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Social Support and Viral Reactivation in US and Foreign-Born Mexican Americans

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Social Support and Viral Reactivation in US and Foreign-Born Mexican Americans

by

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Dedication

To my late grandfather, Morris Minkin, whose support was and will remain invaluable to my education and professional aspirations.

Social Support and Viral Reactivation in US and Foreign-Born Mexican Americans

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Social support may explain a part of the Hispanic Paradox, the persistent pattern of mortality outcomes for low-SES Hispanic Americans that more closely compare to higher-SES Caucasians than lower-SES African Americans. Curiously, Hispanics, especially those born outside the United States, have higher levels of infection and reactivation of herpesviruses that are carcinogenic or associated with cancer, and cancer is one outcome in which Hispanics do not appear to be at an advantage.

To more closely understand the relationship between social support, herpesvirus reactivation, race, ethnicity and place-of-birth, a secondary analysis of cross-sectional data from the Texas City Stress and Health Study was conducted. A maximum of 2,708 Non-Hispanic White (NHW), Non-Hispanic Black (NHB), US-Born and Foreign-Born Mexican Americans (MA) interviewed between 2004 and 2006 were studied. Perceived social support among NHW, NHB, US-Born MA and Foreign-Born MA was compared. Logistic regressions controlling for sociodemographic, health status and health behavior variables were conducted to test the association between low social support and race/ethnicity, the focal independent variables, and reactivation on two or more antigens against Epstein Barr Virus (EBV), cytomegalovirus (CMV) and herpes simplex virus-1 (HSV-1), the dependent variable. Interactions between race/ethnicity and low social support were assessed, as well as the potential confounding effect of acculturation within Mexican Americans.

Results indicate that NHB reported significantly lower social support than both NHW and MA, while NHW reported lower social support than US-Born MA but not Foreign-Born MA. Low social support, Black race, and female gender were significantly associated with reactivation, while no interaction effect was identified between race/ethnicity and low social support. In analysis restricted to Mexican Americans, low social support and female gender were again associated with reactivation, and a significant and large interaction effect between nativity (country-of-birth) and low social support was identified. Subgroup analyses confirmed that low social support was strongly associated with reactivation in US-Born MA but not Foreign-Born MA. Controlling for acculturation removed the association between low social support and reactivation and the interaction between nativity and social support.

The results suggest that nativity, acculturation and race/ethnicity are relevant factors to consider when assessing the relationship between social support and herpesvirus reactivation. Acculturation may mediate the relationship between social support and herpesvirus reactivation in Hispanics, and further study is needed to elucidate this relationship. Our study contributes to the role of perceived social support in the Hispanic Paradox and an understanding of the buffering hypothesis of social support among distinct cultures.

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List of Abbreviations

ACC	Acculturation variable
AD	Alzheimer's Disease
AIM	Adult Interaction Mainstream
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BMI	Body Mass Index
BRFSS	Behavioral Risk Factor Surveillance System
CI	Confidence Interval
CIM	Childhood Interaction Mainstream
CMV	Cytomegalovirus
EA	Early Antigen
EBV	Epstein Barr Virus
ELU	English Language Usage
HSV-1	Herpes Simplex Virus-1
HSV-2	Herpes Simplex Virus-2
IM	Infectious Mononucleosis
LMP	Latent Membrane Protein
MA	Mexican American
MOS	Medical Outcome Survey
NHANES	National Health and Nutrition Examination Survey
NHB	Non-Hispanic Black
NHW	Non-Hispanic White
OR	Odds Ratio
PSS	Perceived Stress
SD	Standard Deviation
SES	Socioeconomic Status

SS	Social Support
UTMB	University of Texas Medical Branch
VCA	Viral Capsid Antigen

Chapter 1 Introduction

Chapter 1 introduces the study question, the overarching hypothesis and the specific aims that explain how the study will address the hypothesis. The chapter will conclude with a discussion of the rationale for the significance of the study question. Theoretical and evidence bases for the hypothesis that draw on findings from the Texas City Stress and Health Study, the parent study for this secondary data analysis, will also be discussed.

STUDY QUESTION:

How is social support associated with reactivation of Herpes Simplex Virus (HSV-1), Cytomegalovirus (CMV) and Epstein Barr Virus (EBV) among Non-Hispanic whites (NHW), Non-Hispanic blacks (NHB), US-born Mexican Americans (US-Born MA), and Foreign-Born Mexican Americans (Foreign-Born MA)?

HYPOTHESIS:

Low social support is associated with elevated reactivation of EBV, CMV and HSV-1 in US and Foreign-Born MA, but not in Non-Hispanic Whites or Non-Hispanic Blacks.

SPECIFIC AIMS

Specific Aim 1:

Determine the mean difference in social support scores between NHW, NHB, Foreign-Born MA and US-Born MA.

Specific Aim 2:

Determine the relationship between social support and viral reactivation in NHW, NHB, US-Born MA and Foreign-Born MA.

Specific Aim 3:

Determine the nature of the relationship between social support, viral reactivation, nativity and acculturation in US and Foreign-Born Mexican Americans.

SIGNIFICANCE:

The Hispanic Paradox describes a phenomenon in which Hispanics (especially those of Mexican-origin) experience equivalent or lower all-cause mortality than white and black Americans, despite having lower levels of income and educational attainment (1). Curiously, a recent systematic review and meta-analysis found that this survival advantage is not conferred to Hispanics diagnosed with cancer (2). Indeed, several studies of Epstein Barr Virus (EBV), a known carcinogen (3), in lymphoma patients found a stronger association between EBV positive tumors and Hispanic origin than other racial/ethnic groups (4) (5) (6). A suggested component of oncogenesis in some EBV-associated cancers, such as Hodgkin's lymphoma, Burkitt's lymphoma, gastric cancer, nasopharyngeal carcinoma and central nervous system lymphomas (7) (8), is reactivation, the process by which a latent provirus in the lysogenic stage begins active

viral replication and lysis of the host cell (9) (10). Other common herpesviruses, such as herpes simplex I and cytomegalovirus, reactivate easily in immunosuppressed populations, such as those suffering from HIV and cancer patients receiving immunosuppressants, leading to worsening of cancerous lesions (11) or increased risk of mortality (12) (13). Few studies have described rates of viral reactivation between different racial and ethnic groups or the association and contribution of social support to these differences.

The Texas City Stress and Health Study (14), a cross-sectional study of viral reactivation in elderly MA (foreign and US-born), Non-Hispanic Whites, and Non-Hispanic Blacks, found significantly lower expression of EBV viral capsid antigen in Foreign-Born MA compared to Non-Hispanic Blacks (15). EBV early antigen expression was reduced in Foreign-Born Mexican Americans compared to US-Born MA, Non-Hispanic Whites, and Non-Hispanic Blacks. Non-Hispanic Whites, however, had significantly lower levels of herpes simplex virus-1 (HSV-1) titer than Non-Hispanic Blacks and US and Foreign-Born MA (15).

Despite the relationship between social support and reactivation of herpesviruses (16) (17) (18) (19) (20) (21) (22) (23) and the relationship between EBV and Hispanic ethnicity in various cancers, the relationship between social support and immune dysfunction among racial/ethnic groups is not well-understood, with most research focused on populations living with HIV. In a study of CD4 count and serostatus disclosure among Hispanic and Non-Hispanic white men living with HIV and AIDS, Hispanic men did not benefit from high familial social support when disclosing to their mothers while Non-Hispanic White men did. Conversely, Non-Hispanic White men who disclosed were unaffected by low familial social support while Hispanic men

experienced a decrease in CD4 count. Neither norephinephrine, psychological stress, perceived stress, or medication adherence explained these findings (24). Nevertheless, Eisenberger and colleagues (25) found a relationship between psychological inhibition and CD4 count in Non-Hispanic White females living with HIV and AIDS but not Hispanic females. Also, in research on herpes zoster, a risk factor for certain cancers (26), Non-Hispanic Blacks were less likely to acquire herpes zoster than Non-Hispanic Whites, and social support was not related to herpes zoster in either group (27) (28).

The findings of Fekete and colleagues (2009) (24) are consistent with those of Pole and colleagues (2005) (29) who identify that Hispanic police officers have more severe PTSD than NHW and NHB, and that this difference is associated with lower perceived social support and higher social desirability. The authors hypothesize that high social desirability and low support may lead Hispanic individuals to downplay the severity of psychological stressors to remain amenable to social contacts, and that Hispanics may be more vulnerable to lack of social support, due to the primacy of familial social support in Hispanic cultures (29). Such hypotheses have yet to be associated with measurable disparities in health outcomes, although plentiful evidence suggests that higher levels of social support in Hispanic communities may buffer members against mortality (30) (31) (32). The lack of clarity on the relationship between social support and herpesvirus reactivation between Non-Hispanic Whites, Non-Hispanic Blacks, and US and Foreign-Born Hispanics merits further study. The described study tests a predicted association between social support and herpesvirus reactivation in participants of the Texas City Stress and Health Study. Deciphering this relationship may strengthen our understanding of the role of social support in the Hispanic Paradox.

Chapter 2 Background and Literature Review

Chapter 2 provides background on the descriptive epidemiology of infection and reactivation of Epstein Barr Virus, cytomegalovirus and herpes simplex virus-1 in the United States. The health consequences of reactivation, with a special focus on cancer, will also be summarized. Following the descriptive section, evidence for possible mechanisms by which acculturation and social support differentially modulate the risk of reactivation between racial/ethnic groups will be synthesized. The chapter will conclude by framing the study aims and analysis as a potential explanation of the improved mortality outcomes outlined by the Hispanic Paradox for Foreign-Born Mexican Americans.

DESCRIPTIVE EPIDEMIOLOGY OF EBV

While over 90% of Americans are infected with EBV by the time they reach adulthood (33), Non-Hispanic Black and Mexican American children become infected at much earlier ages. A survey of National Health and Nutrition Examination Survey (NHANES) data on children ages 6-19 collected between 2003-2004, 2005-2006, 2007-2008 and 2009-2010 found that Non-Hispanic Black and Mexican American children ages 6-8 were almost twice as likely to be infected with EBV (80%) as Non-Hispanic White children (48%), where EBV infection was measured by detecting EBV IgM antibody in serology. While 83% of Non-Hispanic White teenagers aged 18 and 19 were ultimately infected, just 6% of Non-Hispanic Black and Mexican American teens were uninfected in this age group (34). Factors associated with higher rates of infection included older age, lack of health insurance, lower household income, and lower

education level, suggesting that these social disparities between Non-Hispanic White and other racial/ethnic groups contributed to the differences in prevalence of infection (34).

Primary EBV infection can cause infectious mononucleosis (IM), an outcome associated with increased risk of chronic diseases including lupus, multiple sclerosis and Hodgkin's lymphoma later in life (35) (36) (37). In most immunocompetent individuals infected with EBV, including those who experience IM, the virus ultimately establishes latency in the B lymphocytes, where the virus lies dormant in the host genome and maintains equilibrium with the host (38). EBV reactivation, whereby the virus escapes latency, begins replicating, and actively lyses the host cell, can occur in healthy immunocompetent hosts (39), although reactivation is more likely during times of stress including pregnancy and old age (40) (41) (42) (43). In healthy adults, reactivation is seldom accompanied by clinical symptoms (44) (45). A prospective cohort study measuring EBV replication in healthy Germans detected asymptomatic reactivation in 27% of individuals over 15 months of follow up (39). In a cohort of pregnant women, 35% of subjects experienced reactivation, detected via serum antibodies, by the second trimester (40). Another study, in which reactivation was identified by detecting EBV early antigen, DNA in peripheral blood and serum, and RNA transcripts of replication genes, found that reactivation was more common in adults over 55 than in younger individuals (42). Although social support is negatively associated with EBV reactivation in many populations, including women diagnosed with or suspected of having breast cancer (17) and medical students (21), the importance of social support to racial/ethnic disparities in EBV infection and reactivation is not well understood.

In 2016, the United States National Institute of Environmental Health Sciences classified EBV as a Group-1 confirmed carcinogen (3). EBV reactivation has been implicated in oncogenesis of various cancers, including Hodgkin's lymphoma, Burkitt's lymphoma, gastric cancer, nasopharyngeal carcinoma and central nervous system lymphomas (7) (8). It should be noted that latency stages I-III, characterized by expression of EBV proteins, are also associated with B-cell immortalization and various cancers, although most immunocompetent adults do not progress past latency 0, a stage in which no EBV proteins are expressed (3). Strong associations between EBV+ malignant tumors and Hispanic origin have been established, particularly in lymphomas. Compared to white Americans, an odds ratio of 4.3 (95% confidence interval 3.5-20.3) was observed between EBV positivity and Hispanic origin in Reed-Sternberg tumors of mixed cellularity in Hodgkin's lymphoma patients (4). Similarly, Glaser and colleagues (1997) noted that patients with EBV+ Hodgkin's tumors were 4.1 times as likely to be Hispanic than white (95% CI 1.8-9.6) (5). In a cross-sectional comparison between German and Mexican patients with diffuse large B-cell lymphoma, EBV was found in 7% of Mexican patients, higher than the prevalence of EBV+ tumors in German patients (2%) and various studies of lymphoma in Western populations (1-3%) (6). Mexican patients were also younger at diagnosis and more likely to express a variant of the EBV latent membrane protein (LMP-1) with a 10 amino-acid deletion. LMP-1, the only EBV protein capable of transforming benign cells (46), is a known oncogene, and the deletion mutant transforms cells more efficiently than wild-type LMP-1 (47).

DESCRIPTIVE EPIDEMIOLOGY OF CMV

The distribution of human cytomegalovirus (CMV) in the American population bears resemblance to that of EBV, in which a higher proportion of Non-Hispanic Blacks and Mexican Americans are seropositive, especially within younger age groups. In the cross sectional NHANES III study, recruiting 14,538 subjects ages 6-49 between 1988 and 1994, the age-adjusted prevalence of CMV seropositivity was 50.4%, with a racial/ethnic distribution of 41.7% in NHW, 70.9% in NHB, and 77.6% in Mexican Americans, where prevalences were calculated using the 2000 US Census population as the standard (48) (49). In an additional 15,310 NHANES participants sampled between 1999-2004, a similar pattern of racial and ethnic disparity appears, with the overall age-adjusted prevalence of CMV remaining nearly identical to 1988-1994 (50.6%), yet higher prevalences in Mexican Americans (76.9%), and NHB (70.6%) but a markedly lower prevalence in NHW (39.5%) (48) (49). Here, prevalences were also standardized to the 2000 Population Census. In both study periods, prevalences between NHW, NHB and Mexican Americans differ significantly. Like EBV, Mexican American and Non-Hispanic Black children are infected with CMV at an earlier age, but unlike EBV, large racial/ethnic disparities persist into middle age. Among children ages 6-11 in NHANES III (1988-1994), Mexican American males had the highest proportion of seroprevalence at 62.3%, higher than both Non-Hispanic Black males (46.4%) and Non-Hispanic White males (28.3%). A similar pattern emerged among females, in which Mexican Americans reported the highest percentage of seroprevalence (61.3%) compared to Non-Hispanic Blacks (45.6%) and Non-Hispanic whites (29.6%). Even at middle age (40-49 years), large racial/ethnic disparities persisted. Just 57.5% of Non-Hispanic White females were seropositive, compared to 90.3% of Non-Hispanic Black females and Mexican American females (90.1%). Among middle-aged

males, while only 42.5% of Non-Hispanic Whites were seropositive for CMV, that number increased to 70% of Non-Hispanic Blacks and 86% of Hispanics (48)..

In the NHANES III participants, additional factors associated with increasing prevalence of CMV seropositivity included older age, female sex, birthplace outside the US, low household income, high household crowding, and low household education (48) (50). Foreign birth in men (OR 6.40) and women (8.04) had a particularly strong association with CMV infection. Household income was also strongly associated with CMV infection: a doubling of family income was associated with 8 fewer years of seropositivity over the life course (50). This relationship may help predict all-cause mortality as well: when Feinstein and colleagues (2016) investigated all-cause mortality within 16 years of the NHANES III sample collected between 1988 and 1994, 6-15% of the association between low SES and mortality could be explained by CMV seropositivity (51). Additional studies on healthy participants confirm the association between socioeconomic status and CMV seropositivity while also suggesting psychosocial contributions to infection. In a sample of 212 healthy adults aged 18-55 from Pittsburgh, individuals whose parents spent fewer years as home owners or who smoked as well as individuals who lived in poor or dangerous neighborhoods were more likely to be seropositive. Among seropositive individuals, childhood psychosocial determinants such as lower family warmth and harmony and parental bonding and higher family dysfunction were associated with higher antibody titers to CMV (52).

When analyzing reactivation of CMV in adults, both increasing age and low socioeconomic status appear as risk factors in multiple studies. In the Sacramento Area Latino Study on Aging

(SALSA), an analysis of approximately 1500 California Latino residents ages 60-100, individuals with the highest 30% of anti-CMV IgG antibody titers were approximately 50% more likely to have 0-3 years of formal education compared to greater than 12 years (95% CI 1.18-2.01) (53). In a registry of healthy Houston-area adults ages 55 and over, older age groups were more likely to experience chronic subclinical CMV reactivation, evidenced by the shedding of CMV DNA in urine but not blood (42), a pattern consistent with studies of CMV reactivation in immunocompetent individuals (54) (55). While subclinical, CMV reactivation may still increase the risk that other herpesviruses reactivate. Khan and colleagues (2004), find that individuals with subclinical CMV reactivation have fewer CD8 T cells expressing EBV peptides, indicating a poorer immune response to EBV (56). Like EBV, while social support is thought to be associated with CMV reactivation in older adults (57), it is unclear whether social support accounts for racial/ethnic differences in CMV reactivation.

While CMV reactivation has not been proven to be oncogenic unlike EBV, various tumor studies in-vivo have found pieces of the CMV genome and protein products in tumors, but not healthy surrounding cells. Studies of the virus in-vitro suggest that CMV modulates tumor growth by dysregulating p53, shielding tumor cells from cell-cycle checkpoints, inhibiting apoptosis, promoting angiogenesis, and promoting growth factors (58) (59). Accordingly, various studies have identified an association between CMV and cancers including glioblastoma (60) (61) (62), lymphoma, nasopharyngeal cancer, cervical cancer, Kaposi's sarcoma, colorectal carcinoma, prostate cancer, skin cancer, and astrocytomas (61) (60), though disagreement exists on the relationship between CMV reactivation and colon cancer (63) (64) and tumors of the brain and central nervous system (65) (66) (67). CMV reactivation is also associated with poor health

outcomes beyond cancer. In a prospective study of mortality and hospitalization in a pool of immunocompetent ICU patients, individuals with reactivated CMV were more likely to die or remain in the hospital within 30 days of admission (68).

DESCRIPTIVE EPIDEMIOLOGY OF HSV-1

Analyses of the NHANES III cross section demonstrate age-related and racial/ethnic disparities in HSV-1 seroprevalence comparable to EBV and CMV. On average, about 65% of US adults between 1988 and 1994 were infected with HSV-1, though seroprevalence rose sharply over the life course, from 40.5% of 12-19 year olds to 90.5% of 70-74 year olds (69). Even among children ages 6-13, a significantly greater proportion of Non-Hispanic Black children (47.8%; 95% CI 42.8-53.3%) and Mexican American children (42.1%; 95% CI 37.7-46.9%) were infected, with infection twice as common in children born in Mexico than in the United States (30% v. 59.3%) (70). The 100% increase in seroprevalence between children born at or above the poverty level (24.0%) to children born below the poverty level (51.8%) (70) suggests that differential rates of poverty between racial/ethnic subgroups may contribute to disparities in HSV-1 seroprevalence. Although most of the US population (~90%) ultimately becomes infected with HSV-1 by age 70 (71) (69), racial disparities in infection persist until middle age. Even among 40-49 year olds, a significantly higher proportion of Non-Hispanic Blacks were HSV-1 positive (84.0%; 95% CI 80.9-87.2%) than Non-Hispanic Whites (68.9%; 95% CI 64.5-73.6%) (69). Similarly, HSV-1 infected individuals were over 2 times more likely to be Mexican American (OR 2.68) and/or foreign-born (2.48) than Non-Hispanic White or US-born (69).

However, patterns of racial/ethnic disparities differ depending on whether co-infection with HSV-2 and HSV-1 is considered. In the NHANES III analysis, Mexican Americans were more likely to be infected with HSV-1 than Non-Hispanic Whites or Non-Hispanic Blacks, while Non-Hispanic Blacks were the least likely to be infected with HSV-1 only but the most likely to be co-infected. Non-Hispanic Whites were the most likely to be uninfected with either infection (71). Here, poverty may also play a role, as a greater proportion of coinfected individuals lived below the poverty index than non-coinfected individuals, while being uninfected with both HSV-1 and HSV-2 was more common in individuals living above the poverty index. Curiously, no poverty-related disparities were found in individuals infected with HSV-1 but not HSV-2 (71).

Like CMV, reactivation of HSV-1 becomes more common among populations of older adults, although reactivation frequencies may differ by educational attainment and race/ethnicity. The Texas City Stress and Health Study of adults living in Texas City, Texas found that more adults ages 45-64 and 65 and older had experienced HSV-1 reactivation than adults under 45 (72), with significantly greater reactivation in Non-Hispanic Blacks than Non-Hispanic Whites or Mexican Americans (72). Among older Latino adults ages 60-100 in Sacramento, individuals with the highest 30% of HSV-1 reactivation titers were 66% more likely to have 0-3 years of formal education than those with at least 12 years of schooling (53).

Like CMV, reactivated HSV-1 can express proteins which can help it evade apoptosis (73) (74). In a case control study comparing individuals with oral cancer, precancer and a control group, HSV-1 IgGs were significantly higher in individuals with oral cancer compared to controls, but no differences were found between participants with cancer and pre-cancer (75). Perhaps the

most well-studied and well-supported complication of HSV-1 reactivation is Alzheimer's disease. HSV-1 DNA localizes specifically in beta amyloid plaques of the brains of individuals with the type-4 mutation in the apolipoprotein E gene, a known risk factor for AD. It is thought that the defunct ApoE4 protein in these individuals may weaken the blood brain barrier and allow reactivated HSV-1 DNA to enter the brain and cause inflammation, tau phosphorylation, beta amyloid plaque formation and apoptosis of neurons (76). Indeed, IgG levels for HSV-1 in patients with AD is correlated to cortical gray matter volume, while no such association was found for CMV (77). Although the mechanism behind the relationship between HSV-1 reactivation and Alzheimer's is unclear, HSV-1 reactivation has been demonstrated to increase the risk of acquiring Alzheimer's by a factor of 2-2.5 in two separate longitudinal studies (78) (79).

SOCIAL SUPPORT, ACCULTURATION AND HERPESVIRUS REACTIVATION

While the above studies describe patterns of EBV, CMV and HSV-1 infection and reactivation in populations, the mechanisms behind racial/ethnic differences in reactivation are not well understood. The Texas City Stress and Health Study of viral reactivation in a cohort of elderly Mexican Americans (foreign and US-born), Non-Hispanic Whites, and Non-Hispanic Blacks, observed significantly lower expression of EBV viral capsid antigen in Foreign-Born Mexican Americans compared to Non-Hispanic Blacks (15). EBV early antigen expression was reduced in Foreign-Born Mexican Americans compared to US-born Mexican Americans, Non-Hispanic Whites, and Non-Hispanic Blacks. (15). These findings suggest a difference in risk factor exposure for herpesvirus reactivation between US and Foreign-Born Mexican Americans.

It is possible that social support and familial relationships are a key component in the ethnicity and viral reactivation relationship. Differences in social support between US and Foreign-Born Mexican Americans may explain in part the divergence in viral reactivation between the two populations. An inverse relationship between social support and herpesvirus reactivation or impaired immune function has been demonstrated in various populations. Caregivers of dementia patients and medical students with low social support and higher loneliness were shown to have higher reactivation of EBV (21) (20). Social support was also found as a mediating factor between a cognitive behavioral intervention for HIV+ gay men and HSV-2 reactivation (22) and a modifier of the effect of loneliness on reactivation of human herpesvirus-6 in HIV+ gay and bisexual survivors of Hurricane Andrew (23).

In women of middle or high socioeconomic status recently diagnosed or awaiting diagnosis of breast cancer, higher social support was associated with lower EBV reactivation, although women of lower SES experienced no such benefit (17). In this same population, individuals with high attachment anxiety, or the fear of rejection and unavailability from loved ones, also experienced higher EBV reactivation than individuals without attachment anxiety independent of depression and generalized anxiety, suggesting that perceived social support is as important to buffer against biopsychosocial stress as received social support, an idea long supported by scholars (80) (81). Received support has even been associated with harmful health outcomes (82) (83) (84), possibly because receiving support indicates an unmet need for support (84). Furthermore, among gay men living with HIV and AIDS, higher perceived social support was associated with lower reactivation of herpes simplex virus-2 (18) (19). However, the relationship between high perceived social support and lower reactivation may not apply to all populations.

For example, in several anthropological studies of Bolivian female craftworkers, emotional support from godparents of the participants' children was associated with lower EBV antibodies, but not perceived access to social or economic support (85). However, in a survey of Mexican farm workers in Oregon, social support was negatively associated with EBV titer and systolic and diastolic blood pressure, lending credence to the buffering hypothesis in Mexicans (83). Cultural differences in the extent to which social support can buffer against external stressors may depend on the propensity of a cultural group to identify an internal locus of control over life circumstances, a pattern identified in studies of Anglo-American college undergraduates (1982) (86) and business administration students (87). However, when this relationship was tested in both American and Chinese student populations, the stress-buffering property of perceived social support was associated with an external locus of control in Chinese students and an internal locus in Americans. Furthermore, received support was negatively associated with buffering in Chinese students (82). These studies suggest that locus of control may be a potential mechanism behind cultural differences in the stress-buffering property of social support.

Cultural differences in the extent to which social support buffers stress may also depend on differences in the support networks between groups. Commenting on the relationship between social support and health outcomes, Berkman (2000) urged scholars to consider the cultural and economic backdrop which determine the type of social support available to individuals and the interactions of individuals with their social support networks (88). Studies utilizing nationally representative surveys identify key differences in the structure and function of social support networks between Caucasians and minority populations, including African Americans, Hispanics, and Asian Americans (89) (90). Comparing the social networks of Black and White

Americans sampled between 1987 and 1988 in the National Survey of Families and Households (n>13,000), Silverstein and Waite (1993) find that Blacks and Whites are equally likely to provide and receive instrumental (material) and emotional support. Throughout adulthood, White women were more likely to provide instrumental support to others, although this difference disappeared in older age groups, with Black women more likely to receive instrumental support in older age. In contrast to our study, Silverstein and Waite (1993) study received rather than perceived support (89).

In another secondary analysis of the National Survey of Families and Households, Kim and McKenry (1998) study differences between Blacks, Hispanics, Asians and Caucasians in the perception of instrumental and emotional support provided in three different scenarios: 1) needing emergency assistance in the middle of the night, 2) needing a loan of $200 for the week, and 3) needing advice for a difficult decision. Like our study population, most participants were lower income, with a mean annual household income <$29,000, and a low level of education (<12 years of formal schooling). Unlike many of our participants, most immigrants in Kim and McKenry's (1998) analysis had lived in the US for many years (on average, 22 years). While all groups identified individuals that they could rely on in each scenario, the relationship between the supporter and the recipient differed between each racial/ethnic group. In all three scenarios, African Americans, Asian Americans and Hispanic Americans were more likely to call upon their children, where Whites were more likely to rely on coworkers and other relatives. However, the biggest differences in social networks were identified between men and women, rather than racial/ethnic subgroups (90).

Social support has long been suggested to contribute to the Hispanic Paradox, or the consistent pattern of mortality outcomes observed in low-SES Hispanic Americans, especially those of Mexican origin, that more closely mimic higher SES White Americans than low-SES African Americans (91) (1) (92). Studies in large cohorts, such as the Whitehall II (93) and Heinz Nixdorf Recall (94) cohorts have demonstrated that social support can buffer individuals against the harmful effects of low socioeconomic status on mortality (92), lending credence to the hypothesis that mortality patterns identified by the Hispanic Paradox could be explained by social support in Hispanic Americans.

The present study uses acculturation to better understand the association between social support and herpesvirus reactivation in Mexican Americans. Acculturation, or the cultural, social and psychological changes incurred from blurring two cultures, may contribute to the Hispanic Paradox, such that the health behaviors, diets and familial support in Mexican American communities may protect this population from mortality (14). In a seminal article on Hispanic acculturation and health, Lara and colleagues (2005) describe three major phases of acculturation in Hispanic Americans: 1) the process of learning and forgetting one's history and traditions while changing one's food and media consumption, 2) change in one's language use and preference for social contacts to be primarily from one's nationality or not, and 3) maintenance of one's traditional social norms and adoption of new ones (95). An example of the third phase identified by Sabogal and colleagues (1987) is that while more acculturated Hispanics tend not to feel obligated to their families, nor to use their families as a frame of reference for social norms, they still expect, perceive and receive strong social support from relatives (96).

In their literature review, Lara and colleagues (2005) identify that more acculturated Hispanics generally had poorer illicit drug use, alcohol use, tobacco use, diet, and birth outcomes, although outcome inconsistencies were found based on the outcome studied and the measures for outcome and acculturation variables (95). Complicating our understanding of acculturation and Hispanic health is that more acculturated Hispanics may enjoy greater access to healthcare (97) (98), and that some outcomes are determined more strongly by mother's place of birth rather than time spent or degree of acculturation in the United States. Like Lara and colleagues, other scholars have also identified generally negative health outcomes for more acculturated immigrants who have spent more time in the US and consistently speak English (99) (100). Perhaps unsurprisingly, highly acculturated Latino migrant farm workers who reported high acculturation stress reported poorer self-rated physical and mental health (100). These findings complement anthropological data from regions including Samoa and Siberia, in which individuals with greater exposure to Western influences who have material lifestyles that exceed their incomes have greater EBV reactivation than more rural individuals that live within their means (101) (102) (103).

Our study allows us to better understand the relationship between social support, acculturation and immune function in Mexican Americans, building on work by Eschbach, Markides and colleagues (30) and Ford and Browning (104) who identified favorable mortality outcomes for Mexicans Americans living in high-density Mexican neighborhoods, despite high poverty. This work may help identify potential mechanisms of the Hispanic Paradox and targets for effective public health interventions in the Mexican American community.

Chapter 3 Data and Methods

Chapter 3 will describe the data and methods employed by the study to address the hypothesis and the specific aims. The chapter will begin with a description of the data set generated by the parent study, including the sampling scheme and selection criteria of participants, followed by a discussion of the focal independent variables, dependent variable, and covariates employed in the multivariate models. The chapter will conclude by outlining the analyses planned to address the three specific aims.

DESCRIPTION OF DATA SET

The Texas City Stress and Health Study (15) (14) (105) provides the opportunity to explore differences in the relationship between social support and reactivation of Epstein Barr virus, human cytomegalovirus and herpes simplex virus-1 across racial and ethnic groups. Conducted between 2004 and 2006 in Texas City, Texas, the study provides cross-sectional data on antibody titer of latent EBV viral capsid antigen, EBV early antigen, EBV nuclear antigen, and antigens for CMV and HSV-1 for 1422 participants aged 25 and older (72) (15). Participants lived in a 12-square-mile area bordering oil refineries. The study population comprise 1 in 8 Non-Hispanic households, a census of Mexican American households, and a census of Mexican Americans aged 65 and older in Texas City (14) (105). English or Spanish-language interviews with participants covered topics including demographic characteristics, social support, acculturation and assimilation, stress and coping, and socioeconomic status.

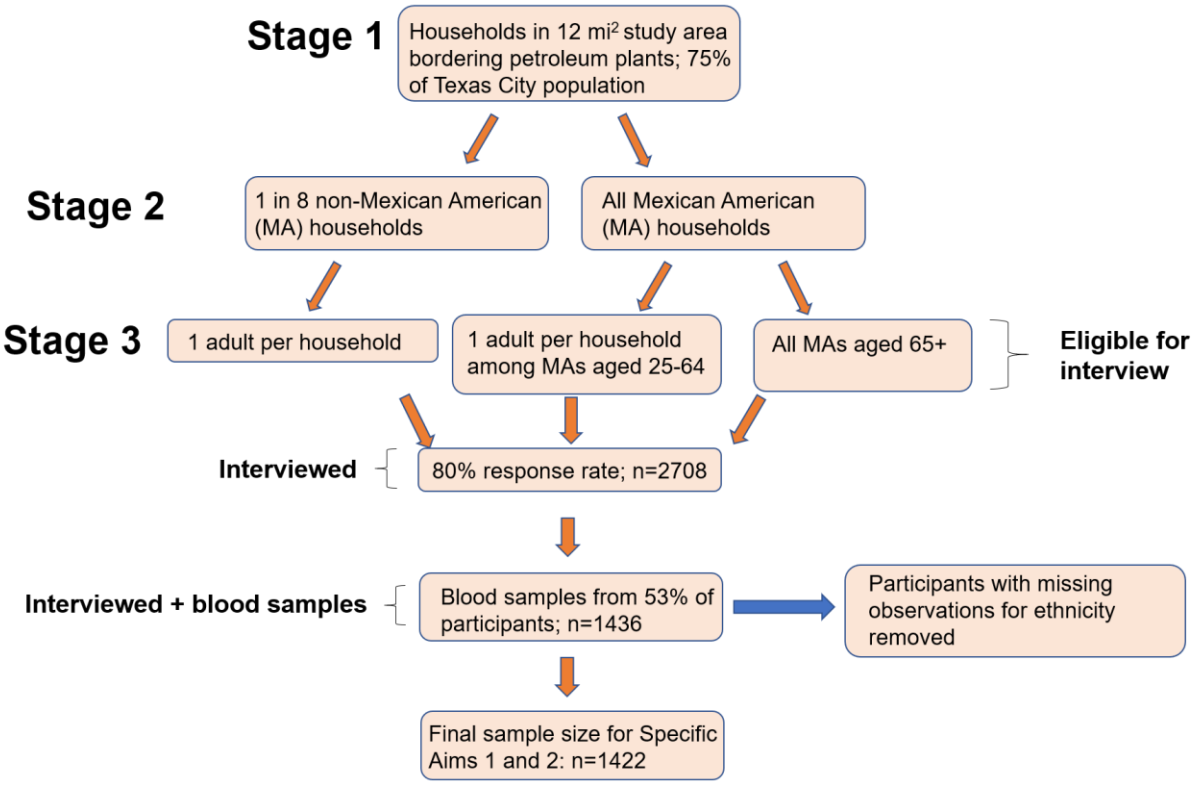

Figure 1 Sampling of participants recruited into the Texas City Stress and Health Study.

INDEPENDENT VARIABLES

The focal independent variables employed were ethnicity, nativity, social support and three measures of acculturation: English language usage, childhood interaction mainstream and adult interaction mainstream (Table 1) (106) (14) (105). Participants fell into one of three categories of ethnicity: Non-Hispanic Black (NHB), Non-Hispanic White (NHW) and Mexican American (both foreign and US-born). Individuals who did not self-identify as one of these three categories, including Hispanics from other Latin American countries, were removed from analysis. Additional analyses separated foreign and US-Born Mexican Americans by nativity, or place of birth, such that four categories emerged: NHW, NHB, US-Born Mexican American and Foreign-Born Mexican American. Social support was measured using a 19-item scale developed

by Sherbourne and colleagues (1991) which detects four dimensions of social support: emotional/informational, tangible, affectionate, and positive social interaction (107). Acculturation instruments were borrowed from Hazuda and colleagues (106) from the San Antonio Heart Study, a study investigating the relationship between Gordon's (1974) seven-stage model of acculturation in Mexican Americans and the prevalence of diabetes and other cardiovascular disease risk factors. The instruments adapted to this study measure the extent to which English is spoken as the dominant language in childhood and adulthood (English Language Usage [ELU]), the distribution of Mexican-origin and Anglo-Americans among neighbors, classmates and friends during childhood (Childhood Interaction Mainstream [CIM]), and the distribution of Mexican-origin and Anglo-Americans among neighbors, coworkers and friends during adulthood (Adult Interaction Mainstream [AIM]).

DEPENDENT VARIABLES

The major dependent variables of the study included reactivation of viral capsid antigen and early antigen of the Epstein Barr Virus (EBV), reactivation of cytomegalovirus and reactivation of herpes simplex virus-1 (HSV-1). Blood samples were taken from participants as described previously (72) (108). Reactivation of each virus was dichotomized, with cutoffs for antibody titers of ≥ 1280 for EBV viral capsid antigen and HSV-1 antigen and ≥ 80 for early antigen (72) (108) (109) (42).

COVARIATES

Age was included as a covariate in the model addressing specific aim 1. In the models addressing specific aims 2 and 3, we controlled for sociodemographic characteristics including age, gender, socioeconomic status (education and income), marital status, health insurance status; health

indicators including perceived stress, physical health problems, and body mass index (BMI); and health behaviors including smoking status and exercising v. sedentary behavior. Education was dichotomized as less than a high school education (12 years of formal education) versus at least a high school education (≥12 years of formal education) and income was dichotomized to less than a $25,000 annual household income versus $25,000 or greater. The two possible responses for marital status were currently married and not currently married, which included statuses such as separated. We did not differentiate between types of health insurance coverage, measuring only its presence or absence. Perceived stress was measured using the standard 10 question Perceived Stress Scale developed by Cohen and colleagues (1983) (110), which detects the severity of perceived stress in the past month using ten questions on a 0-4 Likert scale. The scale was scored as described previously (110) and scores ranged from 0 (low stress) to 40 (high stress). To operationalize physical health, we asked participants if they'd ever experienced or are experiencing the following chronic conditions: stroke/brain hemorrhage, cancer, diabetes, hypertension, overweight, respiratory issues, arthritis, depression, anxiety, heart attack, skin problems, gall bladder disease, and other conditions. Responses were then grouped into four possible categories, from 0 to 3 or more chronic conditions. Clinical BMI was measured and left as a continuous variable in analyses, ranging from 12 to 60. Participants fell into one of three groups for smoking status: former smoker, current smokers and never smokers. Former smokers included individuals who had smoked at least 100 cigarettes or 5 packs of cigarettes in their entire lives. Current smokers are individuals who smoke on some or all days, and never smokers are individuals who have smoked fewer than 5 packs during their life. Smoking questions were adapted from the Behavioral Risk Factor Surveillance System (BRFSS) (111). Physical activity and sedentary behavior questions were modified from the National Health Interview Survey and

International Physical Activity Questionnaire (112). Participants were classified as non-sedentary if they had engaged in at least ten minutes of vigorous activity over the past seven days that caused sweating and large increases in breathing rate or pulse or at least ten minutes of moderate activity over the past seven days that caused light sweating and mild to moderate increases in breathing rate or pulse. Participants were classified as sedentary if neither of these conditions applied.

STATISTICAL ANALYSIS

Specific Aim 1

To determine the mean difference in social support scores between NHW, NHB, Foreign-Born MA and US-Born MA, the normality of the distributions of social support scores within the four groups and the equality of their variances were assessed with the Anderson Darling Goodness-of-Fit test and Levene's test. Because the distributions were found to be non-normal and found to have unequal variances, a Kruskall Wallis test was applied to compare mean social support scores among the four groups. A similar Kruskall Wallis test was conducted, this time pooling the US and Foreign-Born MA. Following both tests, post-hoc Mann Whitney comparisons controlling for age and with Bonferroni corrections were applied to identify individual differences between the four racial/ethnic subgroups.

Next, we sought to determine if the proportion of individuals who were isolated differed between NHB, NHW, US and Foreign-Born MA. Isolation was operationalized by counting the bottom 30% of SS scores. Chi square tests of fit were applied to determine whether the distribution of

isolated v. non-isolated individuals differed between NHW, NHB, US-Born MA and Foreign-Born MA. The tests were repeated pooling the MA.

Specific Aim 2

In Specific Aim 2, we sought to determine main effects of the association between social support and viral reactivation and the interaction effect between black race or Mexican origin and social support on reactivation. For all subsequent analyses, isolation, or the participants who scored in the bottom 30% of SS scores, was used. To examine the main effect, a basic descending logistic regression was constructed, including only the independent variable isolation and the dependent variable, reactivation of two or more herpesvirus antigens (Model 1). Individuals who surpassed the titer cutoff for at least two antigens from any virus were included in this category, including individuals who only surpassed the cutoff for VCA and EA, two types of antigens from EBV. A second descending logistic regression model was constructed with the covariates described above (Model 2). Nativity was not included in this model; US and Foreign-Born Mexican Americans were pooled together. A third model was constructing using the same variables as Models 1 and 2, but adding the interaction terms NHW*isolation and MA*isolation where MA includes both US and Foreign-Born Mexican Americans (Model 3). For Models 1-3, the global null hypothesis (B=0) was also evaluated using a Likelihood-Ratio test which generated a global p-value for each model.

Specific Aim 3

In Specific Aim 3, we sought to determine whether acculturation and nativity, or birthplace, impact the relationship between isolation and reactivation. We restricted our analysis to US and

Foreign-Born MAs. First, we ran a logistic regression of the main effects of isolation on reactivation of two or more herpesvirus antigens, while controlling for nativity (Model 4). Next, we included the covariates employed in Models 2 and 3 for Specific Aim 2 (Model 5). In Model 6, we included an interaction term nativity*isolation to determine if the effect of isolation on reactivation of two or more herpesvirus antigens was modified by country of birth.

To understand the role of acculturation in the association between isolation and reactivation in Mexican Americans, we constructed a seventh model, adding acculturation as a covariate to Model 6, retaining the interaction term nativity*isolation. Acculturation was measured as a continuous sum of the scores participants received for ELU, CIM and AIM, which collectively measure the extent to which English or Spanish is the participants' dominant language, and the predominance of Anglo Americans or Mexican Americans among social contacts in childhood and adulthood. To ensure that using a summated measure did not bias our results, sensitivity analyses were conducting using only ELU, CIM or AIM. The results were not greatly altered.

Table 1. Variables used in analysis.

Variable Type	**Variable**	**Reference**	**Definition/Measurement**
Focal Independent Variable	Race/Ethnicity	(14) (105)	NHW, NHB, MA
	Race/Ethnicity/Nativity	(14) (105)	NHW, NHB, US-Born MA, Foreign-Born MA
	Nativity	(14) (105)	US-born, foreign-born
	Social Support	(107)	100 item scale ranging from low social support (0) to high social support (100); reflects five dimensions: emotional support, informational support, tangible support, positive social interaction and affectionate support

	Isolation	(107)	Social support dichotomized into bottom 30% and top 70% of scores
	English Language Usage (ELU)	(106)	8 questions concerning the extent to which English or Spanish is used as the dominant language in childhood and adulthood. Scores ranged from 6 (low English usage) to 28 (high English usage)
	Childhood Interaction Mainstream (CIM)	(106)	5 questions on the ethnicity (Anglo American v. Mexican) of neighbors, friends and classmates during childhood. Scores ranged from 3 (mostly Mexican) to 9 (mostly Anglo)
	Adult Interaction Mainstream (AIM)	(106)	6 questions on the ethnicity (Anglo American v. Mexican) of neighbors, friends and coworkers during adulthood. Scores ranged from 4 (mostly Mexican) to 12 (mostly Anglo)
	Acculturation	(106)	Sum of scores on the ELU, CIM and AIM scales
Dependent Variable	Reactivated EBV Viral Capsid Antigen (VCA)	(72)	Reactivated = antibody titers 1280 and above
	Reactivated EBV Early Antigen (EA)	(72)	Reactivated = antibody titers 80 and above
	Reactivated Cytomegalovirus	(113)	
	Reactivated Herpes Simplex Virus-1 (HSV-1)	(72)	Reactivated = antibody titers 1280 and above
	Reactivation of 2 or more antigens	(72) (105)	Individuals with reactivation of two or more antigens. Individuals with missing values on any antigens were removed*
Covariates	Age	N/A	Continuous variable
	Gender	N/A	Male or Female

	Education	(14) (105)	< 12 years formal education v. ≥ 12 years
	Income	(14) (105)	< $25,000 annual income v. ≥ $25,000
	Marital Status	(14) (105)	Currently married v. all other arrangements
	Health Insurance	(14) (105)	Having health insurance (any kind) v. no insurance
	Perceived Stress (PSS)	(110)	10-question perceived stress scale measuring perceived stress in the past month. Responses can range from 0 (no stress) to 40 (high stress)
	Health Conditions	(14) (105)	Experienced or currently experiencing 0, 1, 2 or 3 or more of the following chronic conditions: stroke/brain hemorrhage, cancer, diabetes, hypertension, overweight, respiratory issues, arthritis, depression, anxiety, heart attack, skin problems, gall bladder disease, other condition
	BMI	(14) (105)	Clinical BMI (ranged from 12 to 60)
	Smoking	(111)	Former smoker (has smoked at least 5 packs in lifetime but does not currently smoke some or all days); Current smoker (has smoked at least 5 packs in lifetime and currently smokes some or all days); never smoker (smoked fewer than 5 packs over lifetime)
	Physical Activity	(112) (114)	At least ten minutes of vigorous or moderate physical activity over the past seven days v. fewer than ten minutes

*A sensitivity analysis was conducted retaining participants with missing values to ensure that the results were not affected by the exclusion of these participants.

Chapter 4 Results

Chapter 4 will describe and synthesize the results of the analyses described in chapter 3, preceded by a descriptive analysis of the focal independent variables, dependent variables and covariates used in multivariate models.

DISTRIBUTION OF INDEPENDENT VARIABLES

Table 2 describes the distribution of each variable in our study sample (n=1422). Approximately equal percentages of Non-Hispanic Whites (36.9%) and US-Born Mexican Americans (37.8%) participated in the study, while fewer Non-Hispanic Blacks (10.5%) and Foreign-Born Mexican Americans (14.8%) were found. No observations were missing from the isolation scores. The acculturation measures, childhood interaction mainstream (CIM), adult interaction mainstream (AIM) and English language usage (ELU), demonstrate that this study sample of Mexican American adults was not very acculturated. Between a possible range of 3-9 for CIM, where a higher score indicates that childhood social networks were dominated by Anglo-Americans rather than Mexican-origin individuals, the average score was a 5, although the spread of the CIM scores was large (approximately 2). Perhaps unsurprisingly, given that many participants in the study immigrated from Mexico, adult interaction (AIM) scores were higher than CIM (mean = 7.9), out of a possible score between 4 and 12, indicating that Anglo-Americans played a larger role in the social networks of Mexican-origin participants in adulthood rather than childhood.

The difference between CIM and AIM scores suggests the influence of acculturation in the sample, though it is not possible to tell whether the same adults were given CIM and AIM scores, due to the difference in response rates for each (1294 v. 831). In a possible range of scores between 6 and 28 for English language usage (ELU), adults scored slightly higher than the midpoint (18.1), though this measure too was characterized by a large spread (SD = 6.8). The summed score of the AIM, CIM and ELU dimensions solves the problem of missing observations, which make it difficult to compare scores from the three dimensions, while also allowing us to efficiently control for each acculturation variable in regression models with the least number of covariates possible. The average of the summed scores (31.7), available for 793 participants, was slightly higher than the midpoint of all possible scores (13-49). Acculturation questions were asked only of US-born and foreign-born Mexican American participants, accounting for the sharp decrease in sample size between ethnicity and acculturation variables.

DISTRIBUTION OF DEPENDENT VARIABLES

Among participants with available reactivation scores for each antigen tested, which included antigens for HSV-1, CMV, and two antigens for EBV, over two times as many applicants had reactivation of 1 or fewer antigens (69.3%), compared to two or more (30.7%).

Table 2. Sample (n=1422) Distributions of major independent and dependent variables and covariates in the study.*

	Sample Size	**%**	**Mean (SD)**	**Range**
	Focal Independent Variables			
Ethnicity				
NHW	524	36.9		

NHB	149	10.5		
US-Born MA	538	37.8		
Foreign-Born MA	211	14.8		
Nativity*				
US-born (MA)	977	72.4		
Foreign-born (MA)	373	27.6		
Isolation**				
Isolated	423	29.8		
Non-isolated	999	70.3		
Acculturation*				
Childhood Interaction Mainstream (CIM)	1294		5.0 (1.9)	3-9
Missing	56			
Adult Interaction Mainstream (AIM)	831		7.9 (1.9)	4-12
Missing	15			
English Language Usage (ELU)	1335		18.1 (6.8)	6-28
Missing	15			
Acculturation (summed scores)	793		31.7 (9.2)	13-49
Missing***	557			
	Dependent Variables			
Reactivation**				
Reactivation of two or more antigens	437	30.7		
Reactivation of one or fewer antigens	985	69.3		
	Covariates			
Sociodemographics				
Age	1422		51.8 (16.0)	25-90
Gender				
Female	855	60.1		
Male	567	39.9		
Education				
Fewer than 12 years	537	37.9		
12 years or greater	880	62.1		
Missing	5			

Income				
Low Income (<$25,000)	560	39.4		
Higher Income	862	60.6		
Marital Status				
Married	818	57.5		
Unmarried	604	42.5		
Health Insurance				
Insured	859	60.4		
Uninsured	563	39.6		
Health Indicators				
Perceived Stress	1404		13.2 (7.3)	0-39
Missing	32			
Chronic Conditions				
0 conditions	257	18.1		
1 condition	248	17.4		
2 conditions	253	17.7		
3 or more conditions	666	46.8		
Missing	0			
Clinical BMI	1366		30.5 (7.2)	13-60
Missing	56			
Health Behaviors				
Smoking Status				
Current Smoker	381	26.8		
Former Smoker	342	24.1		
Non-smoker	697	49.1		
Missing	2			
Sedentary Activity				
Sedentary	380	26.7		
Non-sedentary	1042	73.3		
Missing	0			

*Nativity and acculturation frequencies apply only to Mexican-origin participants (n=1350).

**The distribution of isolated v. not-isolated social support scores deviates slightly from the top 70% and bottom 30% of scores. Social support scores were dichotomized before the removal of some participants with missing observations for ethnicity or reactivation variables. The distribution of isolated v. not-isolated participants differs from a 30% to 70% ratio by 0.2-0.3%.

***Frequencies of categorical variables were normalized to exclude missing observations.

****All descriptive statistics and subsequent analyses reported here reflect the group of participants for which reactivation data was available (n=1422).

DESCRIPTION OF COVARIATES

Participants' ages ranged between 25 and 91, with an average age of 52 and a standard deviation of 16 years. There were approximately twenty percent more females (58.4%) than males (41.6%). The predominance of low socioeconomic status in our sample, denoted by the proportion of individuals with fewer than 12 years of formal education (37.7%) and an annual household income fewer than $25,000 (39.3%) underscores our decision to dichotomize education and income measures into fewer than 12 years v. 12 years and greater and fewer than $25,000 v. greater, rather than leave both measures as continuous. Very few missing observations were observed for education (8) and income (0). The distribution of married v. unmarried participants was roughly evenly split (57.7% v. 42.3%), although the distinction between married and unmarried masks other social arrangements, including divorced, separated, cohabiting, and dating, which may have been common in our sample, given that lower income and younger individuals are less likely to be married. Approximately 20% more individuals had health insurance (60.5%) compared to those who lacked it (39.5%), though our categorization of insurance does not differentiate between individuals covered by Medicaid versus insurance offered through employment. Participants were interviewed between 2004 and 2006, well before additional insurance options became available through the Affordable Care Act. Of the 1,404 individuals for which perceived stress scores were available, the average score was a 13.2 out of a total possible score ranging between 0 (low stress) and 40 (high stress), indicating that the study sample was not highly stressed. While almost a quarter of the participants had 0 chronic conditions among the comprehensive list (18.2%), over 40% had three or more. About half the sample had smoked fewer than five packs of cigarettes over their lifetimes (48.9%), although roughly 25% of participants were current smokers and about 25% had formerly smoked. 26.8%

of participants had reported fewer than ten minutes of moderate or vigorous physical activity in the past week.

SPECIFIC AIM 1

To understand the nature of the difference in social support between ethnicities and nativities in our study sample, four comparisons were conducted: a comparison of continuous social support scores between NHW, NHB, US-born Mexican Americans and Foreign-Born Mexican Americans; a similar comparison pooling the US and Foreign-Born Mexican Americans; and comparisons of the frequency of isolation (bottom 30% of social support scores) between the same racial/ethnic groups above.

A Kruskall-Wallis for the first comparison, which consisted of 1,422 observations, identified significant differences between social support scores between the four racial/ethnic subgroups (Chi square = 32.5; $p< 0.0001$). Post-hoc Mann Whitney U comparisons controlling for age, with Bonferroni correction indicate that social support scores did not differ between NHW (82.8) and NHB (79.6). However, NHB did have significantly lower social support than US-Born MA (86.1) and Foreign-Born MA (88.5). NHW had significantly lower social support than Foreign-Born MA, but not US-Born MA. Scores did not differ significantly between US and Foreign-Born MA. When Mexican Americans were pooled (mean SS = 0.56), resulting in three racial/ethnic groups, the Kruskall Wallis test was similarly significant (Chi square = 27.6, $p<0.0001$). Here, post-hoc Mann Whitney U comparisons controlling for age with Bonferroni

correction identified significant differences in SS scores between NHB and NHW and NHB and Mexican Americans, but not between NHW and Mexican Americans.

A chi-square goodness-of-fit test applied to the frequency of isolation among NHW, NHB, US-Born MA and Foreign-Born MA revealed significant differences among the four groups. To identify differences between specific groups, pairwise chi square tests were applied with a Bonferroni corrected p-value of 0.008. The Bonferroni-corrected p-value was determined by dividing the type-1 error rate (0.05) by 6, the number of planned comparisons, representing pairwise comparisons between NHW, NHB, US-Born MA and Foreign-Born MA. No significant differences in the ratio of isolated to non-isolated individuals were identified between US-Born MA (0.27 : 0.73) and Foreign-Born MA (0.20 : 0.80), or between NHW (0.32 : 0.68) and US-Born MA or NHW and NHB (0.42 : 0.58). However, the ratios of isolated to non-isolated individuals differed significantly between NHB and US-Born MA ($p=0.008$), NHB and Foreign-Born MA ($p<0.001$), and NHW and Foreign-Born MA ($p=0.001$). When Mexican Americans were pooled together, the ratio of isolated to non-isolated individuals was 0.25 : 0.75. Pairwise comparisons revealed significant differences in the distribution of isolated to non-isolated individuals among Mexican Americans and NHW ($p=0.006$) and Mexican Americans and NHB ($p<0.001$). For these two planned Mann Whitney comparisons, a Bonferroni-corrected p-value of 0.025 was used.

Table 3. Distribution of isolated and non-isolated individuals among US-born Mexican Americans, Foreign-Born Mexican Americans, Non-Hispanic Whites and Non-Hispanic Blacks.

	US-Born MA	**Foreign-Born MA**	**NHW**	**NHB**
Not isolated	0.73	0.80	0.68	0.58
Isolated	0.27	0.20	0.32	0.42

SPECIFIC AIM 2

To better understand the relationship between social support, Hispanic ethnicity and herpesvirus reactivation, three logistic models were constructed: one which measures the main effect of social support on reactivation; a second which controls for various sociodemographic, health, and behavioral factors; and a third which modifies the second model by testing for an interaction effect between ethnicity and social support. For each model, the event of interest was reactivation of two or more herpesvirus antigens. Mexican American participants were pooled together, irrespective of their place of birth.

Table 4 describes the associations detected with each model. In the first model, with a significant global p-value, generated using a Likelihood ratio test, ($p=0.0002$), isolation was significantly and positively associated with reactivation of two or more herpesvirus antigens (OR 1.59). In the second model (global $p<0.0001$), isolation (OR 1.39), female gender (OR 1.46), and black race (OR 1.72) were significantly and positively associated with reactivation while age (OR 1.03) and BMI (OR 1.03) approached significance. 87 subjects from Model 1 were unable to be included in Model 2 due to missing observations in the independent, dependent or covariate variables. In the third model (global $p<0.0001$), controlling for potential interaction effects between Hispanic

ethnicity and isolation and Black race and isolation removed the significant positive association between isolation and reactivation and Black race and reactivation. Only female gender remained significantly and positively associated with reactivation (OR 1.47) while age (OR 1.03) and BMI (OR 1.03) approached significance. The results did not change greatly when the dependent variable was modified to include all individuals with reactivation of two or more herpesvirus antigens, regardless of missing observations for various antigens (data not shown). Evidence for an interaction effect of black race and isolation and Hispanic ethnicity and isolation on reactivation was not supported.

Table 4. Results of descending logistic regressions estimating the likelihood of reactivation in Non-Hispanic White, Non-Hispanic Black, and Mexican American participants in the Texas City Stress and Health Study (2004-2006).

	OR (95% CI)		
	Model 1	**Model 2**	**Model 3**
Sample Size	1422	1335	1335
Independent Variable			
Isolation	1.59 (1.25, 2.02)*	1.40(1.06, 1.84)*	1.12 (0.72, 1.73)
Age		1.03 (1.02, 1.04)	1.03 (1.02, 1.04)
Male		Referent	Referent
Female		1.47 (1.12, 1.94)*	1.47 (1.11, 1.93)*
Married		1.00 (0.77, 1.30)	0.99 (0.76, 1.30)
NHW		Referent	Referent
NHB		1.70 (1.12, 2.57)*	1.48 (0.86, 2.54)
Hispanic		1.19 (0.89, 1.59)	1.06 (0.75, 1.49)
12 years or greater		Referent	Referent
Fewer than 12 years		1.17 (0.89, 1.54)	1.17 (0.89, 1.54)
Higher Income		Referent	Referent
Low Income		1.04 (0.79, 1.36)	1.04 (0.79, 1.37)
Sedentary		1.06 (0.80, 1.40)	1.07 (0.81, 1.41)
Health Insurance		0.87 (0.65, 1.15)	0.87 (0.65, 1.16)
Clinical BMI		1.03 (1.01, 1.05)	1.03 (1.01, 1.05)*
Non-smoker		Referent	Referent
Former Smoker		1.00 (0.73, 1.37)	1.00 (0.73, 1.37)

Current Smoker		1.00 (0.73, 1.37)	1.00 (0.73, 1.36)
Chronic Conditions		0.89 (0.79, 1.02)	0.89 (0.79, 1.01)
Perceived Stress		1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
NHW X Isolation			Referent
NHB X Isolation			1.43 (0.62, 3.25)
Hispanic X Isolation			1.44 (0.81, 2.53)

*Indicates results significant at the alpha level of 0.05.

SPECIFIC AIM 3

To understand the relationship between nativity, acculturation, social support and reactivation in Mexican Americans, we applied three descending logistic regressions: the first (Model 4) which tests the association between reactivation of two or more herpesviruses and isolation and nativity; the second (Model 5), which includes the covariates from Model 2 and the covariate nativity; and a third model (Model 6), which includes the covariates of Model 5 and an interaction term isolation X nativity. Stratified analyses were conducted where applicable (Models 7 and 8). Lastly, we controlled for the potential influence of acculturation on the interaction between nativity and isolation (Model 9). For all models, as in specific aim 2, the global null hypothesis (B = 0) was also tested and global p values were reported. NHB and NHW participants were not considered in these analyses.

Table 5 describes the associations found for Models 4-9. Sample sizes varied between the models because of missing observations. For each model, we used the maximum number of participants with no missing observations for each of the variables. In the main effects model (Model 4), which was significant overall ($p<0.005$), isolation, but not nativity, was significantly

associated with reactivation of two or more herpesvirus antigens (OR 1.78). Model 5 ($p<0.001$) demonstrated significant positive associations between reactivation and isolation (OR 1.66), while the covariates age (OR 1.03) and BMI (1.03) approached significance. Sixty-three subjects were not incorporated due to missing observations in the independent, dependent or covariate variables, yielding a sample size of 663. Model 6 ($p=0.0001$) demonstrated a strong, positive interaction effect of nativity and isolation on reactivation of two or more herpesviruses (OR 3.59; 95% CI 1.14, 11.3), while no other covariates were significant. Among US-born Mexican Americans (Model 7; $p<0.0001$), isolation was significantly and positively association with reactivation (OR 2.07) while age (OR 1.03) and BMI (1.03) approached significance. Thirty-two US-Born MA were excluded from this analysis due to missing observations in the independent, dependent, or covariate variables. Model 8, an identical subgroup analysis in Foreign-Born Mexican Americans, was not significant. Eighteen Foreign-Born MA subjects were removed from this model due to missing observations in one of the variables. Lastly, controlling for acculturation (Model 9) removes the significant interaction between nativity and social support on reactivation. In this last model ($p<0.005$), female gender was significantly and positively associated with reactivation (OR 2.00), while individuals with reactivation of two or more herpesvirus antigens were less likely to have been former smokers than current smokers or never smokers (OR 0.43). Unfortunately, 369 participants had to be excluded from this model due to missing observations for one or more of the variables in the model.

Table 5. Results of descending logistic regressions estimating the likelihood of reactivation in US and Foreign-Born Mexican American participants of the Texas City Stress and Health Study (2004-2006).

	OR (95% CI)					
	Model 4	**Model 5**	**Model 6**	**Model 7**	**Model 8**	**Model 9**
Sample Size	713	663	663	506	157	344
Independent Variable						
Isolation	1.78 (1.24, 2.54)*	1.66 (1.10, 2.50)*	0.58 (0.20, 1.67)	2.07 (1.30, 3.26)*	0.53 (0.18, 1.60)	1.11 (0.25, 4.89)
Nativity	1.18 (0.80, 1.73)	1.00 (0.63, 1.61)	0.79 (0.48, 1.32)			1.04 (0.41, 2.67)
Age		1.03 (1.02, 1.05)	1.03 (1.02, 1.04)	1.03 (1.02, 1.05)	1.02 (0.99, 1.05)	1.04 (1.02, 1.06)
Male		Referent	Referent	Referent	Referent	Referent
Female		1.41 (0.94, 2.10)	1.46 (0.97, 2.18)	1.59 (1.00, 2.53)	1.08 (0.46, 2.55)	2.00 (1.12, 3.55)*
Married		0.87 (0.60, 1.28)	0.88 (0.60, 1.28)	0.83 (0.54, 1.28)	1.02 (0.42, 2.48)	1.08 (0.62, 1.88)
12 years or greater		Referent	Referent	Referent	Referent	Referent
Fewer than 12 years		0.95 (0.65, 1.40)	0.95 (0.65, 1.39)	0.92 (0.60, 1.43)	0.99 (0.42, 2.30)	1.11 (0.63, 1.96)
Higher Income		Referent	Referent	Referent	Referent	Referent
Low Income		1.11 (0.75, 1.65)	1.13 (0.76, 1.67)	0.96 (0.61, 1.51)	1.80 (0.77, 4.23)	0.92 (0.50, 1.69)
Sedentary		1.14 (0.77, 1.69)	1.14 (0.77, 1.69)	1.22 (0.77, 1.92)	1.00 (0.43, 2.33)	1.63 (0.91, 2.95)
Health Insurance		0.95 (0.64, 1.42)	0.97 (0.65, 1.44)	0.94 (0.59, 1.49)	1.02 (0.39, 2.68)	0.84 (0.45, 1.57)
Clinical BMI		1.03 (1.00, 1.06)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)	1.02 (0.95, 1.09)	1.03 (0.99, 1.07)
Non-smoker		Referent	Referent	Referent	Referent	Referent
Former Smoker		0.77, 0.49, 1.23)	0.80 (0.50, 1.28)	0.73 (0.43, 1.23)	0.99 (0.33, 2.96)	0.43 (0.21, 0.89)
Current Smoker		0.88, 0.55, 1.42)	0.89 (0.55, 1.43)	0.75 (0.44, 1.29)	1.95 (0.63, 6.07)	0.87 (0.46, 1.64)
Chronic Conditions		0.84 (0.71, 1.01)	0.85 (0.71, 1.02)	0.88 (0.72, 1.08)	0.81 (0.55, 1.20)	0.80 (0.63, 1.03)
Perceived Stress		1.00 (0.98, 1.03)	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)	0.99 (0.93, 1.05)	0.99 (0.95, 1.03)
Acculturation						0.99 (0.95, 1.03)
Nativity X Isolation			3.59 (1.14, 11.34)*			1.36 (0.27, 6.90)

Chapter 5 Discussion

Chapter 5 will compare and contextualize the results of the present study to trends from the literature. Directions for further research will also be identified. Following this discussion, the strengths and limitations of the present study will be discussed. A summary of the principal findings of the study will conclude this chapter.

SPECIFIC AIM 1

Non-Hispanic Blacks scored lower on the Medical Outcome Survey (MOS) social support scale than Non-Hispanic Whites and US and Foreign-Born MA (Table 2). However, the largest difference in mean social support scores between any two groups was 6.4 points, out of a scale from 0-100. Large sample sizes for each racial/ethnic group could have contributed to identifying small but significant differences between groups, such as the 2.7-point difference between US-Born MA and NHW. However, when looking at the proportions of individuals who scored in the bottom 30% of the distribution of social support scores, a group we classified as isolated and the prominent exposure variable in our study, the differences became starker. Thirty-two percent more blacks scored in the bottom 30% than NHW, while the difference in isolation among NHB and MA grew to 58%. Nevertheless, out of a total score of 0-100, isolated individuals still scored highly on the Medical Outcome Survey scale, with a five-number summary of 0, 50, 64.5, 75 and 77.6 and a mean of 60.3. Curiously, the distributions of isolated scorers among racial/ethnic subgroups were very similar, with means ranging between 59.0 and 61.5. However, while the

distribution of isolated scorers is strongly and negatively skewed for each racial/ethnic subgroup, with many participants scoring around 75, close to the maximum score among isolated participants, the medians of the distributions of isolated scorers differed among racial/ethnic subgroups, with Foreign-Born MA having the smallest score (61.8), followed by NHB (62.5), and US-Born MA and NHW (both 65.8).

When the MOS social support scale was initially developed and tested in 1991, the participants' average score on each of the five subscales included fell between 69.6 to 73.7 (107), higher than the scores among isolated participants of our study, but lower than the overall mean (85) and median (95) of our study. A few key differences exist between the study population on which the MOS Social Support Scale was developed, and the population targeted in the Texas City Stress and Health Study. Unlike our population, potential MOS participants were excluded if they could not take the survey in English. Additionally, participants had to be diagnosed with at least one of the following chronic conditions: diabetes, hypertension, coronary heart disease, or depression. Although over three quarters of our participants identified as having at least one chronic condition, including diabetes, hypertension, heart disease and depression, others could have had stroke, cancer, overweight, respiratory issues, arthritis, anxiety, skin problems or gall bladder disease, conditions which differ in severity and in potential impact on participants' quality of life than the narrow list of conditions included in the MOS study sample. Additionally, Sherbourne and Stewart identify key selection biases among individuals who chose to participate in their study, who were more likely to be younger, educated, higher income, married or employed than those that declined to participate. A higher proportion of MOS study participants were married than in the Texas City Stress and Health Study, although fewer had graduated high school than in

our sample. MOS participants, on average, were only 6 years older than Texas City participants. The five dimensions tested in the MOS Social Support Survey include emotional support (empathy, positive affect, and allowing the participant to freely express feelings), informational support (advice, information, or guidance), tangible support (material support), positive social interaction (individuals with which to pursue recreational activities), and affectionate support (availability of love and affection). These subscales are not meant to gauge concepts that are related to but distinct from social support, including loneliness, family functioning, social activity limitation, and mental health (107).

Surprisingly, racial and ethnic disparities in social support as measured by the Medical Outcome Survey were not commonly reported. An investigation of a longitudinal cohort of NHW, NHB, US-born Latino, foreign-born Latino, and Asian caregivers living in Chicago, the Project on Human Development in Chicago Neighborhoods, finds that, like our results, foreign-born and US-born Latinos reported higher overall perceived social support than NHW, even after controlling for age, gender, SES and marital status (115). Curiously however, no significant differences in perceived support were identified between US-born Latinos, foreign-born Latinos, and Asians, whereas NHB scored significantly lower on perceived support than every other group in the Texas City study, and more NHB were isolated than in the other groups. In their study, Almeida and colleagues differentiate between perceived familial support and perceived friend support, to study the relationship between acculturation and types of social support, where acculturation was operationalized with citizenship status and dominant language used at home, comparable to the English language usage subscale that we employed to measure acculturation in Texas City participants. In the Chicago-based participants, SES modified the effect of

race/ethnicity on perceived support and the type of support received. Latinos at higher SES groups reported lower familial support than those at lower SES, although a similar effect was not found for friend support. At each SES level, NHW reported higher levels of friend support than Latinos, suggesting that acculturation may influence which type of social support plays a larger role in one's life. Lending credence to this hypothesis were the findings that controlling for citizenship status and language used at home reduced the effect of Latino ethnicity and foreign nativity on perceived social support and the finding that Latinos who spoke English at home reported higher perceived friend support than Spanish-speaking Latinos. Curiously, an interaction effect between SES and race/ethnicity on perceived support was not identified for non-Latinos (115). The results from the Project on Human Development in Chicago Neighborhoods Study suggest that the potential impact of SES and acculturation on racial/ethnic differences in perceived social support should be considered, especially given the dissimilar proportions of low-income participants among racial/ethnic groups in our study (Table 2). The results also suggest that racial/ethnic differences in social support may differ geographically, as the cultural, political, social, and economic conditions shaping communities likely differ between Chicago and Texas City.

Other potential explanations for racial/ethnic differences in perceived social support among Texas City participants abound. Interpreting the findings from the 2003 US Current Populations Report (116), Landale and colleagues (2006) (117) suggest that differences in living arrangements between racial and ethnic groups may influence social support. In 2003, only a year before the start of the Texas City Stress and Health Study, NHW and Mexican American children were much more likely to live in two-parent households than NHB children (77%, 67%,

and 37%, respectively). Among adults between ages 25 and 64 and the elderly over age 65, proportionally more Mexican Americans nationwide were living with extended family members than NHW (10% v. 2% for ages 25-64 and 5% v. 15% for adults over 65).

It is more difficult to interpret the differences in the proportion of individuals scoring within the bottom 30% of the MOS survey distribution among NHW, NHB, US-Born MA and Foreign-Born MA participants, where a considerably higher proportion of NHB scored within the bottom 30% than any other group. According to the 2000 US Census, 60.7% of Texas City residents identified as white, where 50.1% were Non-Hispanic, while 27.5% identified as Black, and 16.3% as Mexican American (118). Social epidemiologist David Williams (119), sociologists Bruce Rankin and James Quane (120) and others have written about the relationship between racial residential segregation and social isolation, where social isolation is defined as a disconnect from mainstream society. However, this is not precisely what the MOS survey measures, the perception of available social support.

SPECIFIC AIM 2

In our three models, isolation was strongly and positively associated with reactivation of at least two herpesvirus antigens (OR 1.57), confirming our hypothesis and the association between social support and reactivation in diverse populations including caregivers and students (20) (21). A well-supported mechanism for the association between social support and reactivation is the “buffering hypothesis” in which the perceived availability of social support buffers an individual against some harmful effects of stressors on immune dysregulation, such as viral

reactivation (121) (122) (123) (124) (84). The hypothesis is thought to function by reducing the likelihood that an individual will appraise a response as stressful (125), reducing or changing a person's harmful psychological response to the event, reducing thoughts that maintain chronic stress responses to problems, or by providing an answer, distraction or reduction of the problem (126) (84). If this model were extended to the Texas City sample, individuals who perceived less support in their lives would have less protection shielding them from the harmful effects of potential stressors on their immune systems, such as aging, poverty, or chronic disease. Indeed, social support has been associated with various improved immune responses to stress in populations such as spouses of cancer patients (127), undergraduate and medical students (128) (43), middle-aged men (129) older adults, cancer patients (130) and HIV patients (131). However, in many of these studies, including those that are specifically linked to reactivation (17) (132) (23) social support acts as an effect mediator or effect modifier in the pathway between stress and immune function, a relationship that differs from the multivariate association between social support and reactivation tested in our study. In the Texas City sample, lack of perceived social support served as the direct stressor that we hypothesized and found was associated to immune dysfunction. Several of the studies above (127) (43) (131) dichotomized social support measures into higher and lower groups as we did.

Also interesting was the identification of female gender (OR 1.45) and black race (OR 1.74) as independent factors positively associated with reactivation (Model 2), especially given that men's immune systems have been demonstrated to age faster than women's (133). Several potential explanations for the increased odds of female gender on individuals with reactivation exist. Female sex is associated with higher prevalence of CMV (48) (50) (53) . It is possible that

a higher proportion of females than males were originally infected with EBV, CMV and HSV-1. However, this is unlikely because of the age of our participants (mean age 45) and the large proportion of participants who were born outside the US. Perhaps some of the women surveyed were pregnant, a source of stress associated with reactivation of EBV and CMV in various prospective studies (40) (134). Forty eight percent of female Texas City participants were of child-bearing age, between 17 and 45 years. Hormonal contraception has also been implicated as a risk factor of HSV-2 reactivation (135); perhaps many of our female participants used this method. It is also possible that differences in social support networks (90) perceived stress, socioeconomic status, or age between women and men contributed to the association of female gender and reactivation, although years of formal education, household income, perceived stress and age were controlled for in the regressions. On average, women scored about 2.5 points higher in the Perceived Stress Scale, a small difference in a scale ranging from 0-40 points. However, women were much more likely to be low income than men: while only 27% of men reported household incomes under $25,000 a year, 47% of women did. Female participants (median 45 years) were generally younger than male participants (median 48 years), opposite of what would be expected given that increasing age is associated with higher prevalence of reactivation (42).

Black-white differences in herpesvirus antibody titers have been observed in nationally-representative samples including NHANES (104). In a study of EBV antibody titers compared between Black, White and Mexican American youth, Black Americans had significantly higher antibody titers than whites, while no difference was found between Mexicans and Whites (104). Several studies support a potential role for racism in exposing Black Americans to greater

psychosocial stress that weakens immune function. In a longitudinal study of Black and White pregnant women, Black expectant mothers had significantly higher EBV viral capsid antigen titers than White mothers, and the difference was greater among Black mothers who reported higher racial discrimination. Furthermore, the association between racism and EBV titer was not explained by other measures of psychosocial stress included in the study (136). Other investigators measured antibody titer to an influenza vaccine longitudinally in Black adults who were randomized to a group instructed to write about their thoughts and feelings of racism v. their shopping for the week. One and three months after the vaccination, adults randomized to the racism group had significantly lower antibodies to 2 of 3 viral strains (137). Notably, after controlling for gender and age in a linear regression between race and scores on the perceived stress scale to determine whether Black Texas City participants experienced more psychosocial stress, Black race was associated with perceived stress (coefficient = 0.94), while Hispanic ethnicity was slightly protective (coefficient = -0.07).

Perhaps the most surprising result in our models addressing Specific Aim 2 was the lack of support for an interaction effect between race and social support on reactivation, contrary to our hypothesis. While not many studies have investigated an interaction effect between race/ethnicity and social support on reactivation, support exists for effect modification by social support of the association between race and hypertension (138) (139). Our results suggest that the association between isolation and reactivation of two or more herpesvirus antigens identified in Model 1 is not modified by the race or ethnicity of the participants. Our cross-sectional study design does not test whether isolation is causally related to herpesvirus reactivation or even whether isolation increases the risk of reactivation. However, if a causal pathway exists between isolation and

reactivation, the lack of an interaction effect between race/ethnicity and support in our study suggests that such a pathway could function similarly among NHB, NHW and Mexican Americans. Prospective studies are needed to establish whether isolation is a risk factor of reactivation of multiple herpesvirus antigens, and if so, whether this risk factor functions similarly among NHB, NHW and Hispanic Americans.

SPECIFIC AIM 3

In Specific Aim 3, we tested whether the association between social support and reactivation in Mexican Americans could be accounted for by nativity, and whether nativity modified the effect of social support on reactivation. Our models build on research by Markides and Eschbach (30), who found that Mexican Americans living in neighborhoods with at least 40% Mexican American households had better 7-year all-cause mortality outcomes than Mexican Americans in the general population. If this observation were consistent with the current study, we would expect that Foreign-Born Mexican Americans, who are more likely to live amongst other Mexican Americans and have lower acculturation scores, would have better health and less reactivation than US-born Mexican Americans. Our work also builds on earlier findings from the Texas City Stress and Health Study, in which fewer Foreign-Born Mexican Americans reactivated on early antigen than US-born Mexican Americans, Non-Hispanic Whites and Non-Hispanic Blacks (15).

Ultimately, our current models demonstrated that isolation remained a significant predictor of reactivation of two or more herpesvirus antigens in Mexican Americans, while nativity was not

significantly associated with reactivation. Nevertheless, nativity and isolation exhibited a strong positive interactive effect (OR 3.64). Subgroup analyses revealed that while isolation was positively associated with reactivation in US-born Mexican Americans, no relationship existed between the two variables for the foreign-born. Finally, the inclusion of acculturation as a covariate removed the significant interaction effect of isolation and nativity, while female gender emerged as a predictor (OR 2.00) while being a former smoker was protective against reactivation. These results suggest that acculturation may mediate the interaction of nativity and social support on reactivation (140), although further analyses are necessary to determine the exact nature of the relationship between social support, acculturation, nativity and reactivation.

It is possible that US-born Mexican Americans either face more acculturative stress or exhibit health behaviors that are more strongly associated with reactivation than Foreign-Born Mexican Americans, although further prospective analyses are needed to ascertain this relationship. Rumbaut (1994) (141) defines acculturative stress as, "distinct from acculturation and including language barriers, perceived discrimination, racism, loss of values, and a decline in social supports." In our study, although we would expect US-born Mexican Americans to face fewer language barriers, we could expect that they may experience more racism, loss of traditional values, and a decline in social support after further acculturation, especially if they choose to live in areas with fewer Mexican neighbors than do immigrants. Our results, placed in the context of acculturative stress, are consistent with the findings of Markides and Eschbach on all-cause mortality in high-density Mexican American communities (30), suggesting a benefit from living with individuals of one's own ethnicity to avoid aspects of acculturative stress including racism and the loss of traditional values and networks of social support. To better integrate our findings

with such neighborhood studies, and to better understand processes of acculturation on health outcomes in Mexican Americans at the individual and community level, it may be beneficial to include neighborhood-level acculturation measures in the future and design multilevel models that capture community and individual aspects of acculturation. Additionally, future analyses should include instruments that measure perceived discrimination, identity and family separation, concepts which better capture the idea of acculturative stress rather than acculturation. Such measures were included in the Texas City battery of instruments.

Unlike our study, most investigations of nativity, social support and acculturation on health outcomes do not focus on herpesvirus reactivation or immune function, but other health outcomes including psychological distress, health behaviors, and obesity. Furthermore, most studies, including ours, are cross-sectional, highlighting a need for prospective designs to determine the direction of the relationship between these variables. In an analysis of the 2007 National Children's Health Survey relating parental perceived social support, race, ethnicity and language use, Watt and colleagues (2013) (142) find that in English-speaking Hispanic fathers only, the father's level of perceived support was strongly protective against obesity in the child. The prevalence of obesity between English-speaking Hispanic fathers with low and high social support differed by 80%. This relationship was not supported in Non-Hispanic Blacks, Non-Hispanic Whites or English-speaking Hispanics. In another cross-sectional convenience sample of foreign-born Mexican day laborers in San Diego, California, social support modified the positive effect of acculturative stress and physical health outcomes, but not mental health outcomes (143). These studies differ from ours in that they do not suggest a possible mediating

effect of acculturation on effect modification of nativity on social support, but rather identify acculturation or acculturative stress as an effect modifier.

Alternative explanations exist for the relationships between acculturation, isolation, nativity and reactivation observed in our study. Given the cross-sectional nature of the data set, the study's principal limitation, it is possible that reactivation and appraisal of social support and acculturation are unrelated events. Additionally, a source of selection bias inherent in our models is the exclusion of participants with missing observations for model's variables, especially the exclusion of 369 participants in Model 9. Because the Medical Outcomes social support survey employed here was developed for Non-Hispanic populations, and because our acculturation instruments capture the process of acculturation rather than stress induced by it, it is possible that both the social support and acculturation scales measured these concepts in ways that didn't capture the dynamics of social support or acculturative stress in Hispanic populations. It is also possible that nearly all the foreign-born participants had reactivated on two or more herpesvirus antigens, consistent with the high prevalence of infection and reactivation among the foreign-born in nationally representative studies (48) (49) (69). However, while the proportion of individuals who had reactivated on two or more herpesviruses did differ significantly between the US and foreign-born, a higher proportion of US-born individuals experienced reactivation (17%) rather than foreign-born (13%). Thus, it is unlikely that high reactivation rates among Foreign-Born Mexican Americans masked a relationship between isolation and social support. Furthermore, the distributions of isolated v. not-isolated individuals within foreign-born and US-born groups were virtually identical, with no significant differences. Hence, our results cannot be explained by a difference in the proportion of isolated individuals between the two groups.

Altogether, our results shed further insight into the mechanism of the Hispanic Paradox. Our results suggest that acculturation may explain the fact that isolated US-Born Mexican Americans had much higher rates of reactivation than the isolated foreign-born. In a discussion of acculturative stress in Hispanic communities, Harley and Eskenazi suggest that more highly-acculturated Hispanics, who are likely to be US-born, may experience acculturative stress if they lose access to traditional support structures from family and friends before they integrate fully into US social and economic institutions, experiencing the "worst of both worlds" (144). Our results and the above definition of acculturative stress are consistent with early work by sociologist Milton Gordon who differentiates acculturation, a process of cultural and behavioral changes, from institutional economic and social integration into society (145). Perhaps Mexican Americans living in Texas City experience a gap between traditional familial and institutional resources and support structures. Nevertheless, the relationship between acculturation, acculturative stress, psychosocial stress, and viral reactivation needs further clarification. Regardless, our results identify potential areas for public health research that identifies whether Mexican Americans perceive and receive needed familial and institutional support and whether they experience psychosocial stress as a result. Possible interventions aimed at improving access to and strengthening networks of social and material support in first, second and subsequent generation Mexican Americans are warranted.

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Vita

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This capstone was typed by the author.