationalized as a positive response to the question, "Have you smoked at least 100 cigarettes in your entire life?" (Yes/ No). Dietary data came from the first 24-hour dietary recall interview at the MEC, which was performed across all examined survey cycles. Additional details on dietary data collection methods can be found elsewhere (CDC, 2013a). Diet was assessed using three separate variables: daily total intake of total fat (in gm), saturated fat (in grams), and cholesterol (in milligrams), which were used in the analysis as continuous variables.

e. **Health-related variables**

Participants' weight, height, and waist circumference were measured by trained examiners using standard NHANES protocols (CDC, 2005). Body mass index (BMI), defined as the weight in kilograms divided by height in meters squared, was categorized as underweight or normal (<24.9 kg/m^2), pre-obese (25.0-29.9 kg/m^2), and obese (=>30 kg/m^2) (CDC, 2015). Waist circumference was categorized as low risk (≤88 cm) and high risk (>88 cm) (CDC, 2015). Participants were categorized as having normal HgA1c levels (<5.7%) and levels indicative of pre-diabetes/diabetes (≥5.7%), according to published professional guidelines (American Diabetes Association, 2014). The pre-diabetes and diabetes categories were combined in the analysis because of small cell sizes. A history of high blood pressure diagnosis was measured based on the response to the questions: "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" (Yes/No). Asthma and chronic bronchitis were defined as positive responses to the questions, "Has a doctor or other health professional ever told you that you had asthma?" and "Has a doctor or other health professional ever told you that you had chronic bronchitis?" respectively. An ordinal variable was created to describe recent illness during the past 30 days, based on the participants'

responses to three questions assessing the experience of: (1) head or chest cold; (2) stomach or intestinal illness; and (3) flu, pneumonia or ear infection during the past 30 days. The variable responses ranged from 0 (no recent illness) to 3 (a history of 3 recent illnesses).

4. **Statistical Analysis**

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). Chi-squared statistics were used to examine bivariate association of socioeconomic, health related and lifestyle variables with viral exposure burden and CRP status. Linear regression was used to examine bivariate associations of the continuous variables (age, total fat, saturated fat, and cholesterol intake) with viral exposure burden and CRP status.

First, binary logistic regression was used to examine whether country of birth modified the association of viral exposure burden with CRP. We entered a viral exposure burden by country of birth product term in the model including viral exposure and country of birth, in addition to age, educational level, waist circumference, HbA1c, and history of birth control pill use. Although the interaction was statistically non-significant (P for interaction = 0.160), we stratified our analysis by country of birth because of the documented differences in the prevalence of infectious exposure between Mexico-born and U.S.-born adults.

Next, in stratified analyses we examined the association of viral exposure burden with CRP after adjusting for socioeconomic, health-related, serum lipid, and reproductive variables. Model 1 showed the crude association. In Model 2, the association was further adjusted for age, educational level, waist circumference, and HbA1c. In Model 3, the association was further adjusted for total cholesterol, HDL-cholesterol, history of birth control pill use, and parity status. Analyses of Mexico-born women were additionally adjusted for duration of residence in the U.S.

Lastly, we examined interactive effects of viral exposure burden with: (1) history of birth control pill use; (2) parity status; and (3) total cholesterol in the full, unstratified sample. A two-

level viral exposure variable ("seropositive" vs. "seronegative") was used in the interaction with total cholesterol because of small cell sizes. In interaction analyses, each logistic regression model included the main effect terms, the product interaction term of categorical variables, and the important covariate terms (age, educational level, waist circumference, HbA1c, history of birth control pill use).

All crude and adjusted multivariate analyses included participants with complete data on all the variables used in the logistic regression models. All sub-population statistics were calculated in domain analysis. Variance estimates were adjusted based on sample weights provided by NHANES. Since the analysis included data from several waves of the NHANES survey, combined 10-year interview, MEC exam, fasting, and dietary sample weights were constructed using NHANES-provided guidelines (CDC, 2013b).

C. **Results**

Of the 1,627 participants for whom valid data on viral exposure for HSV-1, HSV-2 and HBV were available, 83.6% were seropositive for HSV-1, 14.9% were seropositive for HSV-2, and 1.5% were seropositive for HBV. Compared to U.S.-born MA women, Mexico-born MA women were more likely to be seropositive for HSV-1 (64.7% vs. 35.3%, $p< 0.001$), and had a higher prevalence of HSV-2 (55.1% vs. 44.9%, $p=0.366$) and HBV (63.2% vs. 36.8%, $p=0.703$). For the cumulative exposure burden among MA women, 13.2% were seronegative, 73.9% were seropositive for one viral agent, and 12.9% were seropositive for two or three viral agents (data not tabulated). Details on the participants' characteristics by viral exposure burden level are shown in Table VII. Elevated CRP was positively associated with viral exposure burden levels (30.5% vs. 35.6% vs. 36.8%, $p=0.291$). U.S.-born women were more likely to be seronegative compared to Mexico-born women (73.3% vs. 26.7%). For Mexico-born participants, viral

exposure burden was associated with longer duration of residence in the U.S. (p=0.001). Higher viral infection burden was associated with greater age, lower educational level, and crowded household density. Women with high viral exposure burden were more likely to be parous, obese, have high risk waist circumference, HbA1c levels consistent with pre-diabetes/diabetes, and high total cholesterol levels. Women with higher viral infection burden also were more likely to report past histories of oral birth control use, smoking, and chronic bronchitis.

TABLE VII

PARTICIPANT CHARACTERISTICS BY VIRAL EXPOSURE BURDEN LEVELS

	Seronegative		Low		High		
Variable	n	%	n	%	n	%	P-value[a]
	Categorical variables						
CRP	264		1,164		199		0.291
Normal		69.5		64.4		63.2	
Elevated		30.5		35.6		36.8	
Educational Level	262		1,141		199		<0.001
Less Than High School		24.4		50.1		56.1	
High School and Higher		75.6		49.9		43.9	
Household Income	233		999		182		0.066
<$20,000		19.9		25.5		29.6	
$20,000-$44,999		36.5		41.5		38.6	
≥$45,000		43.6		33.0		31.8	
Access to Health Care	264		1,164		199		0.030
Yes		76.1		69.9		78.5	
No		23.9		30.1		21.5	
Household Density	264		1,164		199		<0.001
Average		83.2		67.4		72.2	
Crowded		16.8		32.6		27.8	
History of Birth Control Pill Use	244		1,037		174		<0.001
Yes		50.2		61.2		69.8	
No		49.8		38.8		30.2	

(continued)

TABLE VII (continued)

PARTICIPANT CHARACTERISTICS BY VIRAL EXPOSURE BURDEN LEVELS

	Seronegative		Low		High		
Variable	n	%	n	%	n	%	P-value[a]
Parity Status	211		974		172		<0.001
Parous		51.9		81.9		97.3	
Nulliparous		48.1		18.1		2.7	
Country of birth	261		1,160		199		<0.001
U.S.-born		73.3		36.9		36.4	
Mexico-born		26.7		63.1		63.6	
Duration of U.S. residence (Mexico-born)	66		694		124		0.001
<5.0 Years		30.8		22.1		15.3	
<5.0-9.9 Years		29.3		24.1		16.2	
<10.0-19.9 Years		25.0		33.5		29.6	
≥20.0 Years		14.9		20.3		38.9	
BMI	263		1,151		197		0.023
Underweight/Normal		46.1		33.9		30.5	
Pre-obese		27.9		34.3		33.0	
Obese		26.0		31.8		36.5	
Waist Circumference	261		1,132		196		<0.001
Low Risk		53.7		43.2		36.5	
High Risk		46.3		56.8		63.5	
Hemoglobin A1C	264		1,164		199		<0.001
Normal		96.1		87.8		82.8	
Pre-diabetes/Diabetes		3.9		12.2		17.2	

(continued)

TABLE VII (continued)

PARTICIPANT CHARACTERISTICS BY VIRAL EXPOSURE BURDEN LEVELS

	Seronegative		Low		High		
Variable	n	%	n	%	n	%	P-value[a]
Total Cholesterol	264		1,164		199		0.023
Low		32.4		21.4		20.6	
Normal		42.7		44.9		41.1	
Borderline High		20.3		26.5		23.5	
High		4.6		7.2		9.8	
HDL Cholesterol	264		1,164		199		0.241
Normal		60.6		55.7		50.6	
Low		39.4		44.3		49.4	
History of High Blood Pressure Diagnosis	261		1,148		195		0.117
Yes		6.5		9.2		12.7	
No		93.5		90.8		87.3	
Illness During the Past 30 Days	244		1,038		176		0.731
0		70.3		70.4		70.6	
1		21.8		23.6		20.6	
2		7.2		5.2		7.9	
3		0.7		0.8		0.9	
History of Asthma	264		1,163		199		0.323
Yes		10.0		6.9		7.2	
No		90.0		93.1		92.8	

(continued)

TABLE VII (continued)

PARTICIPANT CHARACTERISTICS BY VIRAL EXPOSURE BURDEN LEVELS

	Seronegative		Low		High		
Variable	n	%	n	%	n	%	P-value[a]
History of Chronic Bronchitis	131		938		194		0.013
Yes		3.4		1.6		7.1	
No		96.6		98.4		92.9	
Smoking History	131		938		194		0.016
Yes		22.4		21.6		33.2	
No		77.6		78.4		66.8	
	Continuous variables						
	n	M (SE)		M (SE)		M (SE)	
Age	1,625	26.8(0.6)		32.5(0.3)		38.2(0.5)	<0.001
Total Fat	1,562	69.0(2.7)		67.4(1.7)		72.9(3.7)	0.393
Saturated Fat	1,562	21.4(0.9)		22.1(0.6)		24.8(1.3)	0.119
Cholesterol	1,562	210.8(13.1)		257.3(7.4)		290.2(19.1)	<0.001

Note. Variable sample sizes vary because of data availability or data restriction.

[a] Based on the Rao-Scott Modified Chi-Square test for categorical variables and linear regression for continuous variables, treating viral exposure burden as independent variable and continuous variables as the outcome variable.

Participants' characteristics by CRP status are shown in Table VIII. Compared to women with normal CRP, women with elevated CRP were more likely to be parous (85.3% vs. 77.5%, p=0.001), obese (19.0% vs. 54.8%, p<0.001), have high risk waist circumference (44.3% vs. 78.4 %, p<0.001), HbA1c levels consistent with pre-diabetes/diabetes (8.4% vs. 18.0%, p<0.001), high total cholesterol (5.3% vs. 10.3%, p<0.001), and low HDL-cholesterol (39.9 % vs. 53.2%, p<0.001). Compared to women with normal CRP, women with elevated CRP were also more likely to report experiencing two or three recent illnesses (4.7% vs. 9.9%, p=0.001) and a history of birth control pill use (58.1% vs. 65.6%, p=0.002). Among Mexico-born women, the occurrence of elevated CRP was greater in women with longer duration of residence in the U.S. (p=0.021). CRP status was not associated with socioeconomic variables, access to health care, country of birth, chronic respiratory diseases, diet, or smoking history.

TABLE VIII

PARTICIPANT CHARACTERISTICS BY CRP STATUS

	Normal		Elevated		
Variable	n	%	n	%	P-value[a]
Categorical variables					
Educational Level	1,072		560		0.151
Less Than High School		45.9		50.1	
High School and Higher		54.1		49.9	
Household Income	939		499		0.153
<$20,000		24.9		26.1	
$20,000-$44,999		38.4		43.4	
≥$45,000		36.7		30.5	
Access to Health Care	1,092		565		0.174
Yes		70.2		74.3	
No		29.8		25.7	
Household Density	1,092		565		0.091
Average		71.7		67.1	
Crowded		28.3		32.9	
History of Birth Control Pill Use	984		499		0.002
Yes		58.1		65.6	
No		41.9		34.4	
Parity Status	910		472		0.001
Parous		77.5		85.3	
Nulliparous		27.5		14.7	
Country of birth	1,087		563		0.936
U.S.-born		41.7		41.5	
Mexico-born		58.3		58.5	
Duration of U.S. residence (Mexico-born)	580		319		0.021
<5.0 Years		23.3		18.8	
<5.0-9.9 Years		25.8		19.2	
<10.0-19.9 Years		29.7		36.7	
≥20.0 Years		21.2		25.3	
BMI	1,081		559		<0.001
Underweight/Normal		45.4		15.4	
Pre-obese		35.6		29.8	
Obese		19.0		54.8	

(continued)

TABLE VIII (continued)

PARTICIPANT CHARACTERISTICS BY CRP STATUS

	Normal		Elevated		
Variable	n	%	n	%	P-value[a]
Waist Circumference	1,070		548		<0.001
Low Risk		55.7		21.6	
High Risk		44.3		78.4	
Hemoglobin A1C	1,092		565		<0.001
Normal		91.6		82.0	
Pre-diabetes/Diabetes		8.4		18.0	
Total Cholesterol	1,090		561		<0.001
Low		25.2		18.5	
Normal		45.3		44.2	
Borderline High		24.1		27.0	
High		5.3		10.3	
HDL Cholesterol	1,090		561		<0.001
Normal		60.1		46.8	
Low		39.9		53.2	
History of High Blood Pressure Diagnosis	1,074		559		0.093
Yes		8.3		11.1	
No		91.7		88.9	
Illness During the Past 30 Days	987		499		0.001
0		72.8		65.6	
1		22.5		24.5	
2		4.1		8.7	
3		0.6		1.2	
History of Asthma	1,091		565		0.772
Yes		7.3		7.8	
No		92.7		92.2	
History of Chronic Bronchitis	813		476		0.553
Yes		2.4		3.0	
No		97.6		97.0	
Smoking History	812		476		0.467
Yes		22.6		24.4	
No		77.4		75.6	

(continued)

TABLE VIII (continued)

PARTICIPANT CHARACTERISTICS BY CRP STATUS

Variable	Normal		Elevated		P-value[a]
	n	%	n	%	
	Continuous variables				
	n	M (SE)		M (SE)	
Age	1,655	32.2(0.3)		33.0(0.4)	0.101
Total Fat	1,591	68.2(1.8)		68.3(2.4)	0.975
Saturated Fat	1,591	22.2(0.6)		22.9(0.9)	0.701
Cholesterol	1,591	255.4(8.9)		251.3(8.1)	0.742

Note. Variable sample sizes vary because of data availability or data restriction.
[a] Based on the Rao-Scott Modified Chi-Square test for categorical variables and linear regression for continuous variables, treating CRP status as independent variable and continuous variables as the outcome variable.

1. The independent association of viral exposure burden status with CRP

Viral exposure burden was significantly associated with elevated CRP among Mexican-born women. Women with high viral exposure burden had 2.49 times (95% CI 1.08-5.70) higher odds of elevated CRP compared to seronegative women, after adjustment for age, education, waist circumference, HbA1c, and duration of residence in the U.S. The association of viral exposure burden with CRP remained largely unchanged when total cholesterol, HDL, and history of birth control pill use were added to the model, but attenuated after the addition of parity status (OR 2.06, 95% CI 0.91-4.68). In the fully adjusted logistic model, high risk waist circumference and HbA1c were independently associated with elevated CRP among Mexico-born women. Women with the duration of residence in the U.S. 5 years to < 10 years (vs. ≥20 years) were at a reduced risk of elevated CRP (Table IX).

TABLE IX

ASSOCIATION OF VIRAL EXPOSURE BURDEN WITH CRP AMONG MEXICO-BORN WOMEN[a]

	Model 1		Model 2		Model 3		Model 4	
Variable	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Viral Exposure Burden								
Seronegative	1.00		1.00		1.00		1.00	
Low	2.21	[1.06, 4.60]	1.83	[0.85, 3.96]	1.85	[0.84, 4.08]	1.57	[0.71, 3.44]
High	2.87	[1.24, 6.62]	2.46	[1.07, 5.68]	2.49	[1.08, 5.70]	2.06	[0.91, 4.68]
Age			0.97	[0.95, 1.00]	0.97	[0.94, 0.99]	0.96	[0.93, 0.98]
Less Than High School Educational Level			1.15	[0.76, 1.73]	1.18	[0.77, 1.81]	1.17	[0.75, 1.83]
High Risk Waist Circumference			4.27	[2.77, 6.57]	4.39	[2.84, 6.77]	4.17	[2.68, 6.49]
Pre-diabetes/Diabetes HgA1c Level			2.21	[1.40, 3.49]	2.08	[1.31, 3.30]	2.07	[1.29, 3.31]
< 5 Years in the U.S.					0.82	[0.51, 1.30]	0.86	[0.52, 1.40]
<10 Years					0.52	[0.34, 0.80]	0.54	[0.35, 0.85]
<20 Years					1.09	[0.77, 1.53]	1.10	[0.77, 1.58]
≥20 Years					1.00		1.00	
High TC							1.90	[0.92, 3.92]
Borderline High TC							1.16	[0.64, 2.11]
Normal TC							1.13	[0.70, 1.82]
Low TC							1.00	
Low HDL Cholesterol							1.16	[0.84, 1.60]
History of Birth Control Pill Use							1.27	[0.91, 1.77]
Parous							1.42	[0.80, 2.50]

Note. OR = odds ratio; CI = confidence interval; TC = total cholesterol. Analysis is based on the participants with complete data on all variables in the models.

[a] N=737.

In contrast to Mexico-born women, high viral exposure burden was not significantly associated with CRP among U.S. born women in the crude and adjusted analyses (OR=0.89, 95% CI 0.45-1.77 and OR=0.51, 95% CI 0.22-1.19, respectively). In the fully adjusted model, high risk waist circumference and low HDL-cholesterol were independently associated with elevated CRP among U.S.-born women. Compared to U.S.-born women with low total cholesterol, U.S.-born women with high total cholesterol, borderline high total cholesterol and normal total cholesterol were at an increased risk of elevated CRP (Table X).

TABLE X

ASSOCIATION OF VIRAL EXPOSURE BURDEN WITH CRP AMONG U.S.-BORN WOMEN[a]

	Model 1		Model 2		Model 3	
Variable	OR	95% CI	OR	95% CI	OR	95% CI
Viral Exposure Burden						
Seronegative	1.00		1.00		1.00	
Low	1.10	[0.65, 1.87]	0.96	[0.56, 1.65]	0.86	[0.48, 1.55]
High	0.89	[0.45, 1.77]	0.59	[0.28, 1.26]	0.51	[0.22, 1.19]
Age			1.01	[0.99, 1.04]	0.99	[0.97, 1.02]
Less Than High School Educational Level			0.89	[0.59, 1.35]	0.88	[0.56, 1.39]
High Risk Waist Circumference			4.97	[3.15, 7.85]	3.90	[2.37, 6.43]
Pre-diabetes/Diabetes HgA1c Level			0.89	[0.38, 2.10]	0.81	[0.36, 1.79]
High TC					3.57	[1.53, 8.37]
Borderline High TC					2.28	[1.05, 4.98]
Normal TC					1.69	[1.01, 2.81]
Low TC					1.00	
Low HDL Cholesterol					1.90	[1.21, 2.99]
History of Birth Control Pill Use					1.42	[0.85, 2.37]
Parous					1.43	[0.80, 2.53]

Note. OR = odds ratio; CI = confidence interval; TC = total cholesterol. Analysis is based on the participants with complete data on all variables in the models.

[a]N=578

Seropositive status for each individual viral agent was not significantly associated with CRP, in the overall and stratified analyses. No significant interactions were observed between viral exposure burden and reproductive factors (parity status and history of birth control pill use).

2. The association of viral exposure burden with CRP by total cholesterol levels

The association between viral exposure burden and elevated CRP varied significantly based on the participants' total cholesterol levels (P for interaction =0.031). Among women with high total cholesterol levels, seropositive women had 5.85 times (95% CI 1.12-30.47) higher odds of having elevated CRP, compared to seronegative women. Among women with borderline high levels of total cholesterol, seropositive women had 2.90 times (95% CI 1.13-7.45) higher odds of having elevated CRP, compared to seronegative women. In women with normal and low total cholesterol levels, seropositive status was not associated with an increased risk of elevated CRP (Table XI).

TABLE XI

ASSOCIATION OF VIRAL EXPOSURE BURDEN WITH CRP BY TOTAL CHOLESTEROL LEVELS[a]

		Crude		Adjusted[b]	
Variable	n	OR	95% CI	OR	95% CI
High Total Cholesterol	104				
Seropositive		2.47	0.50, 12.20]	5.85	1.12, 30.47]
Seronegative		1.00		1.00	
Borderline Total Cholester	347				
Seropositive		3.40	[1.51, 7.65]	2.90	[1.13, 7,45]
Seronegative		1.00		1.00	
Normal Total Cholesterol	622				
Seropositive		1.11	[0.65, 1.88]	1.00	[0.57, 1.75]
Seronegative		1.00		1.00	
Low Total Cholesterol	343				
Seropositive		0.77	[0.38, 1.57]	0.42	[0.17, 1.08]
Seronegative		1.00		1.00	

Note. OR = odds ratio; CI = confidence interval.
[a] N=1,416
[b] Adjusted for age, educational level, waist circumference, Hemoglobin A1c, history of birth control pill use

D. **Discussion**

High viral exposure burden was significantly associated with elevated CRP among Mexico-born women of childbearing age, after adjustment for traditional inflammation risk factors of age, education, waist circumference, and HA1c levels. Further adjustment for history of birth control pill use, total cholesterol, and HDL-cholesterol had no effect on the association. A two-fold elevated risk from high viral exposure on CRP remained but became statistically non-significant after adjusting for parity status. The association of viral exposure with CRP was not significant among U.S. born women.

Our finding that viral exposure burden is significantly associated with CRP among Mexico-born but not among U.S.-born MA women of childbearing age may signify a compromised cellular immune status in the former group. In a prior study, CMV-positive women with a robust T-cell mediated immune response to CMV infection were less likely have angiographic evidence of cardiovascular disease, compared to women in whom such response was lacking or combined with antibody-mediated response (J. Zhu et al., 2000a). Immune vulnerability among Mexico-born women may be mediated by chronic psychological stress. A significant proportion of young and middle-aged MA women report high levels of perceived psychological stress relating to lack of social support, caregiving, financial strain, and perceived discrimination (Gallo et al., 2011; Sanchez-Birkhead et al., 2011; Shattell, Smith, Quinlan-Colwell, & Villalba, 2008; Strutz et al., 2014). Negative psychological experiences have been linked to impaired cellular immunity and greater occurrence of viral reactivation among women (Borders et al., 2010; Christian et al., 2012).

Chronic stress may also potentiate inflammation associated with viral exposure though the mechanism of "glucocorticoid resistance". Glucocorticoid stress hormones "temper" anti-viral inflammatory response by down-regulating inflammatory cytokine production by the

immune cells (Silverman, Pearce, Biron, & Miller, 2005). Chronic overproduction of stress hormones renders the immune cell less responsive to glucocorticoid feedback (G. Miller, Cohen, & Ritchey, 2002), thus leading to the loss of an important mechanism of inflammation control in the context of viral infection. A recent study demonstrated that "glucocorticoid resistance" is more common among low income pregnant African-American and Hispanic women, compared to Caucasian, high income women (Corwin et al., 2013).

An alternative explanation for the higher risk of inflammation from viral exposure among Mexico-born, compared to U.S.-born MA women, is that country of origin-associated environmental factors may have a lasting impact on how the immune system responds to infectious agents. This could be explained by higher risk of viral exposure among Mexico-born versus U.S. born individuals (Schillinger et al., 2004; Wasley et al., 2010). Prior evidence suggests that greater infectious exposure during early life is protective against CRP elevations during adulthood (McDade, Rutherford, Adair, & Kuzawa, 2008; McDade, Rutherford, Adair, & Kuzawa, 2010). This is not consistent with our findings, which showed that Mexico-born women had both higher likelihood of viral exposure and higher inflammation risk related to it. The difference in inflammatory sequelae from viral exposure by country of birth needs further examination.

Another major finding in the study is that viral exposure burden significantly interacts with serum total cholesterol in the association with CRP among MA women of childbearing age. The joint role of total cholesterol and viral exposure burden in increasing inflammation risk among women is in agreement with earlier animal based studies, which found pro-inflammatory cellular changes following viral infections and amplification of these changes in hosts with systemic hypercholesterolemia (Khoretonenko et al., 2010; Ludewig et al., 2000; Zhou, Paulsson, Stemme, & Hansson, 1998). The upregulation of the innate and cellular inflammatory

responses may be the common mechanism through which viral exposure and systemic hypercholesterolemia together create heightened inflammation risk. Hypercholesterolemia is independently associated with chronic T-cell mediated inflammation in the vasculature (Weber & Noels, 2011) and recently has been also shown to contribute to the proliferation of macrophages with enhanced inflammatory activity (Seijkens et al., 2014). Likewise, viral agents stimulate the innate immune system macrophage activity (Castrillo et al., 2003; Lathe et al., 2014) and invoke a T-cell mediated inflammatory response, which may be targeted at viral particles within the endothelial cells (Ludewig et al., 2004). In the current study, even borderline high levels of total cholesterol carried a significant inflammatory risk when combined with at least one prior viral exposure. While further research is needed to confirm our results with regard to the viral exposure – total cholesterol interaction, our findings provide preliminary evidence to support more consistent lipid screening and viral exposure evaluation among MA women of childbearing age and other at-risk female populations. According to national data, lipid screening among women of reproductive age remain below 50% (Kuklina, Yoon, & Keenan, 2010).

Notably, almost 40% of women in our sample had low HDL- cholesterol levels, slightly lower than the previous estimate of approximately 45% among MA/Hispanic women of childbearing age (Ramos & Olden, 2008). It has been recently shown in animal models that long-term persistent infections are associated with reductions in HDL-cholesterol (Maekawa et al., 2011). Similarly, a significant association between infection burden and low HDL-cholesterol has been reported in human studies (Georges et al., 2003; Vilkuna-Rautiainen et al., 2006). In this study, viral exposure burden showed an inverse association with HDL-cholesterol levels, although this finding was not significant. Further examination of the relationship between viral exposure and HDL-cholesterol among MA women is warranted. HDL-cholesterol plays a

critical role in anti-inflammatory and anti-atherogenic regulatory functions (Kontush & Chapman, 2006) and modulates inflammatory response during infections (Norata, Pirillo, Ammirati, & Catapano, 2012). Therefore, reduced HDL-cholesterol levels among MA women of childbearing age may represent a loss of an important means of inflammation control in this population.

In this study, seroprevalences of Hepatitis B (1.5%) and HSV-2 (14.9%) were lower than the respective national estimates of 4.6% for Hepatitis B among adults ages 20-49 years (Wasley et al., 2010) and 19 % for HSV-2 among adults aged 18-49 years (Beydoun, Dail, Ugwu, Boueiz, & Beydoun, 2010). The prevalence of co-infection with two and three viral agents was 12.9%, nearly identical to the previous estimate of 12% for HSV-1/HSV-2 co-infection among U.S. adults aged 18-49 years (Beydoun et al., 2010). On the other hand, seroprevalence for HSV-1 (83.6%) was considerably higher than the estimate of 60% among U.S. men and women aged 18-49 years (Beydoun et al., 2010). A significant association of HSV-2 infection and CVD was found in previous studies (Espinola-Klein et al., 2002; Mendy et al., 2013). However, in this study seropositivity for HSV-2 was not significantly associated with elevated CRP. Likewise, HSV-1 infection was not significantly associated with elevated CRP (data not shown). Several previous investigations found no significant association of HSV-1 infection with elevated CRP or CVD risk (Espinola-Klein et al., 2002; Simanek et al., 2009; J. Zhu et al., 2000b). It is likely that HSV-1 infection may increase CVD risk through interactions with other infectious agents (Roivainen et al., 2000; Vilkuna-Rautiainen et al., 2006). Therefore, disproportionately high prevalence of HSV-1 among MA women of childbearing age is noteworthy.

The study has several methodological limitations. The cross-sectional nature of the study does not allow us to draw conclusions about the direction of the observed relationships. The study results would have been strengthened if elevations in CRP were directly related to

elevations in viral antibody titers, instead of seropositivity status (Nazmi et al., 2010). With only seropositivity data at our disposal, we had limited ability to distinguish whether the health effects were due to greater infectious exposure or greater susceptibility of the host to infections (S. Epstein, Zhou, & Zhu, 1999). The timing of exposure and occurrence of viral reactivation are not known.

The study has several strengths. First, our study involved a highly vulnerable and demographically important population of women, which remains underrepresented in research of biological markers. To our knowledge, this is the first epidemiological study to identify viral exposure burden as a non-traditional risk factor of chronic systemic inflammation among Mexico-born MA women. Previous studies have shown that traditional risk factors, such as obesity, diabetes and hypercholesterolemia, do not fully explain CRP elevations among MA women (E. S. Ford et al., 2003; E. S. Ford et al., 2004). Second, we examined a viral exposure-total cholesterol interaction which, despite strong biological foundation, has not been previously examined in epidemiological studies. Lastly, we used a nationally representative sample of childbearing age MA women, which increases generalizability of results.

In conclusion, our results show that viral exposure burden is associated with an increased risk of elevated CRP among Mexican-born but not U.S. born MA women of childbearing age. We also found that the risk of elevated CRP was significantly higher in MA women with a positive history of viral exposure and elevated total cholesterol levels. Additional research is needed to further explore the effect of immune-metabolic interaction on inflammation among MA women.

IV. CONCLUSIONS AND SIGNIFICANCE

Even though non-pregnant MA women of childbearing age have one of the highest levels of the inflammatory marker CRP among similarly aged non-Hispanic White and Black women in the U.S. (Danner et al., 2003; E. S. Ford et al., 2004; Ramos & Olden, 2008) and this poses increased risk of chronic conditions for the women (Kuo et al., 2005; Ridker, 2009; Wang et al., 2013) and their offspring (Heerwagen et al., 2010; Schmatz et al., 2010; Segovia et al., 2014), studies that identify factors associated with elevated CRP in this population have been limited. The research presented in this thesis addresses this gap in the research literature. We utilized nationally representative data from the NHANES to examine the association of parity and viral exposure burden with CRP among MA women of childbearing age.

In the first analysis we found that parity was associated with an increased risk of elevated CRP among MA women with low level of acculturation. In this group, having a live birth within one year was associated with significantly elevated odds of inflammation, which were not fully explained by the measured socioeconomic, lifestyle, and health related variables. Our findings indicate that childbirth and the first year since childbirth may be a critical period for triggering or perpetuating chronic systemic inflammation among recent MA immigrant women and suggest that the risk factors during the peripartum period in this group require further research scrutiny. The study findings support a previously expressed view in the health literature that childbearing may reveal health vulnerabilities in women (Catalano, 2010; Kaaja & Greer, 2005) and offers additional justification to focus more health preventative efforts on women during childbearing years, especially recent MA immigrant women. These preventative measures may include an examination of CRP levels during the first year after childbirth in at risk women populations.

In the second analysis, we found that viral exposure burden was associated with an increased risk of elevated CRP among Mexico-born but not U.S.-born MA women of childbearing age, which suggests a compromised cellular immune status in the former group. We also found joint effects of elevated total cholesterol levels and viral exposure burden on increased inflammation risk among MA women of childbearing age. The risk of elevated CRP was significantly increased in seropositive women with high or borderline high serum total cholesterol levels. The viral exposure-total cholesterol interaction found in this study supports the emerging research paradigm which postulates that metabolic and immune functions are biologically integrated (Hotamisligil, 2006; M. Karin et al., 2006a). Within this framework, any environmental stimulus which can serve as an antigen in the immune response, (i.e. infectious agent), has the potential to trigger metabolic disturbances and exacerbate them (Egger & Dixon, 2010; Licastro et al., 2005; Prescott, 2013). While further research is needed to confirm our results, our findings provide preliminary evidence to support more consistent lipid screening and viral exposure evaluation among MA women of childbearing age and other at-risk female populations.

Acculturation is a highly relevant social phenomenon for MA women of childbearing age because a significant proportion of MA women migrate to the U.S. during childbearing years (Holguin et al., 2005; Pew Research Center, 2011). The salience of acculturation as a health-related phenomenon was also demonstrated by our findings. Results of both analyses showed that inflammation risk associated with parity and viral exposure burden was concentrated among Mexico-born women or women with low acculturation level. The discrepancies in inflammation risk by acculturation level were not explained by the socioeconomic, lifestyle, and health-related variables in the study. These findings suggest new directions for future research. First, a potential mediating role of acculturation-related psychological stress in the association of viral

exposure with CRP among immigrant MA women needs to be examined in future studies, since psychological stress is associated with impaired cellular immunity (Borders et al., 2010; Christian et al., 2012) and CRP among women (Coussons-Read et al., 2007; Johnson et al., 2013). Future studies should also examine whether recent immigrant MA mothers with stress exposure during and after pregnancy may be more vulnerable to unsuccessful resolution of pregnancy-associated insulin resistance with resulting persistent inflammation.

This research adds to the growing literature showing that lower acculturation is associated with increased health risks among MA adults (Dinwiddie et al., 2014; Espinosa de Los Monteros et al., 2008; Salinas et al., 2014). Further, health risks among recent MA immigrants may be underestimated because of inadequate chronic condition diagnosis (Barcellos et al., 2012) and screening (S. D. Guendelman et al., 2013), underutilization of preventative health care (Azofeifa et al., 2014) or low socioeconomic status-related barriers to receiving timely preventative health care (Bryant, Worjoloh, Caughey, & Washington, 2010). Since MAs are one of the largest and youngest racial/ethnic groups in the U.S. (Ennis et al., 2011; Passel et al., 2012), increased research and clinical attention to the health status of MA women of childbearing age is needed and can make a significant impact on future health in the U.S.

In summary, to our knowledge, this study was the first to find a significant association between parity status and elevated CRP in a subpopulation of American women of childbearing age and to link viral exposure burden to an increased inflammation risk among MA women of childbearing age. We also discovered a significant viral exposure-total cholesterol interaction which, despite strong biological foundation, has not been previously examined in epidemiological studies. Viral exposure burden and recent childbirth may be important non-traditional risk factors of inflammation among Mexico-born MA women, in addition to traditional risk factors, such as abdominal obesity, diabetes and hypercholesterolemia This

thesis advances our understanding of how environmental, acculturation, and developmental contextual factors shape inflammation risk in a demographically important U.S. population.

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