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Systemic Inflammation and Viral Exposure among Young Mexican American Women: Nativity-Related Differences

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Background: Factors contributing to elevated inflammation in racial/ethnic minority populations are not well understood. We examined the association of viral exposure with C-reactive protein (CRP) in young Mexican American women.

Methods and Results: Participants (N=1,141) were currently non-pregnant women of Mexican background, aged 18-39 years, from the cross-sectional National Health and Nutrition Examination Survey (NHANES) 1999-2010. Viral exposure was defined as seropositive status for hepatitis B, and herpes simplex types 1 and 2, and classified as seronegative, seropositive for any one agent, and seropositive for 2 or 3 agents. The association of viral exposure with elevated CRP (3.01-10.00 mg/L) varied by country of birth (P=.001). Among Mexico-born women, those seropositive for 2 or 3 agents had 3.79 times (95% CI: 1.28-11.27) and those seropositive for any one agent 2.56 times (95% CI: 1.12-5.86) the odds of elevated CRP compared with seronegative women, after adjustment for age, country of birth, household density, waist circumference, glycated hemoglobin, and total cholesterol. Among US-born women, the corresponding odds were OR: .32, 95% CI: .12-.86 and OR: .71, 95% CI .43-1.17.

Conclusions: In Mexico-born Mexican American women, viral exposure is associated with higher odds of elevated CRP. *Ethn Dis*. 2017;27(2):133-142; doi:10.18865/ed.27.2.133.

Keywords: Inflammation; Viruses; Women

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Introduction

Mexican American (MA) women are a part of the largest and most rapidly growing ethnic group in the United States, expected to account for 29% of the US population by the mid-century.[1] The burden of cardiovascular risk factors in MA women is high,[2] with a substantial prevalence of obesity[3] and diabetes[4] during young adulthood. Studies have consistently indicated that MA women have higher concentrations of C-reactive protein (CRP) than White women[5-7] (age adjusted means for White and MA women, 2.2 mg/L and 3.4 mg/L, respectively[5]). According to current clinical guidelines, in the presence of other traditional risk factors, CRP levels >3.0 mg/L denote high cardiovascular risk.[8] Meta-analyses estimate that the relative risk for diabetes increases by 26% per one increment in logarithmically scaled (log) CRP[9] and relative risks for coronary heart disease and cardiovascular mortality increase by 37% and 55%, respectively, per each standard deviation change in log CRP.[8]

The exceptionally elevated CRP levels among MA women are not fully explained by traditional or socioeconomic risk factors.[5,10] Meanwhile, investigations of the environmental influence on CRP in this population have been lacking, even though patterns in the distribution of various cardiovascular factors in this population by country of birth and duration of US residence[11-13] suggest such influence. Infectious exposures are more common among MAs, compared with non-Hispanic Whites[14,15] and known to vary between Mexico-born and US-born MA adults.[16] Exposure to persistent viruses, such as herpes simplex type 1 (HSV-1) and type 2 (HSV-2), cytomegalovirus (CMV), and hepatitis B (HBV), has been implicated in promoting atherogenic changes,[17,18] and linked to inflammation[19,20] in some studies. Furthermore, factors previously linked to heightened immune response to persistent viral infections, including female sex, minority status,[21,22] and low educational levels[23,24] are heavily con-

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centrated among MA women. Since disparities in CRP levels[25] and viral seroprevalence[14,15,26] are already present by young adulthood, examining the association of viral exposure with elevated CRP in young MA women will improve our understanding of excess inflammation in this group. We examined seroprevalence of three persistent viral agents (HSV- 1, HSV-2, and HBV) among young MA women and assessed the association of viral exposure, defined as the sum score of seropositivity status for three viral agents, with CRP among these women. Based on previous research, we hypothesized that higher levels of viral exposure will be significantly associated with higher odds of elevated CRP.

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Methods

Study Population

Data from the cross-sectional National Health and Nutrition Examination Survey (NHANES) were used. To increase sample size, we pooled data from six two-year cycles of NHANES: 1999-2010. NHANES uses a complex multistage sampling design to collect data from a nationally representative sample of civilian, non-institutionalized US residents. Information about NHANES data collection can be found elsewhere.[27] Participants were women of Mexican background, as self-reported on survey questions about race and Hispanic origin. Participants' immigrant status was captured by the survey question about the participant's country of birth (born in the United States vs born in Mexico). Among a total of 1,818 MA women aged 18-39 years, 1,689 women had data on all examined viral exposures and CRP. Participants who had missing data on viral exposure (n=26) or both viral exposure and CRP (n=103) tended to be Mexico-born and have less than high school educational level. Of 1,689 participants with main exposure and outcome data, 356 pregnant women were excluded because pregnancy is associated with adaptive elevations in CRP.[28] An additional 156 participants with CRP levels >10.0 mg/L were excluded since such high levels may represent acute infectious or immune-related conditions. Also excluded were 3 women who reported using lipid lowering statin medications, resulting in a total of 1,174 women. An additional 33 women had missing covariate data, resulting in the final analytic sample of 1,141 women. This study was determined to be exempt by the Institutional Board of Review.

Viral Exposure

Seropositivity status for HBV 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 HBV 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,[20] viral exposure was defined as the sum of seropositive status scores (1=positive, 0=negative) for the three examined viral pathogens (range 0-3). In this sample, only two Mexico-born participants had the maximum number of 3 exposures. Thus, viral exposure was categorized as seronegative (score=0), seropositive for any one infection (score=1), or seropositive for two or all three infections (score=2 or 3). CMV exposure was only measured in NHANES 1999-2004 surveys and therefore could not be included in the viral exposure measure.

C-reactive Protein

Serum high sensitivity CRP (hsCRP) levels were measured using latex-enhanced nephelometry technique. To enhance interpretation of clinical risk, a dichotomous CRP variable was created based on clinical guidelines.[8] For these analyses, low risk (<1.0 mg/L) and average risk CRP (1.0-3.0 mg/L) categories were combined into one "normal" category (i.e. levels ≤3.00 mg/L) and compared with the high

risk category, here defined as "elevated" category (3.01-10.00 mg/L).

Covariates

Age represented the participant's age, in years, at the time of the exam. Educational level was categorized as: less than high school, high school, and above high school level. Annual family income categories were: <$20,000 and ≥$20,000. Household density was defined as the total number of persons in the household divided by the number of rooms in the house and categorized as "average" if a household had ≤1 person per room and "crowded" if a household had >1 person per room. 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?" Country of birth was ascertained from the question: "In what country were you born?" (US-born or Mexico-born). Duration of residence in the United States was categorized as: less than 5 years, 5 years to less than 10 years, 10 years to less than 20 years, and 20 years or more. 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). Waist circumference, total cholesterol (mg/dL), high density lipoprotein cholesterol (HDL-cholesterol, mg/dL), and hemoglobin A1c (HgA1c, %) levels were measured in serum and used as continuous variables. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or a participant report of being on antihypertensive medications. Smoking status was defined based on the question, "Have you smoked at least 100 cigarettes in your entire life?" (Yes/ No). Segmented neutrophil percent (%) was measured as a continuous variable.

Statistical Methods

All data analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC). NHANES uses complex sampling estimation methods; therefore, all survey statistical procedures were adjusted using NHANES-provided weights to account for nonresponse, sampling error, oversampling, and post-stratification. Since this analysis used six biannual NHANES cycles from 1999 to 2010, a combined 12-year MEC sample weight was constructed using the appropriate NHANES-provided formula. To obtain valid variance estimates for our subpopulation of interest, we followed NHANES guidelines on subsetting data by using SAS survey procedure domain statements. More details on NHANES analytic guidelines are available elsewhere.[29] Seroprevalence was estimated for the total sample and by country of birth because of the previously docu-

Table 1. Weighted proportions of seropositive Mexican American women, aged 16-39 years

	Total n=1,141 n/Weighted %	US-born n=556 n/Weighted %	Mexico-born n=585 n/Weighted %	P[a]
Individual exposures[b]				
HSV-1	884/81.0	358/67.8	526/91.8	<.001
HSV-2	102/11.0	52/13.6	50/8.8	.044
HBV	11/1.2	3/.5	8/1.8	.082
Summed exposures				
Seronegative	236/16.3	180/26.8	56/7.8	<.001
Seropositive any one agent	815/74.4	339/64.5	476/82.5	
Seropositive 2 or 3 agents	90/9.3	37/8.7	53/9.7	
Mean exposure (SE)	-	1.8 (0)	2.0 (0)	<.001

a. Based on the Rao-Scott Modified Chi-Square test for categorical variables and linear regression for continuous variables.
b. Percentages do not add up to 100% due to overlap.
SE; standard error.

mented differences in viral exposure between Mexico-born and US-born MA adults. Chi-squared statistics and linear regression were used to examine bivariate associations of socioeconomic and health-related covariates with viral exposure and CRP status. Age, country of birth, as well as variables with significant bivariate associations with viral exposure and CRP (P<.05) were included in the multivariable logistic regression analysis as potential confounders. The final multivariable logistic regression model included the main effects of viral exposure, age, household density, country of birth, waist circumference, hemoglobin A1c, total cholesterol, and the interaction term between viral exposure and country of birth. In a post-hoc analysis, we examined the association of individual viral exposures with elevated CRP.

Results

The analysis included 1,141 non-pregnant MA women aged 16-39 years. Seroprevalence of viral exposure in the total sample and by country of birth is shown in Table 1. Overall, 81.0% were seropositive for HSV-1, 11.0% for HSV-2, and 1.2% for HBV. Seroprevalence of HSV-1 was higher in Mexico-born than US-born women (91.8% vs 67.8%, P<.001). Seroprevalence of HSV-2 was lower in Mexico-born than US-born women (8.8% vs 13.6%, P=.044). Seroprevalence for HBV was low and did not significantly differ between Mexico- and US-born women (1.8% vs.

Table 2. Characteristics by viral exposure level

Variables	N	Negative %[a]	Low %	High %	P[b]
Age[c]	1,141	24.7(.6)	28.4(.2)	32.4(.7)	<.001
Educational level	1,118				<.001
< High school		24.2	48.7	57.7	
High school		23.7	23.4	19.0	
Above high school		52.1	27.9	20.3	
Annual family income	1,078				.079
<$20,000		28.9	36.6	40.3	
≥$20,000		71.1	63.4	59.7	
Crowded household density	1,141	17.9	34.7	34.4	.001
No access to health care	1,141	23.4	32.7	20.3	.005
County of birth	1,141				<.001
US-born		73.8	38.9	42.3	
Mexico-born		26.2	61.1	57.7	
Duration of US residence if Mexico-born	568				.312
< 5.0 years		37.0	26.9	27.3	
5.0-9.9 years		27.4	27.6	19.6	
10.0-19.9 years		23.8	35.2	32.8	
≥20.0 years		11.8	10.3	20.3	
History of birth control pill use	1,031	45.9	57.4	62.2	.064
Waist circumference[c]	1,141	88.0(1.0)	90.6(.6)	91.7(1.7)	.035
Hemoglobin A1C[c]	1,141	5.1(.0)	5.2(.0)	5.3(.1)	.000
Total cholesterol[c]	1,141	172.3(2.4)	182.2(1.6)	183.4(3.7)	.003
HDL-cholesterol[c]	1,141	54.0(1.2)	53.0(.6)	51.8(1.4)	.537
Hypertension	914	2.4	3.8	6.8	.444
Smoking history[d]	785	19.5	18.6	33.6	.047
Segmented neutrophil %[c]	929	59.6(.7)	58.8(.3)	59.6(1.4)	.459

a. Weighted proportions based on the complex sampling estimation method.
b. Based on the Rao-Scott Modified Chi-Square test for categorical variables and linear regression for continuous variables.
c. Mean (standard error).
d. Measured in women aged ≥20 years.

.5%, P=.082). Of the total sample, 16.3% were seronegative, 74.4% were seropositive for any one viral agent, and 9.3% were seropositive for any two or all three viral agents. The mean exposure and proportion of women with any viral exposure was significantly higher among Mexico-born women compared with US-born women (P<.001).

Table 2 shows bivariate associations of viral exposure levels with covariates. Higher level of viral exposure was significantly associated with greater age, lower educational level, crowded household density, no access to health care, Mexico birthplace, greater waist circumference, HbA1c, total cholesterol, and smoking. Women seropositivive for any one agent had the greatest proportion of women reporting no access to health care.

Results of bivariate associations between CRP status and covariates are shown in Table 3. The overall prevalence of elevated CRP was 34.4%. Elevated CRP was significantly associated with crowded household density, greater waist circumference, HbA1c, total cholesterol, lower HDL-cholesterol, and history of birth control pill use. There was no association between country of birth or duration of US residence and CRP status. The prevalence of elevated CRP among MA women did not vary significantly across the examined NHANES periods (not shown).

In the multivariable logistic regression analysis adjusted for age,

Table 3. Characteristics by C-reactive protein status

		Normal	Elevated	
		n=770 (65.6%)	n=371 (34.4%)	
Variables	**n**	**%[a]**	**%**	**P[b]**
Age[c]	1,141	27.9 (.3)	28.7 (.3)	.060
Educational level	1,118			.070
< High school		42.9	50.4	
High school		23.8	21.7	
Above high school		33.3	27.9	
Annual Family Income	1,078			.482
<$20,000		34.8	37.4	
≥$20,000		65.2	62.6	
Crowded household density	1,141	29.2	37.3	.018
No access to health care	1,141	30.8	28.4	.506
Country of birth	1,141			.337
US-born		46.0	42.8	
Mexico-born		54.0	57.2	
Duration of US residence (if Mexico-born)	568			.259
< 5.0 years		29.8	24.1	
5.0-9.9 years		28.1	24.8	
10.0-19.9 years		31.8	38.0	
≥20.0 years		10.3	13.1	
History of birth control pill use	1,031	52.0	63.6	.001
Waist circumference[c]	1,141	86.4 (.6)	97.7 (.9)	<.001
Hemoglobin A1C[c]	1,141	5.2 (0)	5.3 (0)	.001
Total cholesterol[c]	1,141	177.4 (1.5)	186.9 (2.3)	.001
HDL-cholesterol[c]	1,141	54.7 (.6)	50.0 (.6)	<.001
Hypertension	914	3.6	4.3	.703
Smoking history[d]	785	19.7	21.3	.604
Segmented neutrophil %[c]	929	58.7 (.3)	59.5 (.4)	.127

a. Weighted proportions based on the complex sampling estimation method.
b. Based on the Rao-Scott Modified Chi-Square test for categorical variables and linear regression for continuous variables.
c. Mean (standard error).
d. Measured in women aged ≥20 years.

household density, country of birth, waist circumference, hemoglobin A1c, total cholesterol, and the interaction term between viral exposure and country of birth, the interaction was significant ($P_{interaction}$=.001). Therefore, stratum specific odds ratios (OR) by country of birth were estimated using a single model approach. Crude and adjusted ORs for the association of viral exposure with elevated CRP by country of birth are shown in Table 4. Among US-born women, those seropositive for 2 or 3 agents had significantly lower odds of elevated CRP compared with seronegative women, after adjustment for covariates (OR: .32; 95% CI: .12-.86). US-born women seropositive for any one agent also had lower adjusted odds (OR: .71; 95% CI: .43-1.17). Among Mexico-born women, those seropositive for 2 or 3 agents had 3.79 times (95% CI: 1.28-11.27) and Mexico-born women seropositive for any one agent 2.56 times (95% CI: 1.12-5.86) the odds of elevated CRP compared with seronegative women. In multivariable models, the only covariate with independent significant association with elevated CRP was continuously measured waist circumference (OR: 1.07, 95% CI 1.05-1.09) (data not shown).

In the post-hoc analysis we examined the association of individual viral exposures with elevated CRP. Among US-born women, HSV-1and HSV-2 seropositive status were associated with lower odds of elevated CRP compared with seronegative women (HSV-1 adjusted OR: .71, 95% CI: .47-1.08; HSV-2 adjusted OR: .58, 95% CI: .22-1.54). Among Mexico-born women, HSV-1 and HSV-2 seropositive status were associated with higher odds of elevated CRP compared with seronegative women (HSV-1 adjusted OR: 2.67, 95% CI: 1.22-5.83; HSV-2 adjusted OR: 1.68, 95% CI: .81-3.50). The ORs for HBV could not be estimated due to a small sample size.

Table 4. Crude and adjusted odds ratios (OR) and 95% CI for the association of viral exposure with elevated CRP among Mexican American women by country of birth[a], n=1,141

Variable	Crude		Adjusted[b]	
	OR	95% CI	OR	95% CI
US-born and seropositive 2 or 3 agents[c]	.45	.20-.98	.32	.12-.86
US-born and seropositive any one agent	.91	.56-1.48	.71	.43-1.17
Seronegative	1.00		1.00	
Mexico-born and seropositive 2 or 3 agents[b]	4.80	1.69-13.62	3.79	1.28-11.27
Mexico-born and seropositive any one agent	3.28	1.38-7.79	2.56	1.12-5.86
Seronegative	1.00		1.00	

a. Viral exposure*country of birth $P_{interaction}$=.001.
b. Adjusted for age, household density, country of birth, waist circumference, hemoglobin A1c, total cholesterol.
c. n=2 participants in Mexico-born group were seropositive for 3 agents.

Discussion

We examined the association of viral exposure, defined as the sum score of seropositivity status for three persistent viral agents (HSV-1, HSV-2, and HBV), with elevated CRP among young MA women. Our hypothesis was supported among Mexico-born women, in whom seropositivity for 2 or 3 viral agents was associated with over 3-times the odds of elevated CRP. However, among US-born women, viral exposure was inversely associated with elevated CRP. HSV-1 was by far the most prevalent infection, reaching 90% seroprevalence among Mexico-born women. On the other hand, the contribution of HBV was negligible in our study due to low seroprevalence.

Some previous studies have identified the presence of multiple persistent and non-persistent infections as a risk factor for elevated CRP.[19,20] There is emerging evidence that Mexico-born MA women are at

an increased risk of some inflammation-based outcomes, eg, gestational and non-gestational diabetes, especially with increasing length of residence in the United States.[30,31] The presence of the strong association between viral exposure and elevated CRP among Mexico-born women thus may be supportive of the cumulative pro-inflammatory burden in this population, encompassing viral exposure and such unmeasured factors as acculturation–related diet and stress. The direct associations of unhealthy dietary patterns[32,33] and stress[34] with elevated CRP levels have been documented. Acculturation stress has also been linked with elevated CRP in immigrant women.[35]

Host immune characteristics may also play a role in the discovered nativity-based differences. Previously, a differential relationship between CMV seropositive status and CRP has been reported among predominantly white adults, leading the authors to hypothesize genetic or environmentally-induced variations in the immune response to infections.[36] Innate immunity is important for control of viral infections at younger ages, specifically HSV.[37] HSV-1 seroprevalence is significantly higher among Mexico-born than US-born children,[38] suggesting an earlier exposure to this, and perhaps other viruses, among Mexico-born individuals. Prior studies have shown higher prevalences of HSV-1,[16,26] Epstein-Barr virus,[16] CMV,[39] and *C. pneumoniae* bacterium[16] among Mexico-born, compared with US-born MA adults. Early and cumulative infectious exposures may be pro-inflammatory; these are believed to have a role in promoting vascular dysfunction in children[40] and overactive innate immunity in adults.[41] These hypotheses may be examined in future studies of young adults with more comprehensive measures of infectious burden.

The implications of our findings for clinical uses of CRP as a predictor of CVD risk are still unclear. To review, literature on the infection-linked origins of CVD has not been consistent. While some investigations found no independent association of HSV-1 infection with elevated CRP or CVD risk,[20,42,43] others have found that combined histories of HSV-1, respiratory chlamydia pneumonia[44] or periodontal infections[45] may be related to an increased CVD risk. HSV-2 infection has been linked with advanced atherosclerosis[42] and premature CVD.[46] Others reported a lack of association between infection burden and subclinical atherosclerosis.[47] Since the existing studies have been primarily based on middle-aged and older adults in whom the influence of early risk factors may be masked by the cumulative effects of age, elevated CRP levels associated with viral exposure among young Mexico-born MA women should be treated with concern. If our findings are confirmed in other studies, elevated CRP levels among immigrant MA women may suggest the presence of endemic chronic inflammation in this group and necessitate longitudinal studies to examine the implications for future CVD risk.

Our hypothesis was supported among Mexico-born women, in whom seropositivity for 2 or 3 viral agents was associated with over 3-times the odds of elevated CRP.

A limitation of this study is the lack of objective assessment of the host immune response to the examined viral exposures. Quantitative viral antibody levels are a more specific measure of the strength of the immune response and more consistently associated with inflammatory status compared with positive serological status alone.[48] Future investigations using such quantitative measures are needed to ascertain whether the earlier reports of increased susceptibility for viral reactivation among vulnerable subgroups have validity in young minority populations. Another limitation is that the cross-sectional nature of the study introduces uncertainty in the direction of the observed relationships. The total viral exposure burden among participants is unknown; selection bias, eg, underrepresentation of individuals with extremely high levels of exposure, is possible. Lastly, presented stratified estimates may be imprecise due to the small sample size.

The strength of the study is that it is one of the first to examine variations in CRP status within

a homogenous ethnic group. The observed unique associations of viral exposure with elevated CRP among young MA women point to the interaction of native and acquired Westernized environments with inflammation. It has been previously hypothesized that gene-environment interactions affect the expression of complex chronic conditions.[49] Persistent periodontal infections have been shown to play a role in epigenetic gene modification, including the genes involved in the immune response regulation.[50] Thus, investigations of infectious exposures during earlier life stages are needed. As indispensable yet modifiable elements of early environments, they may play a role in healthy aging in diverse populations.

Conclusions

Our results show that viral exposure is associated with higher odds of elevated CRP among Mexico-born but not US-born young MA women. Additional research is needed to explore interactive influences of country of birth and infectious exposures on inflammation status among MA women.

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Rosenberg, Daviglus, DeVon, DeVon, Eldeirawi; Acquisition of data: Rosenberg; Data analysis and interpretation: Rosenberg, Daviglus, DeVon, Park, Eldeirawi; Manuscript draft: Rosenberg, DeVon; Statistical expertise: Rosenberg, Park; Supervision: Daviglus, DeVon, Eldeirawi

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