

Life Course Socioeconomic Status and Immune Response to Persistent Infection
in Mexican Americans

by

Helen Carmon Spink Meier

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Doctoral Committee:

Professor Carlos F. Mendes de Leon, Co-Chair
Professor Allison E. Aiello, University of North Carolina, Co-Chair
Associate Professor Jennifer B. Dowd, Hunter College, City University of New York
Associate Professor Brisa N. Sánchez
Assistant Professor Amanda M. Simanek, University of Wisconsin-Milwaukee

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List of Abbreviations

CMV	Cytomegalovirus
EBV	Esptein-Barr Virus
<i>H. pylori</i>	<i>Helicobacter pylori</i>
HSV-1	Herpes Simplex Virus-1
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LPA	Latent Profile Analysis
SALSA	Sacramento Area Latino Study on Aging
SES	Socioeconomic status
SEM	Structural equation modeling
<i>T. gondii</i>	<i>Toxoplasma gondii</i>

Abstract

Immune response to persistent pathogens, such as cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), *Toxoplasma gondii* (*T. gondii*), and *Helicobacter pylori* (*H. pylori*), are patterned by socioeconomic status and race/ethnicity in the United States. Though persistent infections are often acquired early in life, studies of social exposures and these pathogens in adults are often limited to concurrent measures of socioeconomic status. Further, significant disparities in persistent infections exist by race/ethnicity, indicating that minority populations, Mexican Americans in particular, are more likely to experience the detrimental effects of life course socioeconomic disadvantage on immune response, however, early life cultural exposures are rarely examined. Using data from the Sacramento Area Latino Study on Aging (SALSA), a longitudinal cohort study of community dwelling Mexican Americans, this dissertation examines the life course mechanisms by which early life socioeconomic status may operate to influence immune response to persistent infections and pathogen burden later in life. In addition, nativity (place of birth) and acculturation, important components of social and racial/ethnic disparities in health, are investigated as independent predictors of immune response, as well as modifiers of the life course social patterning of immune response to persistent infections later in life.

The main findings of this dissertation indicate that 1) the early life social environment indirectly influences later life immune response and pathogen burden by a chain of risk mechanism, 2) nativity is independently associated with CMV, but not HSV-1, *T. gondii*, *H. pylori* IgG antibody response or pathogen burden, 3) acculturation is not independently

associated with immune response to persistent infections or pathogen burden, and 4) nativity and acculturation modify the association between life course socioeconomic status and immune response to CMV and *T. gondii*. This work contributes new knowledge and understanding of the life course mechanisms by which early life social conditions act to influence later life immune response to persistent infections and the early life cultural factors that impact these social exposures. The results from these studies provide insight on points of intervention over the life course where addressing social disadvantage may improve immunological response to persistent infections later in life. Given the link between persistent infections examined in these studies and adverse health outcomes, this work may have more broad implications for targeting and preventing chronic health conditions and mortality from a life course perspective and disrupting the development of social disparities in chronic conditions.

Chapter 1. Introduction

1.1 Introduction

Socioeconomic gradients in health have been well established.¹ Evidence suggests that early life socioeconomic status (SES) may influence health across the life course.^{2,3} Infection with persistent pathogens, such as cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), *Toxoplasma gondii*, and *Helicobacter pylori*, may be one pathway by which early life socioeconomic status gets “under the skin” to influence later life health.⁴⁻⁸ Persistent pathogens establish chronic, latent infections in the body, which are never fully cleared.⁹ Some pathogens, *H. pylori* for example, may be treated with antibiotics, however, many infections are never diagnosed or receive treatment because most people do not develop symptoms.^{10,11} Persistent pathogens evade the immune system by various mechanisms, including molecular homologues, suppression of immune factors (cytokines, major histocompatibility complex-1), and transcriptional and translational control of cellular processes.^{9,12,13} Periodically, often during times of stress or a weakened immunological state, these pathogens reactivate from latency to produce an active infection.^{9,14-16} Reactivation represents some level of immunological impairment, as a regularly functioning immune system is able to keep the infection in a latent state.^{9,16,17} Reactivation of persistent pathogens may have detrimental effects on the body, such as direct damage to host tissues, immune system exhaustion and elevated inflammation.^{9,17-20} Persistent pathogens have also been linked to numerous chronic diseases of aging, including diabetes, cardiovascular disease, cognitive impairment, frailty, Alzheimer’s disease, autoimmune

diseases and mortality.²¹⁻²⁹ In addition, seropositivity to multiple persistent infections (i.e. increase total pathogen burden) may not only increase the risk of infection to other pathogens but also heighten the severity of subsequent infections.^{5,30-34} Moreover, higher pathogen burden is associated with coronary artery disease, atherosclerotic progression, metabolic disease, depression and mortality.³⁴⁻³⁷

Numerous studies have demonstrated social patterning of persistent pathogens.^{6,38-41} Individuals with lower socioeconomic status (SES) have a higher risk of seropositivity to persistent pathogens, are infected with persistent pathogens earlier in life, and exhibit poorer immune control of the infection in adulthood.^{6,33,39,42} Minorities, independent of SES, have higher seroprevalences to persistent pathogens and are more likely to be infected with common persistent pathogens at an earlier age.^{33,42} Furthermore, social disparities in the seroprevalence of persistent pathogens are prevalent within racial/ethnic groups.^{5,33} An inverse, graded association between SES and persistent pathogens was found in Mexican Americans, the largest subpopulation of U.S. Latinos.^{5,39,43} This social gradient is evident even in early life, indicating that Mexican Americans with low SES during childhood are more likely to acquire these pathogens earlier in life than their high SES counterparts.^{5,44}

Other early life exposures that may influence individual susceptibility and control of persistent pathogens are not well known. Geographical location is one potential early life factor that may influence risk of persistent pathogens. Birth and residence outside of the U.S. in a developing nation may increase the likelihood for exposure to persistent pathogens through differences in the physical environment, such as poorer living conditions, sanitation and hygiene practices.⁴⁵ Another important early life factor to consider is lifestyle, particularly in relation to cultural identity. Lifestyle exposures may lead to poorer nutrition, poor health behaviors, and

higher stress, and consequently increase susceptibility to persistent pathogens as well as contribute to more frequent exposures over the life course.⁴⁵ Geographic location and lifestyle factors are important independent early life factors to consider among Mexican Americans as large proportion of this population are immigrants.⁴⁶ Additionally, variation in these early life exposures are important to consider when investigating social determinants of persistent infection in this population.^{5,6,33,38,47}

Most previous studies of SES and immune response to persistent infection have been cross-sectional and only assessed the seropositivity or immune response with one corresponding measure of SES at a single point in the life course. Evidence suggests that persistent pathogens are often acquired during childhood and that a social gradient exists in seroprevalence even among children.^{5,42} Children with lower SES are at greater risk for infection with persistent pathogens due to increased exposure to the agents and decreased resistance to infection.⁴⁵ The early acquisition and subsequent lifetime immunological control of persistent pathogens may negatively impact adult health. Lower early life SES has been linked to poorer adult immune function, specifically reduced resistance to upper respiratory infections.⁴⁸ Another study showed that individuals who reported higher levels of childhood adversity exhibited higher immune response to EBV and CMV in adulthood independent of SES.⁴⁹ Childhood, therefore, may be a period of the life course where social exposures have lasting effects on the risk of acquiring persistent pathogens and the ability of the immune system to control these infections as adults. To date, no studies have examined the role of life course SES on immune response to persistent infections later in life.

There are several mechanisms by which early life socioeconomic status may be operating to influence immune response to persistent pathogens during adulthood, including the critical

period model and the chain of risk model. The critical period model suggests that an event early in life, acting during a specific period of time, has a lasting independent effect on later life health.^{50,51} The chain of risk model proposes that a set of exposures are linked over the life course, since one experience may lead to another, to influence later life health.⁵¹ These two life course models provide a framework for evaluating the mechanism by which SES acts across the life course to influence immune control of persistent pathogens later in life. A better understanding of the mechanism by which childhood SES influences later life immune response to persistent pathogens will help guide prevention efforts to diminish the clear socioeconomic disparities observed in these infections.

The objectives of this dissertation are to 1) determine if childhood is a critical period for exposure to socioeconomic status in relation to immune response to persistent pathogens, 2) determine if childhood is a critical period for exposure to socioeconomic status in relation to pathogen burden, and 3) examine if nativity and acculturation, independent of early life social factors, is associated with immune response to persistent pathogens, as well as if nativity and acculturation modify the social gradient in immune response to persistent infection and pathogen burden among Mexican Americans using data from the Sacramento Area Latino Study on Aging (SALSA), a longitudinal cohort of community dwelling Mexican Americans from the Sacramento, CA metropolitan area.

1.2 Specific Aims and Hypotheses

Aim 1: To examine whether early life SES influences later life immune response to persistent pathogens via a critical period or a chain of risk model.

Hypothesis 1: Higher early life socioeconomic status is associated with better immune response to persistent infections (i.e. lower IgG antibody levels) independent of later life SES controlling for confounders.

Aim 2: To examine whether early life SES influences later pathogen burden via a critical period or a chain of risk mechanism.

Hypothesis 2: Higher early life socioeconomic status is associated with lower total pathogen burden independent of later life SES controlling for confounders.

Aim 3: Evaluate the association between nativity and acculturation and immune response to persistent pathogens (i.e. lower IgG antibody levels) and pathogen burden later in life, independent of early life social factors among Mexican Americans and whether nativity and acculturation as modify the association between life course SES and immune response to persistent pathoogens and total pathogen burden later in life.

Hypothesis 3a: Foreign born individuals will have higher immune response to persistent infections (i.e. higher IgG antibody levels) and higher total pathogen burden than individuals born in the U.S., independent of early life SES controlling for confounders.

Hypothesis 3b: Mexican oriented individuals will have higher immune response (i.e. higher IgG antibody levels) to persistent infections and higher total pathogen burden than Anglo oriented individuals, independent of early life SES controlling for confounders.

Hypothesis 3c: U.S. born individuals with high socioeconomic status have lower immune response (i.e. lower antibody levels) and lower total pathogen burden later in life than foreign born individuals with high SES.

Hypothesis 3d: Anglo oriented (high acculturation) individuals with higher socioeconomic status have lower immune response (i.e. lower antibody levels) and lower pathogen burden later in life than Mexican oriented (low acculturation) individuals with high SES.

1.3 Socioeconomic Status and Health across the Life Course

There is a well-established graded relationship between socioeconomic status (SES) and health that has been observed across the life course in the U.S.^{1,51,52} Understanding the pathways by which social and biological exposures throughout life affect adult and later life health characterize a life course approach to disease production.⁵⁰ From a life course perspective, adverse effects of low SES beginning in childhood may accumulate, interact, or act independently across the life course to influence later life health. Kuh et al.'s simplified framework for the pathways between the childhood social environment and later life health is depicted in Figure 1-4. As shown in this figure, the childhood social environment may directly or indirectly influence health through biological resources and resiliency (health capital), education, health behaviors, and the adult socioeconomic environment.⁵¹ Employing life course conceptual models, early life social environments may act through developmental critical periods, cumulative damage to biological systems, or chains of risk (biological, psychological, or social).⁵¹ Of particular interest in the life course approach is the timing and duration of exposures related to increase in disease risk.⁵¹ Life course conceptual models, such as the critical period and the chain of risk, provide a framework for evaluating hypotheses regarding the early life origins of adult health. In a critical period model, low SES during a childhood has lasting effects on the structure or function of the body and long term health effects.⁵¹ This model is also known

as the latent effects model since low SES in childhood affects later life health independently of subsequent adverse exposures.⁵⁰ Alternatively, low SES in childhood may set off a chain of risk whereby low SES in early life leads to low SES in middle- and later-adulthood and these subsequent exposures to low SES trigger poor health in later life.⁵⁰ The life course mechanism by which early life SES influences later life immune control of persistent pathogens is elucidated in this dissertation.

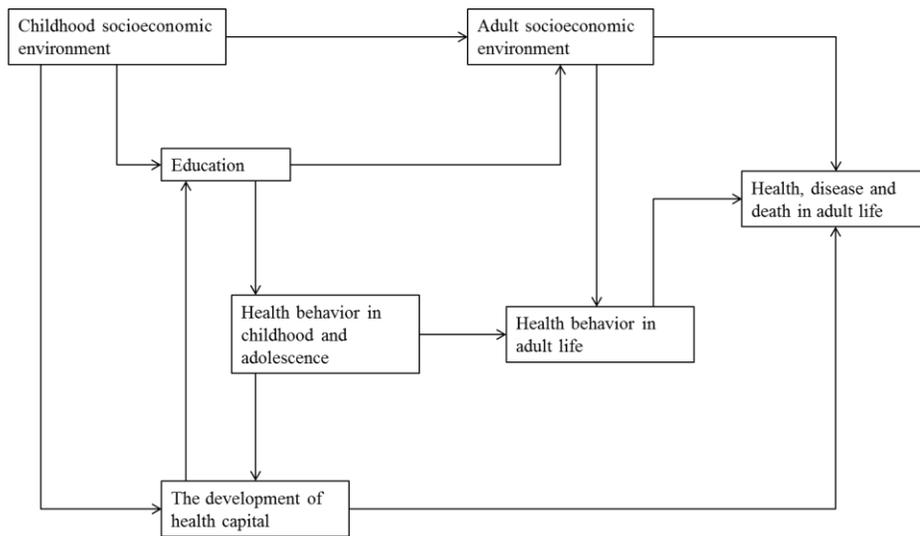


Figure 1-1. Kuh et al.’s Pathways between childhood and adult health: a simplified framework⁵¹

1.4 Pathophysiology of Persistent Pathogens

1.4.1 Persistent Pathogens

Infectious diseases that are not cleared from the body post primary infection are known as persistent pathogens. Common persistent pathogens in humans include the herpesviruses, CMV HSV-1, Epstein-Barr Virus (EBV), and varicella zoster virus (VZV), bacterial pathogens *H. pylori* and *Chlamydia pneumoniae* (*C. pneumoniae*), the hepatitis viruses B and C, and the parasite *T. gondii*. Exposure to these pathogens is based on background prevalence in the population as well as individual susceptibility.^{32,53,54} Once acquired, persistent pathogens may

adversely affect health via multiple pathophysiologic pathways. Elevated immune response to persistent pathogens is a marker of poor immunological control and has been implicated in the etiology of various chronic diseases. Several persistent pathogens of interest in this dissertation are described below in more detail and a summary of each pathogen's initial cell target, pathology, and latency cellular reservoir is depicted in Table 1-1.

1.4.1.1 *Helicobacter pylori* (*H. pylori*)

H. pylori is a bacterium that colonizes the mucosal layer of the gastric epithelium (stomach) and generates a state of chronic inflammation.⁵⁵ Persistent infection with *H. pylori* causes gastritis, peptic ulcer disease and is associated with other gastric conditions, such as cancer.⁵⁵ This organism evades the immune system through a variety of mechanisms, including circumventing recognition by the innate immune system, inhibition of phagocytic killing, modulation of antigen presenting cell functions, and manipulation of host T cell responses.⁵⁵ Furthermore, while many individuals infected with *H. pylori* develop an antibody response, and most have a high serum antibody titer, this response is not normally sufficient to clear the infection from the body.⁵⁵ *H. pylori* infection may be eliminated with antibiotics, though most infections are asymptomatic and are not treated.¹⁰

1.4.1.2 *Toxoplasma gondii* (*T. gondii*)

T. gondii is an obligate parasite that infects intestinal epithelial cells and establishes latency with intracellular bradyzoite cysts in muscle and brain cells.^{56,57} *T. gondii* is found worldwide with prevalence in adult populations ranging from 10% - 80%.⁵⁸ This pathogen is transmitted by ingesting oocyte cysts located in raw or undercooked meat, food items cross-contaminated with raw or undercooked meat, or contaminated soil or water.⁴⁷ A major source of soil and water contamination may be felines, such as domestic cats, the host in which sexual

reproduction of the parasite takes place.⁵⁸ Infection with *T. gondii* is often asymptomatic or manifests as non-descript symptoms such as fever, malaise and lymphadenopathy that are self-resolving.⁴⁷ *T. gondii* infection has been linked to mental health disorders, including schizophrenia, bipolar depression and self-harm, in immunocompetent persons, and severe encephalitis among immunocompromised individuals.⁴⁷ No medical treatment to date can eradicate chronic infection in humans.⁵⁷

1.4.1.3 Herpes Simplex Virus-1 (HSV-1)

HSV-1 is a highly common alpha herpesvirus with adult prevalence ranging from 50 to more than 90%.⁵⁹ Infections with HSV-1 are common worldwide and are characterized by recurrent oral lesions on the lips, mouth and gums.⁶⁰ Among immunocompromised individuals, severe infection of the eyes and central nervous system may be caused by HSV-1.⁶⁰ HSV-1 is transmitted by contact with bodily secretions containing the virus and infects the mucoepithelia.⁶⁰ Latent infection is established in the sensory and cranial nerve ganglia.⁶¹ Lytic reactivation affects epidermal cells in the face.⁵⁹ HSV-1 may also be an etiologic agent for chronic neurologic and cardiovascular disorders.⁶⁰ HSV-1 interferes with host defenses by blocking inflammatory processes, prohibiting lysis of host cells by cytotoxic T cells, suppressing apoptosis of infected cells and blocking antibody adherence to infected cells.⁵⁹

1.4.1.5 Cytomegalovirus (CMV)

CMV is a beta herpesvirus and ubiquitous worldwide.³⁸ CMV is transmitted by contact with body fluids from CMV-infected individuals and initially establishes infection in monocytes, lymphocytes and epithelial cells. CMV most often reactivates from latent infection of monocytes and lymphocytes with asymptomatic, subclinical infection in immunocompetent hosts.⁶² During latency, it is difficult for the immune system to identify CMV-infected cells because this virus

persists at such a low level.¹⁷ CMV has co-evolved with humans over time and as a result has developed many mechanisms for immune evasion. CMV has the largest number of genes committed immune response alteration of any herpesvirus.¹² CMV encodes for proteins involved in immune evasion, modulation and manipulation to establish latency and long-term viral shedding.¹² CMV was thought to be a harmless bystander in immunocompetent individuals, however, CMV has recently been associated with cancer, cardiovascular disease, declines in cognitive functioning, depression and is a marker of immune dysfunction.^{62,63}

Table 1-1. Summary of Primary Target Cells, Pathology and Latency Sites for Common Persistent Pathogens

Pathogen	Primary Target Cells	Pathology of Primary Infection	Main Sites of Latency
CMV ⁶¹	Monocytes, lymphocytes, epithelia	Mononucleosis	Monocytes, lymphocytes
HSV-1 ⁶¹	Mucoepithelia	Genital ulcers, skin lesions, keratitis, encephalitis, meningitis	Sensory and cranial nerve ganglia
<i>T. gondii</i> ⁶⁴	Intestinal epithelial cells	Toxoplasmosis	Muscle and CNS
<i>H. pylori</i> ⁶⁵	Mucosal layer of gastric epithelium	Peptic ulcer disease, chronic inflammation	Mucosal layer of gastric epithelium

1.4.2 Immune System and Persistent Pathogens

The immune system protects the body from invasion by organisms via two defenses, the innate immune response and the adaptive immune response.⁶⁶ Innate immunity is the first line of defense and includes physical, chemical and cellular components, which act quickly and non-specifically to prevent entry, colonization and the spread of foreign organisms.⁶⁶ Adaptive immunity is a lymphocyte response that effectively targets antigens and establishes immunological memory.⁶⁶ The adaptive immune response is composed of humoral immunity (B

lymphocytes and antibodies) and cell-mediated immunity (T lymphocytes and effector macrophages) working together to identify and eliminate pathogens.⁶⁶

1.4.3 Humoral Immunity

Once an antigen has been recognized in the body, it is processed by antigen presenting cells (APCs) and helper T cells. Activated helper T cells stimulate B cells to differentiate and expand into plasma cells which subsequently produce antibodies against the antigen.⁶⁶

Antibodies adhere to cellular surfaces and function to tag pathogens for phagocytosis, neutralize antigenic sites on pathogens, and agglutinate and precipitate antigen-antibody complexes.⁶⁶ The first time an antigen is recognized by the immune system, antibody production may take 1-2 weeks and is known as a primary response (Figure 1-1).⁶⁶ The process is much faster after any additional insult by the antigen occurs, due to the presence of B cells with memory of the antigen.⁶⁶

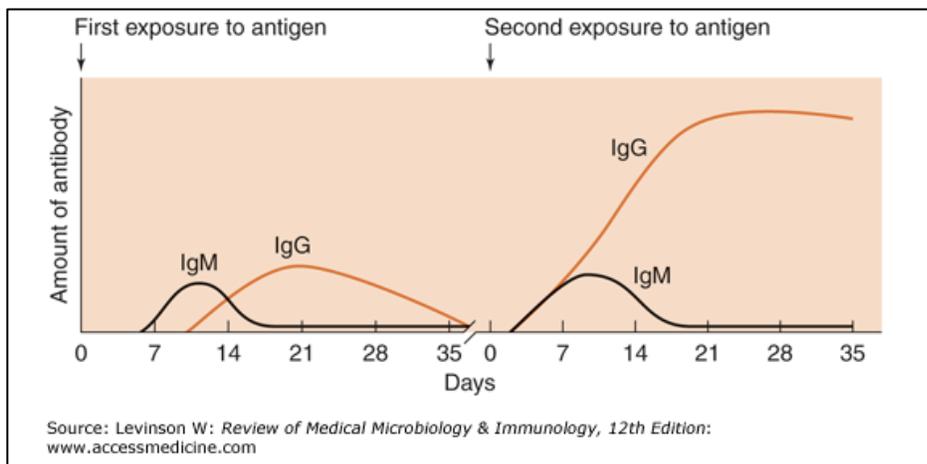


Figure 1-2. Primary and secondary antibody response to antigen

Antibodies are composed of proteins called immunoglobulins of which there are five classes (IgG, IgA, IgM, IgD, and IgE).⁶⁶ Immunoglobulin M (IgM), a pentamer, is the first type of antibody to be produced and, when bound to antigen, activates the complement system, as well as quickly gives way to the production immunoglobulin G (IgG).⁶⁶ IgG is a monomer and

the most abundant antibody isotype circulating in the internal body fluids.⁶⁶ Exposure to pathogens is commonly measured by the presence of IgG, specific to an antigenic marker of the pathogen, in the blood. This is an indirect measurement of infection as the pathogen itself is not isolated from the body.

Indirect enzyme-linked immunosorbent assays (ELISAs) are a laboratory diagnostic tool used to quantify the presence of serum antibody and the most common antibody assay used in epidemiologic studies.⁶⁷ Microtiter plates are coated with the antigen of interest.⁶⁷ The plates are incubated with serum samples that may contain specific antibodies to that antigen.⁶⁷ The plates are then washed to remove any unbound antibodies and remaining serum sample, and a developing reagent is added to tag the antibodies bound to the antigen on the plate surface.⁶⁷ The developing reagent is washed away and a substrate solution is added.⁶⁷ The amount of substrate hydrolyzed is assessed with a spectrophotometer or spectrofluorometer, depending on the type of developer and substrate used.⁶⁷ Other similar techniques for detecting the presence of antibodies include double antibody-sandwich ELISAs and indirect cellular ELISAs.⁶⁷

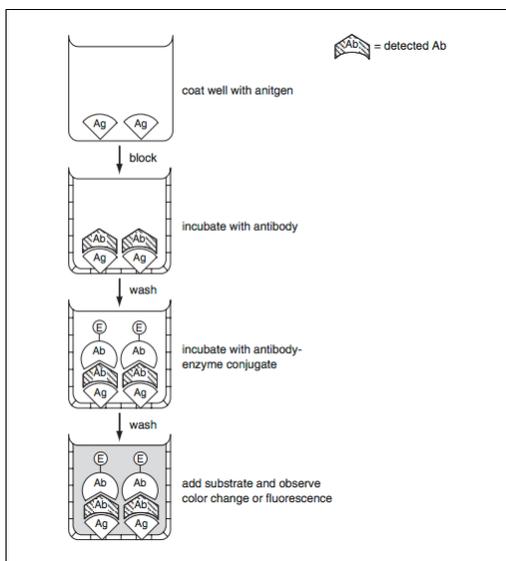


Figure 1-3. Protocol for Indirect ELISA to detect specific antibodies. Ag = antigen; Ab=antibody; E=enzyme.⁶⁷

Persistent pathogens are never fully cleared from the body by the immune system. Instead such pathogens establish latency in specific host cells where they are protected from the immune system. The relationship between the immune system and persistent pathogens is complex as many pathogens have co-evolved with human hosts over time and infection early in life may influence the development of the immune system.⁶⁸ Though many primary infections are asymptomatic, the continued presence of persistent pathogens may cause a variable degree of harm in the host.⁶⁹

Persistent pathogens in latent stages continue to undergo a low level of replication.⁹ Reactivation to lytic stages occurs in response to impaired cell-mediated immune processes, which contribute to the development of chronic diseases via direct and indirect pathways, and lead to immune system exhaustion.^{9,70} Elevated IgG antibody levels for certain herpesviruses is associated with an elevated leukocyte load, and pathogen-specific DNA shedding in urine and thus considered a marker of reactivation and, therefore, poor immunological control of persistent pathogens (see Figure 1-3).^{14,71}

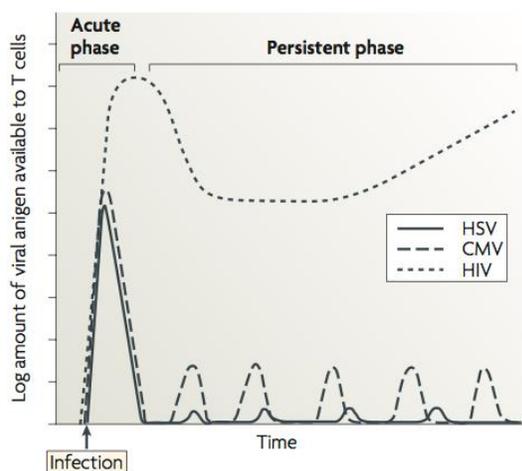


Figure 1-4. IgG Response to Reactivation of Persistent Infections⁹

1.5 Persistent Pathogens and Chronic Disease

A variety of chronic health outcomes, such as cardiovascular disease, diabetes, cognition, frailty, depression and Alzheimer's disease have been associated with persistent pathogens.^{21-25,33} Persistent pathogens may cause sub-clinical damage and increase the risk of poor health outcomes through several mechanisms. Persistent pathogens may influence chronic disease development through direct damage to host tissue. For example, *H. pylori* plays a causative role in peptic ulcers by damaging the stomach lining.^{18,72} Persistent pathogens may also influence disease progression through inflammatory pathways. CMV, *H. pylori* and *C. pneumonia* have been implicated as having a pro-inflammatory role, inducing cytokines and elevated C-reactive protein (CRP). These inflammatory markers in turn have been implicated in the development of atherosclerosis and cardiovascular disease.^{73,74} Independent of indirect pathways through inflammation, CMV and HSV-1 have been implicated in cardiovascular disease through both direct tissue damage and molecular mimicry.^{31,75-77} Though evidence in humans is inconsistent, animal models have found HSV-1 and CMV in cardiovascular tissue and contributing to endothelial dysfunction.^{8,73,74,76} Moreover, reactivation of persistent pathogens chronically stimulates the immune system and may lead to exhaustion of cell-mediated processes.⁹ Cytokines triggered in response to infection, may lead to localized or systemic inflammation with negative consequences. Last, infections may induce autoimmune related diseases through molecular mimicry of self-peptides. Mechanistically, pathogens have peptides homologous to human proteins that illicit an immune response that targets cross-reactive host tissues.³¹ This is an indirect pathway by which pathogens may cause damage in the host.

Psychosocial stress also has harmful effects on the immune system and may lead to more frequent reactivation of persistent pathogens and consequently more damage in the host.^{16,78}

Stress (i.e. stressful life events, bereavement, anxiety and loneliness) and biological processes in reaction to stress may affect both the innate and adaptive immune response.^{79,80} Stress has been shown to reduce natural killer cell activity, reduce lymphocytes proliferation, decrease the ratio of helper T cells to suppressor T cells, and impair antibody response. Stress may lead to dysregulation of immune function through the actions of stress hormones; stress has been shown to delay wound healing, impair vaccine response and reactivate latent herpesviruses.^{16,78} For herpesviruses specifically, psychological stress affects the development, length and reactivation of infection.¹⁶ For example, stressors have been found to increase the development and severity of HSV, but also impair the cell-mediated immune response mounted to this virus.¹⁶ Further, reactivation of HSV was promoted by the occurrence of stress and the length of exposure to the stressor.¹⁶

Research has also shown that exposure to multiple persistent pathogens over the life course may contribute to morbidity over and above the influence of each individual infection alone.³³ For example, seropositivity to multiple infections may not only increase the risk of infection to other pathogens but also increase the severity of subsequent infections.³²⁻³⁴ Moreover, seropositivity for a greater number of persistent pathogens (i.e., higher total pathogen burden level) has been associated with coronary artery disease, atherosclerotic progression, cardiovascular death, cognitive impairment and metabolic disorders, although debate over which particular combination of pathogens are most detrimental to chronic disease-related mortality is ongoing.^{34-37,81}

1.6 Social Patterning of Persistent Pathogens

Persistent pathogens are socially patterned in the U.S. such that those with low SES are more likely to acquire the infections earlier in life, have higher seroprevalence of the infections,

and exhibit poorer immune control of persistent pathogens in adulthood.^{39,42} For example, a social gradient is apparent in the average age of exposure to persistent pathogens. Among those aged 12-49 in the U.S., those with lower SES as measured by income were on average infected with CMV at 22 years old, while those with high SES had an average age of infection of 29 years old.⁴² Low SES individuals were exposed to CMV an average of seven years before those with high SES due to increased exposure to the infection and increased susceptibility than their high SES counterparts.⁴² In addition, U.S. population representative studies have illustrated clear social disparities in the seroprevalence of CMV by income and education in the U.S.³⁹ Among adults aged 25 and older, those with low SES have higher prevalence of CMV seropositivity than those with high SES.³⁹ The social patterning of persistent infections in the U.S. is not limited to adults. Among U.S. children aged 6-16, those with lower parental SES (measured by educational attainment) had higher prevalence of *H. pylori*, CMV, HSV and Hepatitis A than those with higher parental SES.⁵ Further, total pathogen burden (total number of persistent pathogens to which one is seropositive) is inversely related to SES among children and adults.^{5,33} In adults, those with less than a high school education have higher mean pathogen burden levels than those with more than a high school education.³³ Again, this same inverse relationship is apparent among children.⁵

Further, immune response to persistent pathogens is also socially patterned. Those with low SES exhibit elevated humoral immune response to CMV (measured by IgG antibody levels) than those with high SES in U.S. adults, likely due to more frequent reactivation.³⁹ In fact, individuals with the lowest level of education (less than high school) and aged 45-54 had similar CMV IgG antibody levels to those with the highest level of education (more than high school) that were 65-74 years old.³⁹ Therefore, individuals with low SES may acquire the infection

earlier in life and spend more years infected on average over the life course. This earlier onset of infection and longer duration for which pathogens must be immunologically controlled is not without consequence as persistent infections and total pathogen burden are associated with direct damage to body tissues and chronic health outcomes as previously noted. CMV, in particular, is thought to be a driver of immunosenescence, or age-associated alterations in immunity, through changes in the distribution of T cell phenotypes.⁸² CMV is thought to stress the immune system, which accelerates immunological aging processes.^{83,84} These CMV induced immunological changes are associated with reduced vaccine efficacy and mortality, and may have far reaching impacts for our health.^{6,19,82}

1.7 Cultural Differences in the Social Patterning of Persistent Infections

Our study population, the Sacramento Area Latino Study on Aging (SALSA) consists of foreign born and U.S. born elderly Latinos warranting discussion of the relationship between SES and health specifically among Hispanic populations. Hispanics are the largest and most rapidly growing minority population in the U.S. fueled by high levels of immigration and high fertility rates.⁸⁵ Hispanics commonly have lower SES than non-Hispanic whites.^{33,86-89} Even with this inequality, socioeconomic gradients in health are observed less frequently in Hispanics as compared to non-Hispanic whites than other minority groups.^{85,90} This is known as the “Hispanic paradox” where despite lower SES, lower education level and reduced access to health care, Hispanics exhibit better health than non-Hispanic whites.^{85,90} For example, in comparing age-adjusted cause-specific mortality, Hispanics have lower rates of heart disease, cancer and cerebrovascular disease than non-Hispanic whites.⁸⁵ There are multiple hypotheses that attempt

to explain the Hispanic paradox, including the healthy migrant effect, the moribund migrant effect, acculturation effects, and misclassification of data.⁸⁵

The Hispanic paradox, however, does not appear to hold for objective biological markers of health risk, such as inflammation and metabolic risk.⁸⁶ One study found that controlling for SES removed any apparent differences in biological risk profiles between Hispanics and non-Hispanic whites, meaning the effect of ethnicity was driven by differences in SES.⁸⁶ Similarly, studies examining ethnic patterning of persistent pathogens do not find a Hispanic paradox (i.e. Hispanics are more likely to be exposed to persistent pathogens than non-Hispanic whites). One study using NHANES III data reported age-adjusted seroprevalences of several persistent pathogens, Hepatitis A, *T. gondii*, *H. pylori*, Hepatitis B, Hepatitis C, and HSV-2.⁵³ For every pathogen tested, Mexican Americans had a higher percentage of seropositive participants compared to non-Hispanic whites.⁵³ Building on this work, another study examined social disparities in the burden of infection and showed that 54.5% of Mexican Americans were seropositive to three or more pathogens compared to only 20.3% of non-Hispanic whites.³³ For individual persistent pathogens and pathogen burden, socioeconomic gradients were observed between Mexican Americans and non-Hispanic whites.³³ These results illustrate clear ethnic disparities in persistent pathogen prevalence and burden for Mexican Americans.⁵³ Considering this disparity and the fact that persistent pathogens are associated with morbidity and mortality, it is possible that the overall Hispanic health advantage may be driven by a healthy migrant effect, or selective immigration of the healthiest individuals, or salmon bias, where unhealthy immigrants return to their country of origin.

The social patterning of persistent pathogens seen at the U.S. population level is also visible ethnic subgroups of Latinos, who are more likely to be seropositive to persistent

infections than non-Hispanic whites, even at an early age.⁵ Among children aged 6-11, Mexican American children had 93% higher odds of being infected to CMV than non-Hispanic whites.⁶ Mexican Americans aged 6-16 had higher seroprevalences of *H. pylori*, CMV, HSV and hepatitis A, and higher mean total pathogen burden than non-Hispanic whites.⁵ For each of these infections, an inverse graded relationship between SES and seroprevalence was apparent among Mexican American children.⁵ These associations were also seen among adults.³³ Mexican Americans have a younger average age of infection (18 years old) to CMV than non-Hispanic whites (29 years old).⁴² On average, Mexican Americans acquire CMV 10 years before non-Hispanic whites.⁴² Additionally, Mexican American adults are more likely to be seropositive to more infections and have higher pathogen burden levels than non-Hispanic whites.³³ Therefore, Mexican Americans are more likely to acquire persistent pathogens at an earlier age due to increased exposure and susceptibility, have higher seroprevalences of infections both as children and adults, and be exposed to more persistent pathogens than non-Hispanic whites.

While there are clear social gradients in seropositivity and immune control of persistent pathogens among Hispanics in the U.S., this population is comprised of diverse subpopulations, including Mexican Americans, Puerto Ricans, Cuban Americans, and Central and South Americans, the largest of which is Mexican Americans.⁸⁵ Mexican Americans have diverse early life experiences, which may also influence risk of persistent pathogens in this population. Differences by geographic location of birth and levels of acculturation may affect both susceptibility and immunological control of persistent pathogens in adulthood, independently of social factors. For example, U.S.-born Mexican Americans have higher cardiovascular risk than foreign born Mexican Americans even after controlling for SES, health behaviors and health care access, indicating that nativity taps into additional exposures specific to place of birth that

influence adult health.⁸⁶ Explanations for these differences include the healthy migrant effect (only healthy, foreign born individuals migrate to the U.S.), return migration of the unhealthy, or social inequality specific to the U.S. (not captured in SES alone).⁸⁶ It is possible that country of birth (i.e. nativity status) shapes early life exposures among Mexican Americans that play an important role in influencing age of acquisition and immune control of persistent pathogens beginning early in life. Indeed, data suggest that seropositivity to persistent infections varies by nativity status. Using U.S. population representative data from NHANES III, studies have found that those born outside the U.S. were had higher risk of seropositivity to *H. pylori* than those born in the U.S and females born outside the U.S. had higher risk of HSV-1 seropositivity than those born in the U.S.^{41,60} Further, Mexican-born Mexican American adults had significantly higher risk of seroprevalence to CMV and *T. gondii* than U.S. born Mexican American adults.^{38,47}

Additionally, although the childhood socioeconomic environment may vary greatly by country of birth, few studies have examined the effect of both SES and nativity on immune response to persistent infections. For example, one study showed that among Mexican American children aged 6-10 years old, those with a foreign born household member had higher seroprevalence of CMV compared to those with all native-born household members.⁹¹ Moreover, this same study showed that seropositivity decreases as income increases among Mexican American children with a foreign born household member.⁹¹ There are several possible biologic mechanisms by which the influence of SES on susceptibility and immune response to infection may vary by nativity. The prevalence of persistent infections among those born outside the U.S. with low SES is likely to be higher than among those with low SES born in the U.S. Therefore, individuals living in less developed countries have a greater likelihood of exposure to these

pathogens, particularly earlier in life. An individual may experience poorer immune control of persistent pathogens later in life as a result of this early exposure due to either a higher initial immune reaction or increased subsequent immune reactivations to lytic cycles of the pathogens.

It is also possible that nativity status may represent a confounder of the SES-immune response association because place of birth is associated with both exposure to persistent pathogens and SES. Nativity status, however, is likely related to immune response to persistent pathogens only through SES. If all social conditions between countries were equal, we would not expect to see biological differences in the immune system and its function based on country of birth alone. Consequently, we do not conceptualize nativity status as a confounder in the present study. Instead, we hypothesize that nativity may be a modifier of the SES-immune response association, such that those born in foreign countries with low SES will have poorer immunological control than individuals born in the U.S. with low SES.

Acculturation is another factor that may influence the risk of acquiring persistent pathogens independent of SES. Acculturation is the process of individuals adopting practices and beliefs from a dominant culture.^{92,93} This process can lead to both positive and negative exposures or behaviors that may contribute to health or disease risk.⁹² Acculturation of Latinos to U.S. cultural norms has mixed results on health outcomes.⁹² Often, higher acculturation has a negative influence on health behaviors, such as diet and substance abuse, however, higher acculturation is associated with more preventative health care use.⁹² Though a large proportion of the Mexican American population have migrated to the U.S., no study has looked at the relationship between acculturation and persistent pathogens, nor how acculturation may modify the effect of socioeconomic status on immune response to persistent infections.⁹⁴ Combined exposure to low acculturation and low SES may represent exposure to higher levels of stress through

discrimination and exclusion than experienced with each independent effect alone.⁹⁵ As a result, low SES individuals experiencing low acculturation may be more susceptible to persistent pathogens and experience more frequent reactivations over the life course, compared to low or high SES individuals experiencing high acculturation, resulting in poorer immune control of persistent pathogens later in life. Thus, we hypothesize that individuals with low acculturation and low SES will have higher immune response to persistent pathogens than individuals with low SES and high acculturation.

1.8 Life course Approaches to Understanding the Effect of Early Life SES on Immune Control of Persistent Pathogens Later in Life

SES influences health through both the physical (i.e. living and working conditions) and social (i.e. access to resources and psychosocial conditions) environment but the contributions of SES to health may differ based on the stage of life.^{1,51} Moreover, social disadvantage in childhood not only increases the risk of adverse childhood exposures, but may also influence social disadvantage and poor health in adulthood.^{51,96}

Exposure to persistent pathogens and individual susceptibility are influenced over the life course by socioeconomic status. Pathways linking low socioeconomic status to seropositivity for persistent pathogens and higher total pathogen burden include increased frequency of exposure and greater susceptibility to these pathogens.⁹⁷ Those with low socioeconomic status may live in more crowded and poorer living conditions than those with high SES, increasing the frequency of exposure to infections.⁹⁷ Susceptibility to persistent pathogens may be elevated among those with low socioeconomic status through increased levels of stress and poorer nutrition, as well as other related biological risks, such as obesity.⁹⁷ Therefore, those of low socioeconomic status are

not only more likely to be exposed to persistent pathogens, but also may be more susceptible to these infections upon exposure.⁹⁷

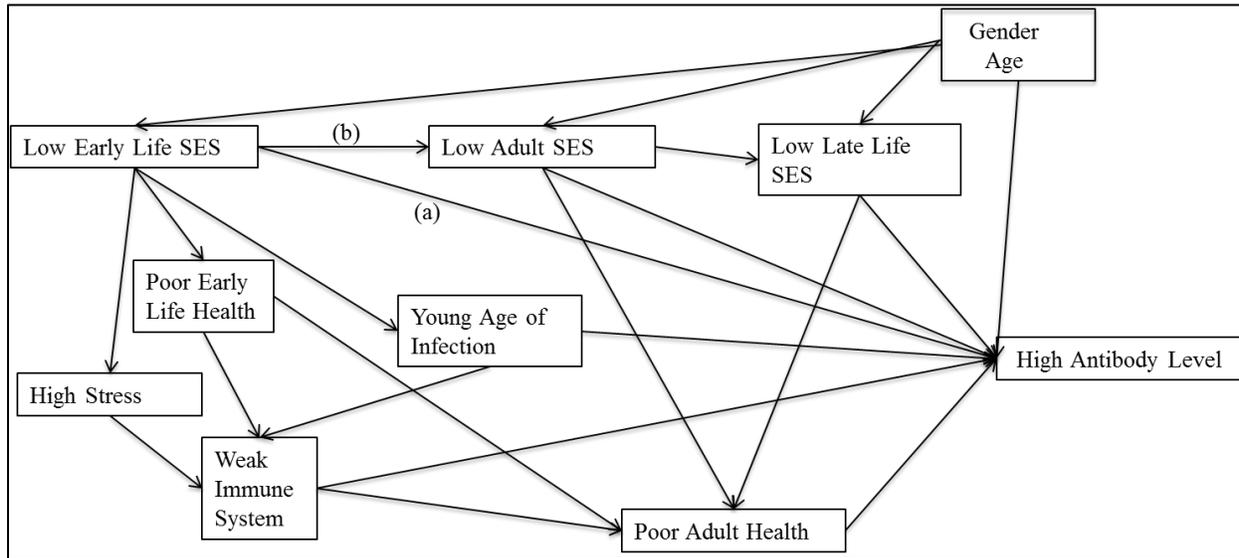
Childhood socioeconomic status may shape later life health via influencing early life access to health care, adequate nutrition, health behaviors, and physical and psychosocial exposures in the home, neighborhood, and school.³ Infection early in life impacts the development and function of the immune system. Exposure to specific antigens will drive the evolution of lymphocyte lines and their maturation.⁶⁸ For example, evidence from vaccination against diarrheal disease in the Philippines suggests that previous exposure to diarrheal disease in the first year was associated with improved diarrheal vaccine effectiveness compared to response among those who were not exposed to a diarrheal disease in the first year of life.⁶⁸ Early exposure to pathogens may however, also influence the resources devoted to the development of the immune system. Increased investment in the immune system may shift resources away from other development, such as growth.⁶⁸

Additionally, stressful early life events may allow for increased reactivation to persistent pathogens in childhood and throughout the life course due to dysregulation of cellular immunity.⁹⁸ Individuals with lower SES are more likely to experience higher stress leading to decreased cell-mediated immunity and more frequent reactivation of latent infections over the life course.^{14,16,78} CMV is thought to be a driver of immunosenescence, or age-associated alterations in immunity, through changes in the distribution of T-cell phenotypes.⁸² CMV is believed to stress the immune system, which accelerates immunological aging processes.⁸⁴ These CMV induced immunological changes are associated with reduced vaccine efficacy and mortality, and may have far reaching impacts for our health.^{6,19,82} Among children and adolescents, stressful events increase reactivation to herpesviruses, indicating poor cellular

immune control.^{4,7} Thus, childhood may be an important period of susceptibility during which low SES increases the likelihood of acquiring persistent pathogens and may directly influence immune control of persistent pathogens later in life. Alternatively, low SES in early life may serve as the first step in a social chain of risk, whereby early life SES influences later life immune control of persistent pathogens via shaping middle- and later-adulthood SES.

Pathogen burden is also socially patterned such that adults in the US with lower SES have higher burden of infection.⁵ Further, it has been shown that mean infection burden is higher in U.S. children with lower educated parents than children of parents with higher education, suggesting differences in pathogen burden emerge early in life.⁵ Little is known, however, about whether low SES in childhood represents a critical period exposure for later life immune control of persistent pathogens or the first step in a chain of risks leading to low SES in middle- and later-adulthood which in turn, influences immune control on later life. These two contrasting life course models, the critical period and the chains of risk models, by which early life SES may influence later life immune control of persistent pathogens and pathogen burden are discussed below.

Figure 1-5. Life course pathways linking SES and adult immune control of persistent pathogens



1.8.1 Critical Period Model

SES at different periods over the life course may have an independent direct effect on exposure to persistent pathogens. Early life may be a critical period where lower SES is associated with poorer later life immunological control of persistent pathogens, independent of later life SES exposures. The direct effect of early life SES on adult antibody levels is illustrated by pathway (a) in Figure 1-5. Early life SES represents the social and physical environments an individual is exposed to in early life. Low early life SES increases the likelihood of exposure to persistent pathogens and decreases immunological resilience for controlling persistent infections. Thus, low early life SES contributes to an earlier age of acquisition and more frequent reactivation over the life course, resulting in higher immune response (i.e. higher antibody levels) later in life.

1.8.2 Chains of Risk Model

Pathway (b) represents the indirect effect of early life SES on immune response, specifically through a chain of risk model. Early life social disadvantage is linked to subsequent

levels of SES in adulthood, such as education, employment grade and income.⁵² Resources and environments correspond to socioeconomic status levels over the life course, which determine exposure to persistent pathogens as well as affect immunological health and the ability to prevent reactivation of persistent infections. Low SES in early life may set up a chain of risk where conditions are such that an individual receives a poor education or low paying employment resulting in high stress and more frequent reactivation to persistent infections. Thus, later life SES may mediate the effect of childhood SES on immune response to pathogens later in life.

1.9 Risk Factors of Immune Response after Childhood

With a life course approach, risk factors of later life immune response that occur as a consequence of early life SES require careful methodological consideration. For example, indicators of adult health, such as body mass index (BMI), might be a consequence of both early life and adult SES, and a risk factor for immunological health later in life. Thus, they may be acting as colliders and statistical control for these measures would result in bias in the estimate of direct effect of childhood SES on later life immune response.⁹⁹ Statistical control of a collider would block the association between the exposure (early life SES) and the mediator (adult SES) and likely result in an under estimation of the direct effect of early life SES on immune response.⁹⁹ To address the potential for collider bias, only confounders of the exposure, mediator and outcome, such as age and gender, were controlled for in this dissertation.

1.10 Evaluating Life Course Model with Structural Equation Models (SEM)

Socioeconomic status is a measure of social stratification representing the social and economic factors that influence an individual's position within a society. Life course

socioeconomic status at the individual level is composed of SES measured at different stages of life, such as childhood, adolescence and adulthood. Multiple indicators of SES may be available at a particular stage and can be combined to produce a more accurate picture of SES at that time in life. For example, parent's education, household conditions, and parent's occupation may all serve as indicators of childhood SES for an individual. In life course analyses, often these variables are categorized and combined into a summary score. This common method places equal emphasis on each measure to capture a picture of the SES condition during childhood. An alternative method is to conceptualize SES as a latent, unmeasured construct for which we have measured indicator variables. Conceptually, the latent variable is the "cause" and the measured manifest variable is the "effect." They are linked by equations that include measurement error for the manifest variable. Conventional regression makes the assumption that there is no measurement error in the indicator variables, whereas models with latent variables explicitly model the connection between the manifest and latent variable in an attempt to estimate the extent of measurement error and then adjust parameter estimates for this measurement error. The latent variable, estimated by the manifest variables, is then used to predict the outcome of interest.

Another difference between SEM and traditional regression is the approach to modeling. Traditional regression methods seek to minimize the residuals of individual observations between predicted and observed values. Structural equation modeling, in contrast, minimizes the difference between the sample covariances and model predicted covariances. The observed covariance matrix is a function of a set of model parameters, thus if the model is correctly specified, the population covariance matrix is reproduced and the differences between the observed and population covariance matrix is minimized.

This dissertation will take advantage of SEM not only to model early life SES as a latent variable, but also conduct analyses that obtain specific effect estimates for direct and mediated pathways connecting early life SES and later life immune response to persistent pathogens. These path analyses will allow inference to be drawn about the life course mechanism by which early life SES and late life immunological control are related.

1.11 Public Health Significance

This dissertation uses life course conceptual models to consider the mechanisms by which early life sociological, biological and psychosocial exposures act to affect later life health. It is well established that persistent pathogens are socially patterned, but this work is the first to use a life course approach to determine how the childhood social environment influences immune control of persistent pathogens and total pathogen burden later in life. Childhood is an important period for acquiring and establishing control of persistent infections, therefore, a better understanding of life course SES pathways may help explain the differences in chronic diseases associated with these pathogens that appear by SES in the U.S. Other early life factors that may influence immune response to persistent pathogens independently of social conditions, such as geographical location and lifestyle, are also considered as they are particularly important for Mexican Americans. Further, few studies have looked at variation of the SES-persistent pathogen relationship by nativity and to our knowledge, no studies have considered variation by level of acculturation. Results from this dissertation will therefore also provide information on how cultural differences influences the social patterning of persistent infections and will help to identify the best points of intervention in the life course to improve immunological response to persistent infections later in life.

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Chapter 2. Early Life Socioeconomic Status and Immune Response to Persistent Pathogens in Later Life in Mexican Americans

2.1 Introduction

Lower socioeconomic status (SES) is linked to poorer individual health outcomes, though the mechanisms underlying this association are unclear.¹⁻³ Persistent pathogens may be one important pathway by which SES influences adult health. Seropositivity to common persistent pathogens, such as cytomegalovirus (CMV), herpes simplex-1 (HSV-1), *Helicobacter pylori*, and *Toxoplasma gondii*, is associated with multiple chronic diseases, including cardiovascular disease, cognitive impairment, frailty, Alzheimer's disease and autoimmune diseases, and mortality.^{1,4-12} Persistent infections are also patterned by race/ethnicity, age and SES in the U.S.^{1,13 14-16} Latinos and Blacks are more likely to be infected at an earlier age by common chronic persistent pathogens.¹⁷ There is also an inverse, graded association between SES and persistent infections within race/ethnic groups such that those with lower SES have higher seroprevalences of these agents.^{13,14,16} The SES gradient is evident even among U.S. children, indicating that those with low SES during childhood are more likely to acquire these pathogens earlier in life than their high SES counterparts.^{16,18}

Lasting immune response to these pathogens is measured by the amount of IgG antibody to the specific pathogen circulating in the blood. IgG is a serum biological marker indicating that an individual received sufficient exposure to the pathogen to activate the cell-mediated immune system at some point over the life course. IgG levels, however, do not indicate recent infection. IgM is the molecule that provides information on recent infection – but it is short lived and

difficult to capture in a population based study. Combined with the fact that the majority of individuals are initially infected with common persistent pathogens at a young age, novel infections in old age are generally rare in the US.¹³ Persistent infections establish residence in the body after initial infection and periodically reactivate inducing an increase in IgG antibody response, due to stress, a compromised immune system, or other physiological stressors. For these reasons, elevated measures of IgG levels among older age individuals are likely due to reactivation of a pathogen from exposure to stressor or age related changes in immune competence. Alternatively, high IgG level may represent a more severe infection, resulting in a higher circulating level of pathogen specific IgG throughout life.¹⁹

Exposure to infections earlier in life influences the development and function of the immune system.²⁰ Individuals with lower SES are more likely to experience higher stress leading to decreased cell-mediated immunity and more frequent reactivation of persistent infections.²¹⁻²³ Among children and adolescents, stressful events increases reactivation to herpes viruses, indicating poor cellular immune control.^{24,25} Thus, childhood may be an important period of susceptibility during which low SES increases the likelihood of acquiring persistent pathogens and may directly influence immune control of these pathogens later in life.

There are several mechanisms by which early life SES may be operating to influence immune response to persistent pathogens during adulthood, including the critical period model and the accumulation of risk model. The critical period model suggests that an event early in life, acting during a specific period of time, has a lasting independent effect on later life health.^{26,27} The critical period model is also known as biological programming and the latent effects hypothesis.^{26,27} The accumulation of risk model proposes that events gradually accumulate over the life course to shape health. The chain of risk model is a specific type of accumulation of risk

model where a set of exposures are linked over the life course, since one experience may lead to another, to influence later life health.²⁷

The way in which the critical period may play a role in infection is through exposure and immune response at an early age, which ultimately has a long-term effect on adult immune function. For example, children with low SES early in life may be more susceptible to infections and exposed to them more often than children with high SES due to unfavorable physical and social environments.²⁸ Increased susceptibility and frequent exposure may not only lead to infection at a younger age, but also influence the development of the immune system.²⁰ Poor immunological control of chronic infections would be evident later in life by higher adult antibody levels to the specific pathogens. Early life SES, therefore, may directly influence adult antibody levels independent of later life SES.

In the chain of risk model, early life SES may be indirectly affecting immune response to persistent infection through later life socioeconomic exposures. Early life social disadvantage is linked to subsequent levels of SES in adulthood, such as education, employment grade and income.²⁹ Resources and environments correspond to socioeconomic status levels over the life course, which determine exposure to persistent pathogens as well as affect immunological health and the ability to maintain immunologic control over the persistent infections. Low SES in early life may set up a chain of risk where conditions are such that an individual receives a poor education or low paying employment resulting in high stress and more frequent reactivation to persistent infections. Thus, later life SES may mediate the effect of childhood SES on immune response to pathogens later in life.

Most existing studies of persistent infections and socioeconomic status are limited to cross-sectional analyses of adult SES and serostatus.^{1,14,15,30} Few studies have examined early life

SES and concurrent infection.^{16,31} Previous findings suggest that prolonged social disadvantage during childhood may negatively influence the immune system, as measured by immune response to CMV.^{24,31} A separate study showed an association between poorer family interpersonal environment during childhood and increased later life immune response to CMV, though their study was limited to a small sample size.¹⁸ This evidence points to a role for early life SES on later life immunological control of persistent pathogens, but these studies only examine one persistent pathogen and they do not examine the potential mechanisms by which early life SES is connected to later life immunological response. Building upon previous work and applying a life course framework, this study is the first to examine the relationship between life course socioeconomic status and immune response to multiple persistent pathogens.

Using structural equation models and data from the Sacramento Area Latino Study on Aging, we evaluated two possible mechanisms by which early-life socioeconomic status may be operating to influence immune response to persistent pathogens during adulthood. To determine if evidence was in support of childhood as a critical period or part of a chain of socioeconomic risk, we tested whether early life SES was associated with immunological control of persistent infections independent of later life SES or if this association was mediated by later life SES.

2.2 Methods

2.2.1 Sample

Data came from the Sacramento Area Latino Study on Aging (SALSA), which was a longitudinal cohort study of 1,789 of Mexican Americans living in the Sacramento, California metropolitan area who were 60-101 years old at baseline in 1998-1999. Additional details about the recruitment and study population have been described previously.³² SALSA participants had full information on covariates (age and sex) and information for at least one childhood SES

indicator or available immune response data to be included in the analytic sample. Of the 1,789 participants enrolled at baseline, 1,779 had full information on covariates of interest. Persistent infection IgG levels measures were available for 1,266 participants (70.8%) and 1,272 (71.1%) had information for at least one early life SES indicator. This resulted in a final analytic sample of 1,562 (87.3%) using full information maximum likelihood methods (Figure 2-1).

2.2.2 Exposures

SALSA participants provided SES information for three time points in their life course, early life, midlife and late life. First, childhood socioeconomic status was conceptualized as a latent variable by using six different variables recalled by the participant: father's education (reference, fixed to 1.0), mother's education, father's occupation, mother's occupation, food availability as a child and sibling mortality. Parental education was measured in years. Parental occupation was measured by a 3-level categorical variable (technical, professional or managerial [high]; sales, administrative support or military [middle]; and services, manual or housewives [low]) and treated as an ordered hierarchical variable. Food availability during childhood was ascertained using the question, "When growing up, how often did you not have enough to eat?" with Likert item responses and also treated as a continuous variable. Sibling mortality was defined as the number of siblings that died before age 18. Next, midlife socioeconomic status was measured by years of education completed by the SALSA participant. Last, to measure late life socioeconomic position, the reported occupation worked by the SALSA participant for most of their life was utilized and included as a 4-level hierarchical variable (technical, professional or managerial; sales, administrative support or military; services or manual; and housewives).

2.2.3 Outcomes

Immune response to persistent pathogens was measured by IgG antibody level values for four separate pathogens, CMV, HSV-1, *H. pylori*, and *T. gondii*. Serum and plasma samples from baseline were tested at the Stanley Neurovirology Laboratory at Johns Hopkins University School of Medicine using high throughput solid-phase enzyme-linked immunosorbent assays (ELISA) to detect pathogen-specific IgG antibody levels. The ELISA methods have been described previously.³³ Briefly, diluted aliquots of serum were reacted with antigen bound to a solid-phase surface. Quantitation of IgG for each virus was determined by reaction of bound antibodies with enzyme labeled anti-human IgG and enzyme substrate and optical densities were read by spectrophotometric instrumentation.³⁴ Continuous antibody level was categorized by first identifying those who were seropositive and seronegative to each infection. Seropositivity was determined by standard cutoffs for each assay such that optical density unit (ODU) values less than 1.1 were classified as seronegative and values 1.1 or greater were seropositive. Among those participants who were seropositive to each infection, the continuous antibody level values were split into tertiles and categorized as low, middle and high antibody level. Combining the seronegative and tertile groupings resulted in a four-level hierarchical variable with the following categories: seronegative, low antibody response, middle antibody response and high antibody response.

2.2.4 Covariates

All final models were adjusted for age and gender. Baseline age of participants was measured in years. Participant gender was categorized as male or female, and male was treated as the referent category.

2.2.5 Statistical Analyses

Means and standard errors for all analysis variables were calculated using SAS version 9.3 (SAS Institute, Inc., Cary, NC). Structural equation modeling (SEM) was used to examine the life course pathways linking early life SES to adult antibody level for each of the 4 pathogens. SEM is comprised of a measurement model and a structural model. A measurement model for the latent variable early life SES was built using 6 indicators, father's education and occupation, mother's education and occupation, sibling mortality, and food availability. This latent variable was then used in structural models to predict the outcomes and adjust for covariates.

Figure 2-2 depicts the theoretical life course model connecting early life SES to later life immune response. The early life SES latent variable was used to test three different pathways, 1) direct, independent association of early life SES on immune response (pathway A), 2) indirect effect of early life SES on immune response mediated by midlife SES alone (pathway B*C), and 3) indirect effect of early life SES on immune response mediated by midlife and later life SES (pathway B*D*E). We did not include a pathway from early life SES directly through later life SES (life-long occupation) as any effect was likely mediated by midlife SES (education). Age and gender were then added to the model with paths extending to each SES measurement as well as the outcome to control for potential confounding. Goodness of fit for the final model was obtained using the root mean squared error of approximation (RMSEA) and comparative fit index (CFI). The CFI compares the model with a baseline null model with no relationships among the variables. The RMSEA considers how much error there is for each degree of freedom and penalizes for a less parsimonious model. Models with a CFI above 0.90 and an RMSEA of

less than or equal to 0.05 were considered to fit well, meaning that the variance in the variance-covariance matrix was well represented by the model.

All SEM analyses were conducted in MPlus version 7.11 (Methuén & Methuén, Los Angeles, CA) using a probit link function, theta parameterization and a weighted least squares estimator (WLSMV) to appropriately model ordered categorical outcomes and categorical mediators.³⁵ We believe that data in this analysis were at least missing at random (MAR). We believe that age, gender and education likely explained the missing data. Age and gender may have influenced the ability or desire to give a biospecimen and consequently the individuals for whom we had infection data. Age may also be related to memory of early life SES. Education level commonly predicts missing information.³⁶ Since age, gender and education were all included in the final models, we did not need to include any additional auxiliary variables to meet MAR criteria.³⁶ Sensitivity analyses were performed using traditional regression and mediation techniques and similar effects sizes to the SEM results were observed.³⁷

2.3 Results

Baseline descriptive statistics for the variables included in this analysis are shown in Table 2-1. The sample had a mean age of 70 years and 58% were female. Seroprevalence of the four infections were similar to other studies and are as follows: 84% of the sample was seropositive to CMV, 91% was seropositive for *H. pylori*, 87% was seropositive to HSV-1, and 35% was seropositive to *T. gondii*.³⁸

2.3.1 Measurement Model

Unstandardized and standardized factor loadings for the early life SES measurement model are presented in Table 2-2. For early life SES, all six indicators were significant at $p < 0.05$. This measurement model fit the data well (RMSEA=0.035, CFI=0.949).

2.3.2 Direct, Indirect and Total Effects of Childhood SES

A general path diagram depicting the SEM analysis with labeled pathways is depicted in Figure 2-3. Direct, indirect and total effects of childhood SES on each of the four infection outcomes, CMV, HSV-1, *T. gondii*, and *H. pylori*, and pathogen burden are summarized in Table 2-3. All models fit the data well. The pathway connecting early life SES to immune response adjusting for all other pathways and covariates was not statistically significant in final models for any of the four infections. Early life SES was found to indirectly influence immune response to infection through pathways mediated by later life SES for *T. gondii* and *H. pylori*. No association was found between early life SES and immune response to HSV-1.

Early life SES was associated with immune response to CMV when all pathways, direct and indirect, were considered collectively (model fit indices: RMSEA=0.034, CFI=0.945). For this total effect, a one standard deviation increase in early life SES, approximately 4 years of father's education, decreased the mean of the underlying variable for CMV antibody level by 0.10 standard deviations holding all covariates constant ($p=0.03$).

The effect of early life SES on *T. gondii* immune response was mediated by later life SES pathways such that a one standard deviation increase in early life SES (4 years of father's education) indirectly decreased the mean of the underlying variable for *T. gondii* antibody level by 0.10 standard deviations holding all covariates constant ($p=0.003$, model fit indices: RMSEA=0.033, CFI=0.941). When this indirect effect was decomposed into the education pathway and the education-occupation pathway, education was found to drive this association ($p<0.002$). Further, the pathway from education directly to *T. gondii* immune response was statistically significant; a one standard deviation increase in education, 5.35 years, decreased the

mean of the underlying variable *T. gondii* antibody level by 0.21 standard deviations, holding all else constant ($p=0.001$).

Early life SES was associated with immune response to *H. pylori* via the education-occupation pathway. A one standard deviation increase in early life SES decreased the mean of the underlying *H. pylori* antibody level by 0.03 standard deviations, holding all else constant ($p=0.005$, model fit indices: RMSEA=0.032, CFI=0.946). The pathway from lifetime occupation to *H. pylori* antibody level was statistically significant such that a one category increase in occupation, decreased the mean of the underlying variable for *H. pylori* level by 0.11 standard deviations, holding all else constant ($p=0.004$).

Additional sensitivity analyses were conducted to with occupation measured as a 6-level hierarchical variable and modeled as continuous. This model also included an error covariance between father's education and father's occupation as well as mother's education and mother's occupation to account for the dependence between these variables. Effect sizes and the statistical significance of pathways were similar.

2.4 Discussion

This was the first study, to our knowledge, to examine the association between life course SES and immune response to persistent infections. Two potential life course mechanisms, the critical period model and the chain of risk model, were evaluated to determine how life course SES impacts immune response to several persistent infections associated with chronic health conditions later in life. Early life SES was not independently associated with immune response to any of the persistent infections included in this study. Instead, later life SES, as measured by education and lifetime occupation, mediated the effect of early life SES on immune response. This finding supports a chain of risk mechanism, whereby early life SES influences later life

SES, which in turn, impacts immune control of these pathogens. For example, low SES in childhood may set up a chain of risk where conditions are such that an individual receives a poor education or low paying employment resulting in high stress and more frequent reactivation to persistent infections and therefore a higher antibody level in adult life. These findings have key public health implications because higher antibody levels to these infections in adult life have been associated with mortality and chronic health conditions.^{2,4,12,34,39} Moreover, there are significant disparities in these infections by race/ethnicity, indicating that minority populations are more likely to experience detrimental impacts of poor life course socioeconomic condition on immune response which may affect overall health and increased mortality. These results support closing SES gaps in childhood to improve trajectories of SES over the life course.

This study provides evidence for a chain of risk mechanism, however, later life SES mediates the effect of early life SES on immune response differently for each infection. All four pathogens establish chronic infections, yet have distinct modes of transmission, cellular targets, and immune evasion strategies which may serve to explain the variable later life SES pathways by which early life SES influences immune response to these pathogens.

Of the four persistent infections examined in this study, early life SES may be most important for later life immune response to CMV. Early life SES was inversely associated with CMV immune response after adjusting for covariates but not mediators. This “total” effect, the effect of early life on CMV immune response by all pathways together, may lend evidence in support of childhood as a critical period for SES in relation to immunological control of CMV later in life. Though the independent effect of early life SES controlling for all mediating pathways was not statistically significant, the role early life may play for acquiring CMV and subsequent immune control of this infection is not diminished. CMV is generally acquired early

in life through direct contact with infected body fluids.⁴⁰ Cross-sectional evidence shows racial and socioeconomic disparities exist for CMV seroprevalence and IgG antibody levels that begin at young ages.^{14,15} In addition, immune response to CMV increases with age and lower SES. Data representative of the U.S. population showed that those aged 45-54 years with low SES have the same immune response to CMV as those aged 65-74 years whom have high SES.¹⁴ Another study predicted the average age of CMV infection to be 10 years younger for minorities, including Mexican Americans, than their non-Hispanic white counterparts.¹⁷ Low SES in childhood may result in earlier infection with CMV and fewer resources available to manage the infection, increasing the frequency of reactivation over the life course. More frequent reactivations may produce negative downstream biological effects, including inducing inflammation and the exhaustion of cell mediated immunity (immunosenescence).⁴¹⁻⁴³

Our study findings also suggests there may be evidence for a “trigger effect” for immune response to *T. gondii* and *H. pylori*. A trigger effect occurs in a chain of risk where only the final link in the chain has a marked effect on the outcome.⁴⁴ We observed a direct effect of adulthood education on immune response to *T. gondii* independent of all other pathways. This may mean that higher educational attainment is a trigger for better immune control of *T. gondii* later in life. Of note, *T. gondii* is transmitted through cat feces, under cooked meat, contaminated water or may be inhaled or ingested directly through soil.⁴⁵ Better education may not only prevent exposure to *T. gondii* through knowledge of these transmission pathways, but it also may represent better access to other resources, such as health care, which influences overall health and ultimately the function of the immune system later in life.

Similarly, we observed a direct effect of lifetime occupation on immune response to *H. pylori* independent of all other pathways and that early life SES was only associated with this

outcome through the education-occupation pathway. Occupation may, therefore, be a trigger for immune control of *H. pylori* later in life. This is consistent with previous studies which have showed that manual or unskilled workers have higher odds of infection than non-manual workers.^{46,47} Lower occupational levels may increase the virulence of *H. pylori* as well as interfere with the immune response to infection through increased energy expenditure or other pathways.⁴⁷ In addition, a recent study found that poor organizational justice, or the inability for employees to make decisions affecting the experience of fairness, was associated with increased long-term levels of inflammatory markers CRP and IL-6 among men.⁴⁸ A systematic review of psychosocial job stress and immunity found that greater job satisfaction may have a positive impact on immune outcomes and that unemployment and job security are significant factors leading to reduced cellular immune response and the deterioration of the immune system.⁴⁹ Thus, lower occupational status may influence immunological control of *H. pylori*, potentially through inflammatory pathways, and result in decreased resources to handle stress and its negative health consequences, leading to poorer immunological control of *H. pylori* later in life. Alternatively, jobs that do not provide health care coverage may result in fewer doctor visits associated with *H. pylori* infection. *H. pylori* is associated with peptic ulcer disease and can be treated with a combination of proton pump inhibitors and antibiotics.⁵⁰ Our study did not directly diagnose *H. pylori* infection but IgG antibody levels to the infection indicate the initial or lasting immune response to the infection once it has cleared.⁵⁰ Treatment for *H. pylori* or other incidental antibiotic use may result in seroreversion or decreased measurable antibody levels.⁵⁰ As a result, higher SES and health care access due to employment with health care benefits may result in lower immune response to *H. pylori*.

This study has some limitations. The SALSA study may be subject to survivor bias because participants were at least 60 years of age at baseline. This may mean the participants are healthier and may exhibit better immunological health and consequently control of persistent infections than those who did not survive long enough to be enrolled in the study. However, this would be expected to bias our results towards the null, meaning our observed effect estimates may be underestimated. In addition, the early life SES measures are prone to recall bias. However, reporting of early life SES is unlikely to vary by immune response, as individuals are unlikely to be aware of their seropositivity status to these infections and immunological response to the infections. None of these infections are routinely diagnosed in populations unless they are associated with overt symptoms, such as current peptic ulcer disease. A previous study in the SALSA cohort found that only 0.8% were taking antibiotics to treat *H. pylori* infection and among those seropositive to *H. pylori* 11% reported taking medications for acid suppression, peptic disorders, or antacids at the time of data collection for this study.⁷ As this is an elderly cohort, poor cognition may influence the recall of childhood SES but we expect this to be non-differential with respect to level of SES, biasing estimates toward the null. As with many studies of infections, we have no information on the timing of primary infection. While it is possible that infections acquired earlier in life may influence later life SES attainment, this does not prevent us from examining the role of SES over the life course in relation to immune control later in life. Finally, there are additional persistent pathogens, such as Epstein Bar Virus and *C. pneumonia*, for which we do not have immune response data, however, the four pathogens that we explore here are important to understand because they are associated with various chronic health outcomes and more prevalent among Latino populations.^{2,4,8,11,42,43}

Despite these limitations, this study has many strengths. It is the first to investigate life course mechanisms underlying the connection between SES and immune response to persistent pathogens. Further, we used a structural equation modeling approach, which is preferable for life course analyses over traditional regression methods for several reasons. First, modeling childhood SES as a latent variable uses multiple indicators and allows measurement error to be incorporated into the model, strengthening predictive power over OLS regression which assumes no measurement error. Second, structural equations model specific mediation pathways and standard errors are estimated allowing us to evaluate life course mechanisms. Third, creating a latent variable for childhood SES is an improvement over more common summary measures described in the literature. Other methods would dichotomize each indicator into low and high SES and then create a summary score, however, this process makes many assumptions, including deciding the proper thresholds for low and high SES and that a summary SES score is a meaningful representation. Using SEM, we are able to maximize the SES information available for the model to include the full range of data as well as the power to detect effects. We performed sensitivity analysis using other regression mediation techniques and the results verified all estimates and conclusions, further supporting SEM as a valid approach for life course analyses with multiple mediators. Finally, this study was conducted in a well-characterized cohort of predominantly Mexican Americans, limiting the influences of significant heterogeneity present among Latino populations.

2.5 Conclusion

Numerous studies have demonstrated that disparities exist in the seroprevalence of persistent infections by SES beginning early in life, suggesting childhood may be an important period during the life course for acquiring and establishing control of persistent infections.

Higher immune response to chronic infections later in life is not just a function of disadvantage during childhood, but instead reflects the end result of a chain of socioeconomic disadvantage throughout the life span. Our findings suggest, therefore, that interventions targeting increased educational attainment as a modifiable risk factor may be effective for improving immune control of persistent pathogens later in life. Moreover, understanding the life course SES pathways that trigger immune response for CMV, HSV-1, *H. pylori* and *T. gondii* may help shed light on why chronic disease disparities associated with these pathogens appear to persist by SES over time and across generations in the U.S.

Table 2-1. Descriptive statistics for the Sacramento Area Latino Study on Aging (SALSA) at baseline

Variable	N	Mean or %	SD
Early Life SES			
Father's Education (years)	732	3.35	4.18
Mother's Education (years)	827	3.37	3.12
Father's Occupation	1132		
High	88	7.80	
Middle	54	4.80	
Low	990	87.50	
Mother's Occupation	1228	3.27	0.65
High	41	3.30	
Middle	15	1.20	
Low	1171	95.40	
Food Availability	1249	4.55	0.98
Sibling Mortality	1247	1.26	1.14
Midlife SES			
Education (years)	1562	7.53	5.35
Late Life SES			
Technical, Professional or Managerial	182	11.80	
Sales, Administrative Support or Military	172	11.15	
Services or Manual	907	58.82	
Housewives	281	18.22	
Covariates			
Age	1562	70.34	6.93
Female	1562	0.58	0.49
Seropositive			
CMV	1263	0.84	0.36
T. gondii	1263	0.35	0.48
H. pylori	1263	0.91	0.28
HSV-1	1263	0.87	0.34

Table 2-2. Measurement Model for Early Life SES, Model Fit: RMSEA=0.035, CFI=0.949

Indicator Loadings	Unstandardized Estimate		SE	Standardized Estimate		SE
Father's Education	1.00 (fixed)			0.742 ***		0.051
Mother's Education	0.806 ***		0.117	0.670 ***		0.049
Father's Occupation	0.158 ***		0.029	0.439 ***		0.055
Mother's Occupation	0.134 ***		0.016	0.384 ***		0.070
Sibling Mortality	0.079 *		0.037	0.110 *		0.050
Food Availability	0.036 *		0.016	0.114 *		0.049

*Significant at $p < 0.05$, **Significant at $p < 0.01$, ***Significant at $p < 0.001$

Table 2-3. Standardized direct and indirect effects of SES on Later Life Immune Response, N=1562

	CMV		HSV-1		Persistent Pathogen			
	CMV	p-value	HSV-1	p-value	<i>T. gondii</i>	p-value	<i>H. pylori</i>	p-value
Early Life SES								
Total Effect	-0.102	0.025	-0.074	0.127	0.015	0.796	-0.071	0.136
Direct Effect (β_1)	-0.076	0.235	-0.087	0.203	0.118	0.155	-0.076	0.248
Total Indirect Effect	-0.026	0.344	0.013	0.645	-0.103	0.003	0.005	0.851
Decomposition of Indirect Effects								
via Education	-0.027	0.382	0.002	0.957	-0.121	0.002	0.037	0.222
via Education and Occupation	0.001	0.946	0.012	0.296	0.019	0.146	-0.032	0.005
Midlife SES								
Direct Effect of Education	-0.047	0.383	0.003	0.957	-0.211	0.001	0.064	0.218
Late Life SES								
Direct Effect of Occupation	0.003	0.946	0.042	0.294	0.067	0.14	-0.114	0.004
Model Fit								
RMSEA	0.034		0.033		0.033		0.032	
CFI	0.945		0.941		0.941		0.946	

All models adjusted for age and sex. **Bold** is statistically significant at p=0.05.

Figure 2-1 Derivation of Sacramento Area Latino Study on Aging (SALSA) analytic sample

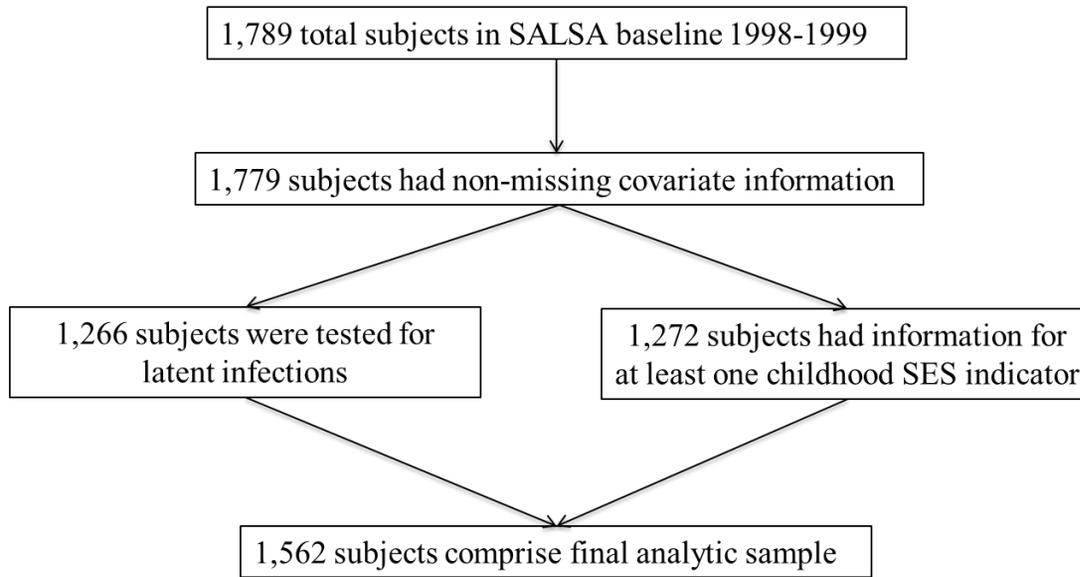


Figure 2-2. Life course model of the association between early life SES and adult immune response to common persistent pathogens

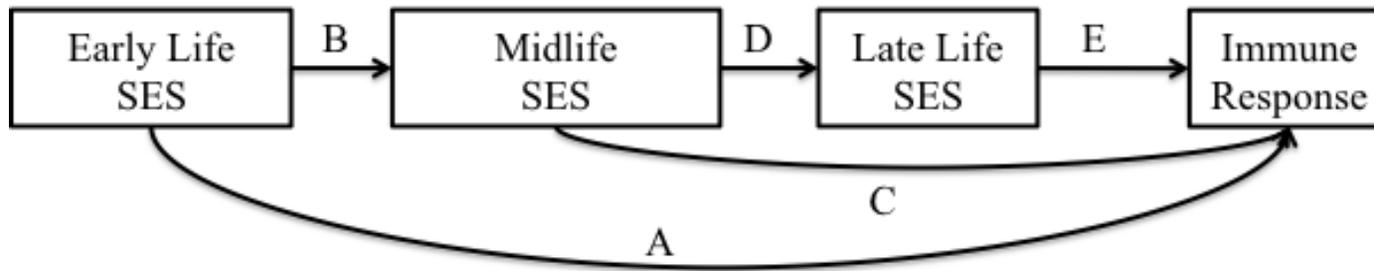
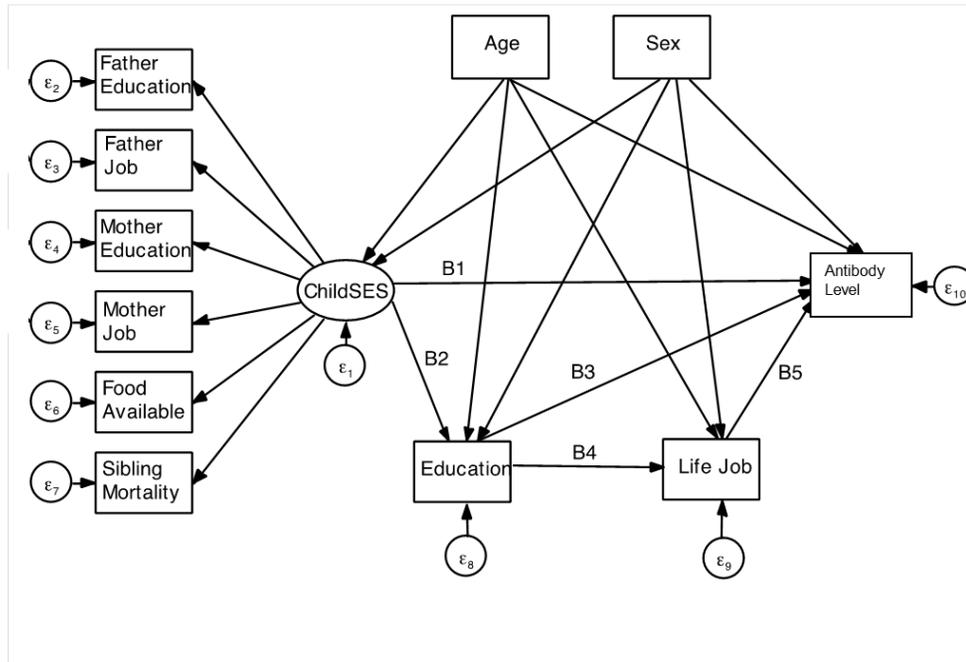


Figure 2-3. General diagram of SEM for indirect and direct effects of childhood SES on antibody level and pathogen burden



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Chapter 3. Early Life Socioeconomic Status and Pathogen Burden in Later Life in Mexican Americans

3.1 Introduction

Individual persistent pathogens are associated with many chronic health outcomes, including diabetes, cardiovascular disease, cognitive impairment, frailty, Alzheimer's disease, autoimmune diseases and mortality.¹⁻⁹ However, an individual is rarely only afflicted with one persistent infection. The immune system must often control multiple pathogens at once, including mitigating damage to body tissues and responding to potential synergistic effects of these infections.¹⁰ Seropositivity to multiple persistent pathogens may not only increase the risk of infection to other pathogens but also heighten the severity of subsequent infections.¹¹⁻¹³ Additionally, higher pathogen burden, the cumulative number of persistent pathogens to which one is seropositive, is associated with coronary artery disease, atherosclerotic progression, metabolic disorder, cognitive impairment and mortality.¹³⁻¹⁷

In the U.S., individuals with lower SES have higher pathogen burden than their high SES counterparts.¹⁸ Differences in pathogen burden by race/ethnicity have also been demonstrated such that Mexican Americans have higher mean pathogen burden than non-Hispanic Whites.¹² This ethnic disparity is not due to variation in socioeconomic status alone, but rather may represent higher transmission rates, at earlier ages and increased susceptibility, potentially due to higher social stress among Mexican Americans.^{12,19,20} Racial and ethnic differences in pathogen burden are particularly important because Latinos are more likely to suffer from the chronic diseases associated with higher pathogen burden.²¹

Persistent pathogens are often acquired early in life.^{18,22-24} Infection with certain persistent pathogens may have harmful effects during growth and development, including a depressed immune response and recurrent microbial infection.²² Further, social gradients in pathogen burden are evident among children. Mean infection burden is higher in U.S. children with lower educated parents than children of parents with higher education.¹⁸ Though socioeconomic exposure during childhood may have life-long implications for pathogen burden later in life, no study, to our knowledge, has evaluated the mechanism by which early life socioeconomic status may influence pathogen burden later in life.

Early life socioeconomic status may affect later life pathogen burden through several pathways. Childhood may be a critical period whereby early life SES directly influences later life pathogen burden independent of SES at later points in life.^{25,26} Early life SES may alter an individual's susceptibility to persistent infections as well as their likelihood of exposure, directly impacting which pathogens one acquires over their life course. Alternatively, early life SES may be operating through a chain of risk to affect later life pathogen burden.^{25,26} In this pathway, early life SES influences later life pathogen burden indirectly, through SES later in life. Social and economic resources in childhood may influence adult SES, which in turn affects risk of pathogen burden later in life.

Additionally, pathogen burden is most often measured as the total number of pathogens to which one is seropositive, however, there is no standard laboratory panel of persistent pathogens for population-based testing and thus the composition of a "total pathogen burden" summary score differs between studies.^{18,27,28} The lack of consistency in measurement makes drawing inference from cross-study comparisons difficult. Moreover, a total pathogen burden summary score assumes a monotonic relationship with the comparison variable of interest when, in

actuality, specific combinations of pathogens may be more important for disease processes.¹⁵ For example, one study found that individuals who were CMV and HSV-2 seropositive or HSV-2 and *H. pylori* seropositive had the greatest rates of all-cause mortality and that there was an absence of a graded relationship between increased total pathogen burden summary score and all-cause mortality.¹⁵ Studies involving pathogen burden and chronic health outcomes have shown inconsistent associations, possibly due to the differing number and composition of the infections in summary scores.^{10,27,29}

The motivation for this study was to evaluate the pathways by which life course SES is associated with pathogen burden using structural equation models (SEM) and path analysis in a well-defined cohort of Mexican Americans. We tested the hypothesis that higher socioeconomic status early in life is associated with lower pathogen burden independent of later life SES. Further, to address limitations with “total pathogen burden,” we conceptualized pathogen burden as a latent variable where class membership was determined by a latent profile analysis, allowing for the effect of specific combinations of pathogens to be evaluated.

3.2 Methods

3.2.1 Study population

Data come from the Sacramento Area Latino Study on Aging (SALSA), a longitudinal study of 1,789 Mexican Americans living in the Sacramento, CA metropolitan area who were 60-101 years old at baseline in 1998-1999. Details on the recruitment and study population have been described previously.³⁰ The final analytic sample comprised of 1,263 participants (71%) who had persistent infection IgG antibody level measures available. Participants without infection data were more likely to be older (mean age of 72 vs. 70, $p < 0.001$) and male (52% vs. 39%, $p < 0.001$). No differences in educational attainment were observed. The SALSA study was

approved by the Institutional Review Boards at the University of California, Davis and the University of Michigan.

3.2.2 Exposures

SALSA collected socioeconomic status information for early life, midlife and late-life. Early life SES was conceptualized as a latent variable from six different variables recalled by the participant: father's education (reference), mother's education, father's occupation, mother's occupation, food availability as a child and sibling mortality. Parental education was measured in years. Parental occupation was measured by a 3-level categorical variable (technical, professional or managerial [high]; sales, administrative support or military [middle]; and services, manual or housewives [low]) and treated as an ordered hierarchical variable. Food availability during childhood was ascertained using the question, "When growing up, how often did you not have enough to eat?" with Likert item responses and also treated as a continuous variable. Sibling mortality was defined as the number of siblings that died before age 18. Next, midlife socioeconomic status was measured by years of education completed by the SALSA participant. Last, to measure late life socioeconomic position, the reported occupation worked by the SALSA participant for most of their life was utilized and included as a 4-level hierarchical variable (technical, professional or managerial; sales, administrative support or military; services or manual; and housewives).

3.2.3 Laboratory Analyses

Serum and plasma samples from baseline were tested at the Stanley Neurovirology Laboratory at Johns Hopkins University School of Medicine using high throughput solid-phase enzyme-linked immunosorbent assays (ELISA) to detect pathogen-specific IgG antibody level. The ELISA methods have been described previously.³¹ Briefly, diluted aliquots of serum were

reacted with antigen bound to a solid-phase surface. Quantitation of IgG for each virus was determined by reaction of bound antibodies with enzyme labeled anti-human IgG and enzyme substrate and optical densities were read by spectrophotometric instrumentation.³² IgG antibody levels for each of the four persistent pathogens, CMV, HSV-1, *T. gondii*, and *H. pylori*, were log-transformed to obtain an approximately normal distribution for each infection.

3.2.4 Pathogen Burden

Pathogen burden was conceptualized as a nominal latent class variable based on the clustering of CMV, HSV-1, *H. pylori*, and *T.gondii* immune response. A latent profile analysis (LPA) measurement model was used on continuous IgG level (log transformed) with each of the four infections as indicators to generate latent class membership. The best class number solution was determined based on comparison of standard fit measures, including the Bayesian Information Criterion (BIC), sample size adjusted BIC, the Lo, Mendell and Ruben log-likelihood ratio test, and the bootstrapped log-likelihood ratio test (BLRT), as well as judgment on the nature of the groups (mean antibody level) and their interpretability in relation to theory and previous research.³³ Predicted class membership from this LPA model was then used as a nominal dependent variable in subsequent analyses. For comparison, a traditional summary measure of total pathogen burden was created and analyzed. Seropositivity was determined for each infection by standard cutoffs for the assay such that optical density unit (ODU) values less than 1.1 were classified as seronegative and values greater than or equal to 1.1 were seropositive. The number of pathogens to which one was seropositive was summed (range 0-4) to give a measure of total pathogen burden.

3.2.5 Covariates

Covariates included age and gender. Age was measured in years and mean centered. A dichotomous gender variable with males as referent was also mean centered.

3.2.6 Statistical Analyses

Descriptive statistics were performed using SAS, version 9.3 (SAS institute, Inc., Cary, NC). MPlus version 7.11 (Methuén & Methuén, Los Angeles, CA) was used for the following analyses. Figure 3-1 depicts the theoretical life course model connecting early life SES to later life pathogen burden. The early life SES latent variable was used to test three different pathways, 1) direct, independent association of early life SES on pathogen burden (pathway A), 2) indirect effect of early life SES on pathogen burden mediated by adult SES alone (pathway B*C), and 3) indirect effect of early life SES on pathogen burden mediated by adult and later life SES (pathway B*D*E). We did not include a pathway from early life SES directly through later life SES (life-long occupation) as any effect was likely mediated by midlife SES (education).

Structural equation modeling (SEM) was used to evaluate the life course pathways connecting early life SES to pathogen burden (example of overall SEM model in Figure 3-2). SEM is comprised of a measurement model and a structural model. A measurement model for the latent variable early life SES was built using 6 indicators, father's education and occupation, mother's education and occupation, sibling mortality, and food availability. The early life latent variable was then used in two separate structural pathway models to predict 1) the class membership from the latent profile analysis using multinomial logistic regression, and 2) total pathogen burden, while adjusting for covariates. Monte Carlo integration was used for the latent class pathogen burden model with the robust maximum likelihood (MLR) estimator to produce parameter estimates and standard errors that were robust to non-normality.³⁴ Standard (trapezoid)

numerical integration was used for the total pathogen burden model with a probit link function, weighted least squares estimator (WLSMV), and theta parameterization to appropriately model categorical mediators with a continuous outcome.³⁴

Predicted class membership from the latent profile analysis was not further adjusted for potential measurement misclassification due to high entropy (class separation). Had class separation not been as clear, a manual three-step method would have been used to generate the underlying latent categorical variable for pathogen burden and then subsequently regressed the latent categorical variable on the early life SES latent variable.^{35,36}

Goodness of fit for the pathogen burden summary model was obtained using the root mean squared error of approximation (RMSEA) and comparative fit index (CFI). The CFI compares the model with a baseline null model with no relationships among the variables. The RMSEA considers how much error there is for each degree of freedom and penalizes for a less parsimonious model. Models with a CFI above 0.90 and an RMSEA of less than or equal to 0.05 were considered to fit well. Model goodness of fit measures were not available for the pathogen burden latent class variable analysis due to the use of Monte Carlo integration.

3.3 Results

Baseline descriptive statistics for the variables included in this analysis are shown in Table 3-1. The sample participants had a mean age of 70 years and 61% was female. Seropositivity to each pathogen was as follows: 84% were seropositive to CMV, 87% were seropositive to HSV-1, 35% were seropositive to *T. gondii* and 91% were seropositive to *H. pylori*. The mean total pathogen burden was three infections.

3.3.1 Measurement Models

Unstandardized and standardized factor loadings for the early life SES measurement model are presented in Table 3-2. For early life SES, father's occupation, all six indicators (father's education and occupation, mother's education and occupation, food availability, and sibling mortality) were significant at $p < 0.01$. This measurement model fit the data very well (RMSEA=0.035, CFI=0.949).

Table 3-3 shows the results of the LPA measurement model from the four infection indicators for a one, two, three, four and five class solution. Fit statistics were used to first compare all possible solutions. The three and four class solutions emerged as suitable for the data as the Lo, Medell, Rubin LRT Test was not statistically significant for the five-class solution. Then, the mean IgG level values for each group was reviewed for the three class and four class solution. Upon considering the nature of the groups and their interpretability, as well as prior research, a three class solution was deemed most appropriate even though the Lo, Mendell, Rubin LRT Test and the BLRT suggested that the four class solution was a numerical improvement over the three class solution. Class membership for this solution is as follows: Class 1 (N=55, 4%) was seronegative to CMV and *T. gondii* and seropositive to HSV-1 and *H. pylori*, Class 2 (N=777, 61%) was seronegative to *T. gondii* and seropositive to CMV, HSV-1 and *H. pylori*, Class 3 (N=431, 34%) was seropositive to all infections. The three class solution had high entropy (0.88), indicating good class separation. Predicted class membership was extracted and then used as a nominal dependent variable in the SEM analysis with class 3 (seropositive to all infections) as the referent category.

3.3.2 SEM Models: Direct, Indirect and Total Effects of Early Life SES

Table 3-4 shows the direct, indirect and total effects of the early life SES latent variable on all pathogen burden outcomes. Specific diagrams of each analysis are depicted in Figures 3-3, 3-4 and 3-5. In the multinomial logistic regression, comparing the lowest pathogen burden group (class 1) to the highest pathogen burden group (class 3) and the middle pathogen burden group (class 2) to highest pathogen burden group (class 3), no statistically significant independent effect of early life SES was found on pathogen burden class. When considering pathways mediated by later life SES, small, but statistically significant, associations were observed. Through all indirect pathways, for a one unit increase in early life SES, the odds of being in the lowest pathogen burden group (seropositive to HSV-1 and *H. pylori* only) were 1.12 times the odds of being in the highest pathogen burden group (seropositive to all pathogens), holding covariates constant ($p=0.02$). This total indirect effect was decomposed into an indirect pathway via education only and an indirect pathway via education and lifetime occupation. The pathway via education only was shown to drive this association ($OR=1.10$, $p=0.04$). In addition, education was found to directly influence pathogen burden class for both the lowest v. highest pathogen burden ($OR=1.09$, $p=0.05$) and middle v. highest pathogen burden ($OR=1.06$, $p=0.01$) comparisons.

For total pathogen burden, the total effect of early life SES (acting through all pathways) was found to be associated with a decrease in mean pathogen burden. A one standard deviation increase early life SES (4 years of father's education) decreased mean pathogen burden by 0.10 ($p=0.02$, model fit indices: RMSEA=0.034, CFI=0.941). The effect of early life SES independent of later life SES (direct effect) on mean pathogen burden was -0.02 and not statistically significant ($p=0.72$), however, early life SES was associated with mean pathogen

burden through all indirect pathways. A one standard deviation increase in early life SES (4 years of father's education) decreased mean pathogen burden by 0.08 ($p < 0.01$). A decomposition of this overall indirect effect showed that early life SES operates through the education only pathway to influence pathogen burden later in life. A statistically significant direct effect of education, controlling for all other pathways and holding all covariates constant (-0.15 , $p < 0.01$) was also observed.

3.4 Discussion

The objective of this study was to determine the mechanism by which life course SES is associated with pathogen burden using structural equation models (SEM) and path analysis. An increase in early life SES was associated with a decrease in pathogen burden, though this direct pathway was not statistically significant. Instead, we found that higher early life socioeconomic status was indirectly associated with lower pathogen burden through subsequent SES exposures later in life. This study provides evidence for a socioeconomic chain of risk whereby early life SES acts through later life SES to influence later life pathogen burden.

A major motivation for this work was to reconsider how pathogen burden is measured. Pathogen burden is most often conceptualized as the total number of pathogens for which individuals are seropositive, however, there is a large inconsistency on the types and number of pathogens included in total pathogen burden measures across studies. Indeed, studies for pathogen burden have shown inconsistent results, possibly due to the differing number and composition of the infections in such summary measures.^{10,27,29} Persistent pathogens include viruses, bacteria and parasites, many of which have different transmission modes, cellular targets and latency sites.³⁸ Biologically, co-infections may interact or influence immune reaction to other pathogens.³⁹ One hypothesis is that specific T-cell surveillance may be impaired when an

individual has a co-infection to 1 or more pathogens.⁴⁰ A study in immunocompetent participants showed that CMV primary infection elicited a higher immune response to Epstein-Barr Virus consistent with viral reactivations.⁴¹ Another study found that EBV co-infection might stimulate immune differentiation in immunocompetent CMV seropositive children and influence the immunological cell composition in early life.⁴² As this evidence indicates, certain combinations co-infections may be more influential on health than an overall summary measure.

To assess the association between life course SES and the specific combinations of persistent pathogens for which individuals were seropositive in this study, a latent profile analysis was conducted. The latent profile analysis produced a three-class pathogen burden grouping participants into specific categories, seropositive to *H. pylori* and HSV-1, seropositive to CMV, *H. pylori* and HSV-1, and seropositive to all four infections. In this population considering these four pathogens, *T. gondii* infection only plays present in the highest pathogen burden group. Modeling clusters of infections instead of a simple summary measure may provide more resolution about the dynamics of co-infections in populations and their influence on health outcomes. Doing so may also improve cross-study inferences because the pathogens composing each cluster and the mean immune response to each infection within a grouping is known.

Higher early life SES was associated with lower pathogen burden when those in the lowest pathogen burden group (seropositive to *H. pylori* and HSV-1) were compared to those in the highest pathogen burden group (seropositive to all infections), however, this association was not independent of later life SES as we hypothesized. Education mediated the effect of early life SES on pathogen burden. These results support a chain of risk mechanism whereby the sequence of SES exposures over the life course are linked because one exposure leads to another.²⁶ Lower SES during early life and midlife may impact individual susceptibility and patterns of exposure

to these infections, as well as immunological control over the life course. Children with lower SES may have worse housing conditions and poorer hygiene than children with higher SES, increasing the likelihood of exposure and acquisition of these persistent pathogens. Further, co-infection may not only increase the risk of infection to other pathogens, but also increase the severity of subsequent infections.¹¹⁻¹³ Seropositivity to multiple persistent infections may contribute to morbidity over and above the influence of each infection alone through additional tolls placed on the immune system and activation of inflammatory pathways.^{12,37}

Interestingly, no statistically significant associations were found when comparing the middle pathogen burden group to the highest pathogen burden group, except for the direct effect of education. This is essentially testing the effect of being seropositive to *T. gondii*. Those with higher education were more likely to be in the middle pathogen burden group (not seropositive to *T. gondii*) than the high pathogen burden group independent of other SES measures. These results reinforce the importance of education on reducing exposure to persistent pathogens and suggest improving educational attainment as a potential target for public health intervention aimed at reducing disparities in chronic health.

For the measure of total pathogen burden, the effect of early life SES was also mediated by later life SES. Specifically, the pathway mediated by education alone was found to drive this association. Lower education was also independently associated with later life total pathogen burden holding all covariates and all other pathways constant. This is consistent with previous results that show low education is a strong and significant predictor of higher total pathogen burden.³⁷ These results are similar to the findings from the multinomial SEM model. This might be due to the fact that SALSA was an elderly cohort with high seroprevalences of the infections. It is possible that in a younger population, or considering additional persistent pathogens, a latent

variable approach would produce different results than a traditional measure of total pathogen burden. However, the latent variable approach did provide greater insight into the specific combinations of infections that are driving the association between SES and pathogen burden in this study. From both analyses, we concluded that education may be the best predictor of socioeconomic exposure patterns that influence pathogen burden and may be the best target for public health intervention.

This study is not without limitations. The SALSA study may be subject to survivor bias because participants were at least 60 years of age at baseline. As a result, participants may be healthier overall and immunologically, resulting in better control of persistent infections. This seems unlikely to bias our results as total pathogen burden was a summation of the number of persistent pathogens to which one was seropositive, and seroreversion is rare in this study. Better immunological control was also unlikely to influence the categorization of pathogen burden classes for the latent profile analysis. The early life SES measures reported in this study are also prone to recall bias, though we do not expect reporting of early life SES to vary by immune response since individuals are not routinely diagnosed for these infections and consequently would be unlikely to know their infection status. It is possible that poor cognition may also influence the recall of early life SES, however, we expect this to be non-differential with respect to level of SES, again biasing the estimates towards the null. Additionally, early life SES was modeled as a latent variable using multiple indicators and incorporated measurement error into the model, strengthening predictive power over OLS regression which assumes no measurement error. A latent variable is an improvement over more common methods where a summary score would be derived after each indicator was dichotomized into low and high SES. Using SEM, we are able to maximize the SES information available for the model to include the full range of

data as well as the power to detect effects. Lastly, IgG is a biological marker isolated from serum that indicates an individual received sufficient exposure to a particular pathogen to activate the cell-mediated immune system. These biomarkers do not provide information on when the individual was exposed. High IgG levels may represent recent primary infection, though this is unlikely in this elderly study population because infection commonly occurs during childhood.

In conclusion, this is the first study, to our knowledge, to evaluate the mechanism by which early life social and economic conditions operate to affect later life pathogen burden. Life course mechanisms were evaluated using structural equations models, which allowed us to measure estimates and standard errors for specific mediation pathways. In this population of elderly Mexican Americans, we found that higher early life socioeconomic status was indirectly associated with lower pathogen burden through educational attainment. Though the effect sizes in this study were small, they provide evidence for a socioeconomic chain of risk whereby early life SES acts through later life SES to influence later life health outcomes. A better understanding of the life course SES pathways that influence pathogen burden may help explain the differences in chronic disease by SES and race/ethnicity in the U.S. Future studies of pathogen burden should continue to consider the specific combinations of co-infections and their biological implications to foster better cross-study comparisons and provide insight into the drivers of pathogen burden.

Table 3-1. Descriptive statistics for the Sacramento Area Latino Study on Aging (SALSA) sample at baseline

	N	Mean or %	SD
Early Life SES			
Father's Education (years)	732	3.35	4.18
Mother's Education (years)	827	3.37	3.12
Father's Occupation	1132		
High	88	7.80	
Middle	54	4.80	
Low	990	87.50	
Mother's Occupation	1228	3.27	0.65
High	41	3.30	
Middle	15	1.20	
Low	1171	95.40	
Food Availability	1249	4.55	0.98
Sibling Mortality	1247	1.26	1.14
Midlife SES			
Education (years)	1562	7.53	5.35
Late Life SES			
Technical, Professional or Managerial	182	11.80	
Sales, Administrative Support or Military	172	11.15	
Services or Manual	907	58.82	
Housewives	281	18.22	
Covariates			
Age	1562	70.34	6.93
Female	1562	0.58	0.49
Seropositive			
CMV	1263	0.84	0.36
<i>T. gondii</i>	1263	0.35	0.48
<i>H. pylori</i>	1263	0.91	0.28
HSV-1	1263	0.87	0.34
Pathogen Burden			
Low	1263	4.00	
Medium	1263	61.00	
High	1263	35.00	
Pathogen Burden Summary Index	1263	3.01	0.91

Table 3-2. Measurement Model for Early Life SES, Model Fit: RMSEA=0.035, CFI=0.949

Indicator Loadings	Unstandardized Estimate		SE	Standardized Estimate		SE
Father's Education	1.00 (fixed)			0.742 ***		0.051
Mother's Education	0.806 ***		0.117	0.670 ***		0.049
Father's Occupation	0.158 ***		0.029	0.439 ***		0.055
Mother's Occupation	0.134 ***		0.016	0.384 ***		0.070
Sibling Mortality	0.079 *		0.037	0.110 *		0.050
Food Availability	0.036 *		0.016	0.114 *		0.049

*Significant at p<0.05, **Significant at p<0.01, ***Significant at p<0.001

Table 3-3. Measurement Models for Pathogen Burden from LPA with Log Continuous IgG level indicators for four infections (n=1263)

Model Fit Measure	1 Class	2 Class	3 Class	4 Class	5 Class
AIC	10112	9747	9653	9507	9435
BIC	10153	9814	9745	9626	9579
Sample Size Adjusted BIC	10128	9773	9688	9552	9489
Entropy	n/a	0.875	0.879	0.836	0.856
Lo, Mendell, Rubin LRT Test	n/a	365 (p<0.001)	102 (0.02)	151 (p<0.001)	80 (0.06)
Bootstrapped Likelihood Ratio Test	n/a	p<0.001	p<0.001	p<0.001	p<0.001

Table 3-4. SES Effects on Later Life Pathogen Burden

	Total Pathogen Burden (N=1562)		Pathogen Burden Latent Variable 1 v.3 (N=1263)		Pathogen Burden Latent Variable 2 v.3 (N=1263)	
	β Estimate*	p-value	OR	p-value	OR	p-value
Early life SES						
Total Effect	-0.10	0.02	1.17	0.06	0.82	0.10
Direct Effect	-0.02	0.72	1.05	0.66	0.92	0.14
Total Indirect Effect	-0.08	<0.01	1.12	0.02	0.88	0.08
Decomposition of Indirect Effects						
via Education	-0.09	<0.01	1.10	0.04	0.91	0.16
via Education and Occupation	0.01	0.55	1.01	0.73	0.97	0.16
Midlife SES						
Direct Effect of Education	-0.15	<0.01	1.09	0.05	1.06	0.01
Late Life SES						
Direct Effect of Occupation	0.02	0.55	1.07	0.73	0.89	0.15

All models adjusted for Age and Sex

*Standardized Estimates. **Bold** is statistically significant at p=0.05

Figure 3-1. Life course SES pathways

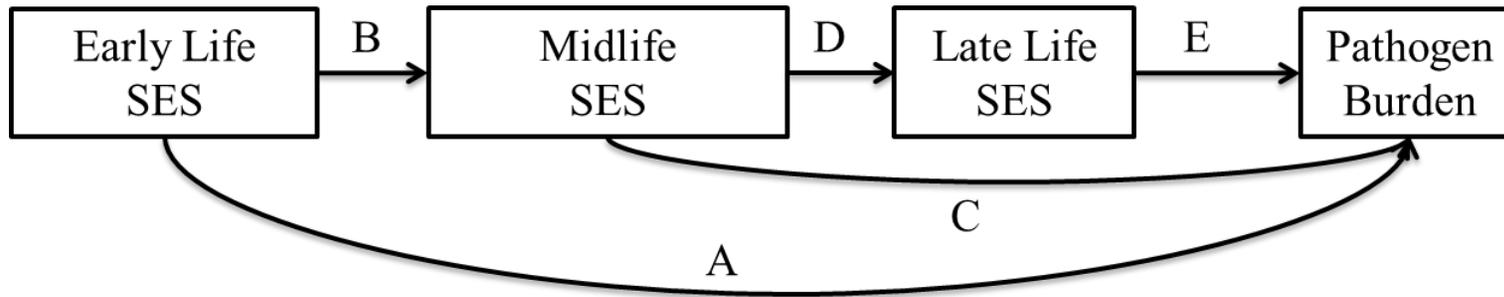


Figure 3-2. Overall SEM Conceptual Model

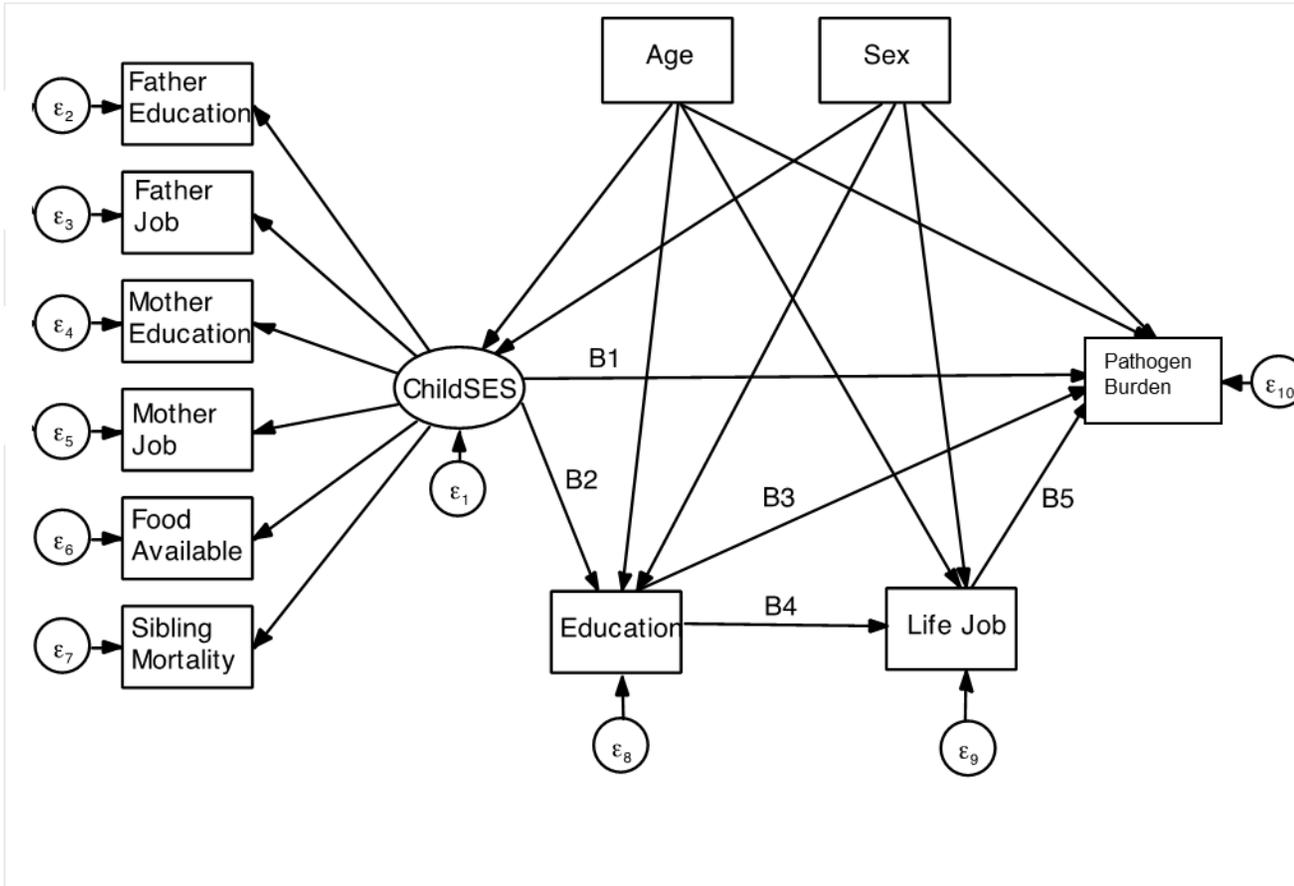
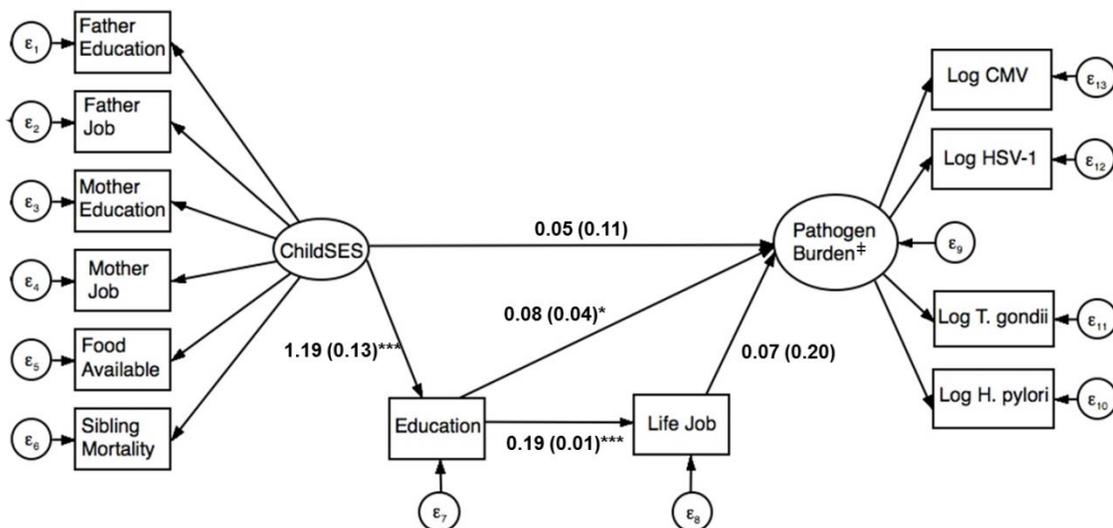


Figure 3-3. Log Odds (SE) for SEM Model of Low v. High Pathogen Burden



Total Effect of ChildSES on Low v. High Pathogen Burden: 0.16 (0.09)
 Total Indirect Effect of ChildSES on Low v. High Pathogen Burden: 0.11 (0.06)*
 Indirect Effect via Education Pathway: 0.01 (0.05)*
 Indirect Effect via Education-Occupation Pathway: 0.02 (0.04)

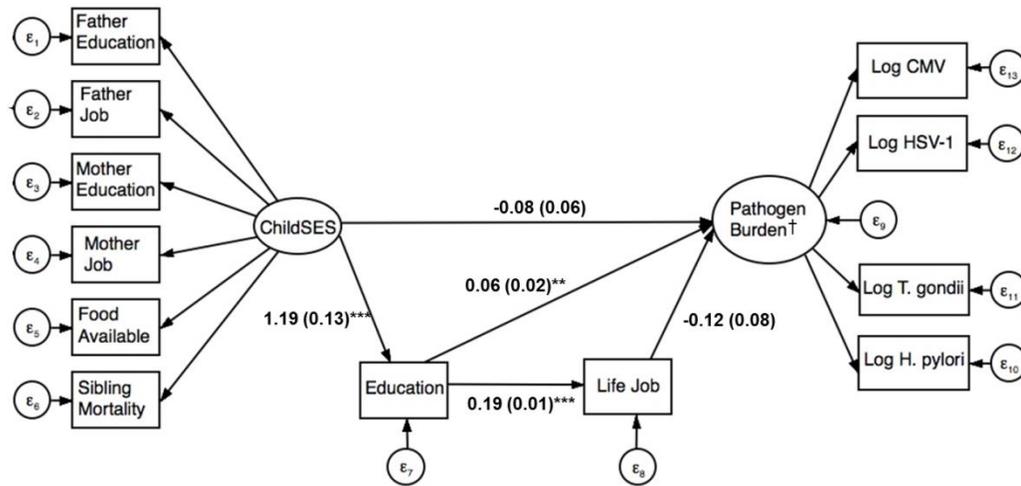
‡ Modeling Low v. High Pathogen Burden Class

* Significant at p=0.05

** Significant at p=0.01

*** Significant at p=0.001

Figure 3-4. Log Odds (SE) for SEM Model of Middle v. High Pathogen Burden

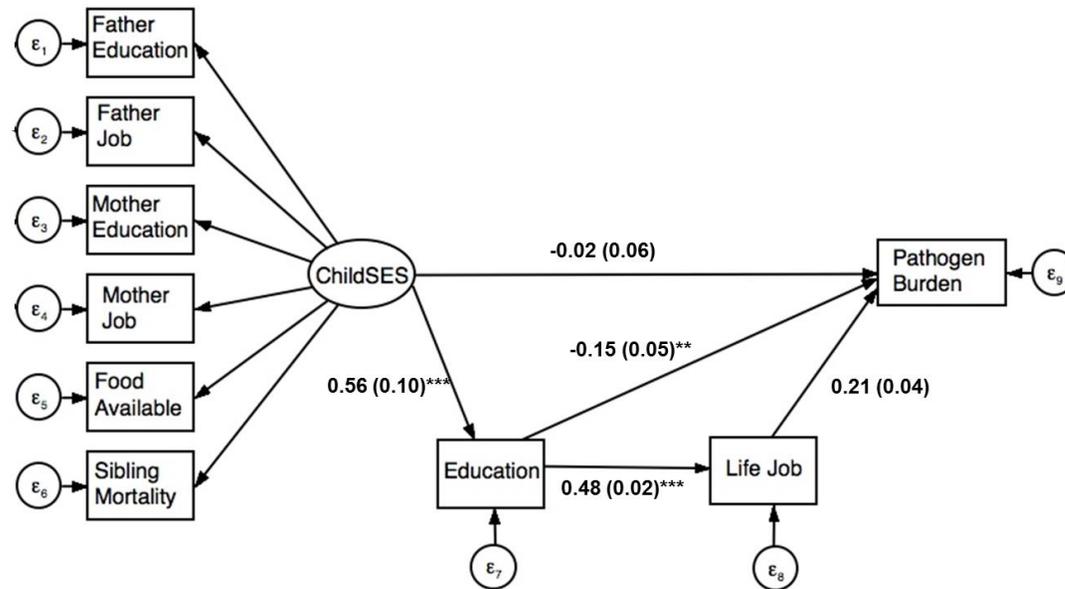


Total Effect of ChildSES on Middle v. High Pathogen Burden: -0.20 (0.13)
 Total Indirect Effect of ChildSES on Middle v. High Pathogen Burden: -0.12 (0.07)
 Indirect Effect via Education Pathway: -0.10 (0.07)
 Indirect Effect via Education-Occupation Pathway: -0.03 (0.02)

† Modeling Middle v. High Pathogen Burden Class

- * Significant at p=0.05
- ** Significant at p=0.01
- *** Significant at p=0.001

Figure 3-5. Estimates (SE) for SEM Model of Total Pathogen Burden



Total Effect of ChildSES on Pathogen Burden: -0.10 (0.02)**
 Total Indirect Effect of ChildSES on Pathogen Burden: -0.08 (0.03)**
 Indirect Effect via Education Pathway: -0.09 (0.03)**
 Indirect Effect via Education-Occupation Pathway: 0.001 (0.01)

* Significant at p=0.05
 ** Significant at p=0.01
 *** Significant at p=0.001

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Chapter 4. Nativity, Acculturation and Immune Response to Persistent Pathogens and Pathogen Burden in Mexican Americans

4.1 Introduction

Persistent pathogens are associated with poorer later life health.¹⁻⁶ Persistent pathogens establish chronic, latent infections in the body and periodically reactivate over the life course, often due to stress.^{7,8} Reactivation contributes to the development of chronic disease via direct and indirect pathways, including direct damage to host tissues, immune system exhaustion and elevated inflammation.^{2,9-13} Persistent pathogens have been linked to numerous chronic diseases of aging, including diabetes, cardiovascular disease, cognitive impairment, frailty, Alzheimer's disease, autoimmune diseases and mortality.^{3,14-21} Additionally, seropositivity to multiple persistent infections is common. Infection to one persistent pathogen may not only increase the risk of infection with other pathogens but also heighten the severity of subsequent infections.²²⁻²⁴ Moreover, higher total pathogen burden is associated with coronary artery disease, atherosclerotic progression, metabolic disease, depression and mortality.^{5,24-26}

Exposure to persistent pathogens tends to occur early in life.²⁷ Early life factors contributing to increased exposure and susceptibility to persistent pathogens are not well characterized. Geographic location early in life may influence exposure to persistent pathogens. Birth and residence outside of the U.S. in a less developed country may increase the opportunity for exposure to persistent pathogens, through poorer living conditions, sanitation and hygiene practices.²⁸ Lifestyle is another early life factor that may influence susceptibility and immunological control of persistent infections. Lifestyle exposures, including those driven by

cultural influences, may influence diet or contribute to higher levels of stress, leading to increased susceptibility to persistent pathogens and more frequent reactivations over the life course.²⁹⁻³¹

These early life factors may be particularly important for understanding immune response to persistent pathogens and pathogen burden in Mexican Americans. Mexican Americans are the largest subgroup of Latinos, the most common ethnic minority in the U.S.³²⁻³⁴ Mexican Americans acquire persistent pathogens at an earlier age and have higher seroprevalences of persistent pathogens and pathogen burden than non-Hispanic whites.^{23,27,35} Further, there is considerable variation in early life exposures to geographic location (nativity) and lifestyle (acculturation) among Mexican Americans.³⁶

The goal of this study was to evaluate the independent associations between nativity and acculturation on immune response to four common persistent infections, cytomegalovirus (CMV), herpes simplex virus-1 (HSV-1), *Toxoplasma gondii*, and *Helicobacter pylori*, and pathogen burden in Mexican Americans while controlling for early life social conditions. We tested the hypotheses that 1) foreign born individuals will exhibit poorer immune response (higher antibody levels) to persistent infections and will have a higher total pathogen burden than individuals born in the U.S., and 2) Mexican oriented individuals will exhibit poorer immune response (higher antibody levels) to persistent infections and will have a higher total pathogen burden than Anglo oriented individuals. Additionally, the influence of variation in nativity and acculturation on life course socioeconomic patterning of immune response to persistent pathogens and pathogen burden was explored.

4.2 Methods

4.2.1 Study population

Data came from the Sacramento Area Latino Study on Aging (SALSA), which was a longitudinal cohort study of 1,789 of Mexican Americans living in the Sacramento, California metropolitan area who were 60-101 years old at baseline in 1998-1999. Additional details about the recruitment and study population have been described previously.³⁷ The SALSA cohort had information on IgG antibody levels for CMV, HSV-1, *H. pylori* and *T. gondii* available for 1,263 participants. Participants for whom there was no infection data available were more likely to be older (mean age of 72 vs. 70, $p < 0.001$) and more likely to be male (52% vs. 39%, $p < 0.001$). There were no differences by educational attainment. An additional two hundred and ninety participants did not have childhood SES information available. These two hundred and ninety participants were more likely to have lower mean education (6 years vs. 8 years, $p < 0.001$) but did not differ by age or gender from those with childhood SES information available. The final analytic sample consisted of 973 participants. The SALSA study was approved by the Institutional Review Boards at the University of California, Davis and the University of Michigan.

4.2.2 Measures

Nativity was ascertained by asking the participant in which country they were born and dichotomized as foreign born or U.S born. Of those classified as foreign born, 87% reported Mexico as their place of birth. The Acculturation Rating Scale for Mexican Americans-II was used to measure acculturation.³⁸ This is a validated bidimensional scale used to assess the degree of cultural adaptation of Mexican Americans to Anglo culture in the U.S.³⁸ The distribution of

acculturation score was bimodal, thus scores were dichotomized into low (Mexican oriented) and high (Anglo oriented) by a median split.

Socioeconomic status was measured for early life and adulthood. Confirmatory factor analysis in MPlus version 7.11 (Methuén & Methuén, Los Angeles, CA) was used to generate a continuous score for early life SES from six different variables recalled by the participant: father's education (reference), mother's education, father's occupation, mother's occupation, food availability as a child and sibling mortality. Parental education was measured in years. Parental occupation was measured by a 3-level categorical variable (technical, professional or managerial [high]; sales, administrative support or military [middle]; and services, manual or housewives [low]) and treated as an ordered hierarchical variable. Food availability during childhood was ascertained using the question, "When growing up, how often did you not have enough to eat?" with Likert item responses and also treated as a continuous variable. Sibling mortality was defined as the number of siblings that died before age 18. The factor scores were split at the mean value into dichotomous variable representing high and low early life SES. Adult SES was measured by educational attainment. The number of years of completed education was dichotomized by a median split into low (less than 7 years) and high (greater than or equal to 7 years) educational attainment groups. To capture life course SES, individuals were dichotomized into high lifetime SES (high early life and high educational attainment) vs. not high lifetime SES (all other combinations of SES levels).

Immune response to four persistent pathogens was measured: CMV, HSV-1, *H. pylori*, and *T. gondii*. Serum and plasma samples from baseline were tested at the Stanley Neurovirology Laboratory at Johns Hopkins University School of Medicine using high throughput solid-phase enzyme-linked immunosorbent assays (ELISA) to detect pathogen-specific IgG antibody levels.

The ELISA methods have been described previously.³⁹ Briefly, diluted aliquots of serum were reacted with antigen bound to a solid-phase surface. Quantitation of IgG for each virus was determined by reaction of bound antibodies with enzyme labeled anti-human IgG and enzyme substrate and optical densities were read by spectrophotometric instrumentation.⁴⁰ Seropositivity was determined by standard cutoffs for the assay such that optical density unit (ODU) values less than 1.1 were classified as seronegative and values 1.1 or greater were seropositive. Among those participants who were seropositive to each infection, the continuous antibody values were divided into tertiles and individuals were categorized as low, middle and high antibody level. A four-level hierarchical variable in which individuals were categorized as seronegative, low antibody response, middle antibody response and high antibody response was then constructed. Total pathogen burden was measured by summing the number of pathogens to which an individual was seropositive (range 0-4) and individuals were categorized seropositive to 0-1, 2, 3, or 4 pathogens.

Other covariates included age and gender. Age was measured in years and mean centered. Gender was included as a dichotomous variable with male being the referent and then mean centered.

4.2.3 Statistical Analyses

Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, NC). Bivariate relationships between seropositivity for CMV, HSV-1, *T. gondii*, and *H. pylori*, and nativity, acculturation, lifetime SES, age and gender were assessed using logistic regression models. All subsequent analyses were conducted using ordered logit models to measure the proportional odds of higher IgG antibody level for each infection (CMV, HSV-1, *T. gondii* and *H. pylori*) or higher pathogen burden level. The proportional odds assumption held for all

models. First, the main effects of nativity and acculturation were assessed with the outcomes, controlling for age, gender and childhood SES. Next, the association between life course SES and each persistent pathogen and pathogen burden was measured, controlling for age, gender, nativity and acculturation. Nativity and acculturation were subsequently evaluated as separate modifiers of the associations between high lifetime SES and each outcome. Models were first stratified by nativity (adjusting for age, gender and acculturation) and then acculturation (adjusting for age, gender and nativity). Interaction terms were considered statistically significant at the alpha level = 0.05.

4.3 Results

Descriptive statistics of the SALSA sample are shown in Table 4-1. The sample had a mean age of 70 years and was 56% female. About 45% of the sample was born in the U.S. and 55% was foreign born. For acculturation, 57% of the sample identified as Anglo oriented and 43% identified as Mexican oriented. Twenty-six percent of the sample had high lifetime SES (high early life SES and high adult SES). Seropositivity to each pathogen was as follows: 85% were seropositive to CMV, 86% were seropositive to HSV-1, 36% were seropositive to *T. gondii* and 91% were seropositive to *H. pylori*. The mean pathogen burden was 3 infections.

Figure 4-1 depicts the proportional ORs for the association between nativity and acculturation and CMV, *T. gondii*, HSV-1 and *H. pylori* IgG antibody level adjusting for age, gender and childhood SES. Table 4-2 shows the results for the ordered logit models of CMV, HSV-1, *T. gondii*, *H. pylori* and pathogen burden for the effects of nativity and acculturation adjusting for age, gender and childhood SES. U.S. born individuals had 1.40 (95% CI: 1.02, 1.86) times the odds of higher CMV antibody level than foreign born individuals. No other statistically significant main effects were observed for nativity or acculturation. Table 4-2 also

depicts the results for the association between life course SES and all four persistent pathogens and pathogen burden adjusting for age, gender, nativity and acculturation. High lifetime SES decreased the odds of higher antibody level for CMV (OR: 0.68, 95% CI: 0.52, 0.90), *T. gondii* (OR: 1.23, 95%CI: 0.83, 1.53), HSV-1 (OR: 0.84, 95%CI: 0.64, 1.10), *H. pylori* (OR: 0.85, 95%CI: 0.64, 1.11), and pathogen burden (OR: 0.76, 95%CI: 0.57, 1.01). The association between high lifetime SES and CMV was statistically significant.

Table 4-3 shows adjusted ordered logit models for the association between life course SES and each outcome, stratified first by place of birth and secondly by acculturation. Figure 2 and 3 also depict these results. High lifetime SES was more protective against higher CMV antibody level among foreign born individuals than U.S. born individuals (p-value for interaction <0.01). Among the foreign born, those with high lifetime SES had 0.40 times the odds of higher CMV antibody levels when compared to those without high lifetime SES. There was no effect of high lifetime SES on IgG antibody level among the U.S. born. High lifetime SES was also more protective against higher CMV antibody levels among Mexican oriented participants than Anglo oriented participants (p-value for interaction =0.01). Among those who were Mexican oriented, high lifetime SES reduced the odds of higher CMV antibody levels by 67% compared to those who did not have high lifetime SES (OR=0.33, 95%CI: 0.18, 0.61). Nativity was also found to modify the effect of high lifetime SES on *T. gondii* antibody level (p-value for interaction = 0.05). Among the foreign born, high lifetime SES increased the odds of higher *T. gondii* antibody levels (OR: 1.68, 95%CI: 1.01, 2.81). No statistically significant effects in the stratified models were found for HSV-1, *H. pylori*, or total pathogen burden.

4.5 Discussion

The goal of this study was to determine if early life factors, such as geographic location and lifestyle, affected immune response to persistent infections and pathogen burden in Mexican Americans. This study, to our knowledge, is the first to investigate the role of acculturation, and one of few to explore nativity, as independent predictors of persistent infection. We found that nativity was only associated with higher CMV such that those born in the U.S. had higher risk of higher CMV antibody levels than those born outside the U.S. Acculturation was not associated with any of the persistent infections in this study. Further, we examined whether the social patterning of these persistent patterns varied by differences in location (nativity) or culture (acculturation) among Mexican Americans. We found that not only did the effect of high lifetime SES depend on both nativity and acculturation, but that the effect of high lifetime SES was different for each infection. These findings extend previous work on the social patterning of persistent infections to show that cultural exposures, such as place of birth and acculturation, matter for our health.

Exposure to persistent pathogens depends on the circulating prevalence of the particular infectious agent in the population as well as host susceptibility and may be associated with cultural exposures such as nativity and acculturation. Nativity represents a physical difference in location and resources available by country. The few studies that examine the main effect of nativity show that foreign birth is associated with higher seroprevalence of persistent infections.⁴¹⁻⁴³ Contrary to the limited evidence available, we found that being born in the U.S. increased the risk of higher CMV antibody levels in the SALSA sample. This result may be due to the uniqueness of the SALSA population, which is elderly and community dwelling. It is possible that CMV seropositive migrants in the SALSA study are not representative of the

foreign born Mexican American population as a whole, perhaps because they are healthier than U.S. born Mexican Americans or due reverse migration of CMV seropositive individuals with advancing age. Acculturation represents adaptation to the dominating cultural influence in a country and other exposures, such as diet, health care usage, and language, which are related to cultural identity. Lower acculturation was found to increase the risk of poorer health in elderly Mexican Americans, potentially as a result of higher stress resulting from cultural barriers and fewer economic opportunities.⁴⁴ Given the strong connection between stress and the immune system, we would expect those with lower acculturation (Mexican oriented) to have more frequent reactivations to persistent infections and elevated risk of higher antibody values.⁷ We found that acculturation was not associated with immune response persistent infections or pathogen burden in the SALSA study, though the direction of the effect estimates indicated that lower acculturation may increase the risk of higher antibody levels to persistent infections. As we are the first, to our knowledge, to examine this association, further studies into the influence of acculturation on immune response to persistent infections are warranted.

Many studies have demonstrated the inverse, graded association between SES and persistent infections but few have looked at factors that may modify these social gradients, such as cultural or geographic exposures.^{42,45-48} We found that nativity and acculturation modify the association between lifetime SES and immune response to persistent infections. Further, the benefit from high lifetime SES was different for each infection, CMV and *T. gondii* in particular. This is not surprising as CMV and *T. gondii* are not only different types of infectious organisms (a virus and a parasite respectively), but they also have different modes of transmission.

CMV is generally acquired early in life through direct contact with infected body fluids.⁴⁹ High lifetime SES was more protective against higher CMV antibody levels for foreign born

participants than U.S. born participants. Foreign born individuals with high lifetime SES were more likely to be CMV seronegative, and less likely to have the highest category of immune response if CMV seropositive, than foreign born individuals without high lifetime SES. Among the U.S. born in this study, no major differences in the distribution of CMV antibody level were observed by lifetime SES. Low SES early in life may increase the likelihood of exposure to CMV through crowded living conditions and higher seroprevalence of the disease in the population. Lower educational attainment could further exacerbate low early life SES through reduced resources, access to health care and higher stress. The average age of migration to the U.S. in the study population was 31.5 years old, thus it is likely that most foreign born participants completed their education outside of the United States. Higher educational attainment in developing countries may confer additional benefits than higher education in the U.S. and influence exposure patterns to persistent pathogens through housing and resources available to support health to a greater extent in foreign countries.

Similar results were found in the acculturation analysis. Mexican oriented individuals with high lifetime SES were more likely to be CMV seronegative, or have lower CMV antibody levels if seropositive, than Mexican oriented individuals without high lifetime SES. Anglo orientation is thought to negatively impact Latino health through poorer diet and reduced exercise, though some of the benefits of adopting cultural norms include higher social capital through better English language ability, improved socioeconomic status, health care accessibility and use of preventive services.^{36,50-52} Thus, higher lifetime SES (perhaps driven by high educational attainment) for those who are less acculturated to the U.S. may overcome limitations, such as language barriers, commonly associated with less acculturated Latinos in the U.S., while still receiving the benefit of healthy behaviors and social support systems in immigrant

communities.^{29,53} These results may also be explained by a healthy migrant effect. Foreign born participants were successful migrants to the U.S. and stayed in the U.S. into old age, meaning they might be healthier than those who did not successfully migrate or who returned back to their country of birth before the start of this study, and thus exhibit better immunological control of persistent infections later in life.

In contrast to CMV, high lifetime SES increased the risk of higher *T. gondii* antibody levels among foreign born individuals. Foreign born individuals with high lifetime SES were more likely to be seropositive to *T. gondii* than foreign born individuals without high lifetime SES. Our results for immune response to *T. gondii* were consistent with previous research showing that foreign born Mexican Americans with low education have lower risk of seropositivity than their more highly educated counterparts.^{54,55} *T. gondii* is transmitted by oocysts from eating undercooked meat, handling cat feces, or handling soil.^{41,54,55} Those with higher socioeconomic status may have higher rates of meat consumption than those with lower socioeconomic status, who tend to eat more grains and vegetable products.^{56,57} Differences in *T. gondii* seroprevalence by poverty level have been documented among Mexicans.⁵⁵ Low seroprevalence of *T. gondii* was observed in rural communities who were poorly educated and had high poverty levels. In contrast, urban communities with similar climate had a higher educational level and lower poverty had a relatively high seroprevalence of *T. gondii*. Thus, those who did not have the resources to purchase meat were less likely to be exposed to *T. gondii*.⁵⁵ As such, it is possible that dietary differences commonly seen in developing countries preceding a nutrition transition may be contributing to the higher risk of *T. gondii* among foreign born individuals with high SES. Among U.S. born participants, higher lifetime SES may mean that individuals have knowledge of proper meat cooking practices or may have access to higher

quality meat that is less likely to be carrying oocysts. Higher lifetime SES also reduces the likelihood that individuals may be employed in jobs with high levels of soil handling. We did not find any differences in the social patterning of *T. gondii* by acculturation, which may reinforce that exposure to contaminated meat is more important for *T. gondii* risk than cooking practices and other cultural exposures.

In this study population, we found no association between high lifetime SES and immune response to *H. pylori*, HSV-1 or pathogen burden. This is contrary to other U.S. population representative studies which found that lower education increased risk of seropositivity to *H. pylori* and HSV-1.^{48,58} In a study of Mexican Americans in Texas, higher education was significantly associated with lower *H. pylori* seroprevalence but no association between education and HSV-1 was found.²² It is possible that among Mexican Americans, other specific socioeconomic exposures, such as income or occupation, may be more predictive of a social gradient in immune response to these particular infections and pathogen burden than an average lifetime SES measure.

This study is not without limitations. IgG antibody level is a biological marker isolated from serum that indicates an individual received sufficient exposure to a particular pathogen to activate the adaptive immune system. Unfortunately, this biomarker does not give an indication as to when the individual was exposed. It is possible high IgG levels may represent recent primary infection, though this is unlikely in this elderly study population because infection commonly occurs during childhood, or that the primary infection elicited a very strong immune response.⁴³ The SALSA study may be subject to survivor bias because participants were at least 60 years of age at baseline. As such, participants may be healthier overall and immunologically, resulting in better control of persistent infections. The early life SES measures reported in this

study are also prone to recall bias, though we do not expect reporting of early life SES to vary by immune response since individuals are not routinely diagnosed for these infections and consequently would be unlikely to know their infection status. It is possible that poor cognition may also influence the recall of childhood SES, however, we expect this to be non-differential with respect to level of SES, again biasing the estimates towards the null. Additionally, the childhood SES variable used was the result of confirmatory factor analysis with six different indicators. It is unlikely that participants would incorrectly recall all of the six questions, minimizing the impact of recall bias in this study.

Findings in this study demonstrate that nativity and acculturation may not be independent early life risk factors for immune response to persistent infection and pathogen burden. However, nativity and acculturation may be important modifiers of the social gradient in immune response to persistent infections. Significant disparities in these infections exist by race/ethnicity, indicating that minority populations are more likely to experience the detrimental impacts of poor life course socioeconomic condition on immune response. This underscores the public health importance of this work as higher antibody levels to these persistent infections during adulthood have been associated with chronic health conditions and mortality.^{1,3,4,21,40} Further investigation of nativity, acculturation and life course social differences in immune response to persistent infections may help explain perpetuating health disparities in chronic conditions associated with persistent infections over time.

Table 4-1. Demographics for SALSA sample (N = 973)

Characteristic	Mean (SD) or %
Age at baseline (years)	70 (6.32)
Female gender	56%
Years of education	8 (5.41)
Childhood SES	
High	37%
Low	64%
Educational attainment	
High	55%
Low	45%
Lifetime SES	
High	26%
Low	74%
Nativity	
US born	45%
Foreign born	55%
Acculturation	
Anglo oriented	57%
Mexican oriented	43%
Seropositivity	
CMV	84%
HSV-1	86%
<i>T. gondii</i>	36%
<i>H. pylori</i>	91%
Total Pathogen burden	3 (0.78)

Figure 4-1. Odds ratio of higher antibody level for nativity and acculturation. Nativity model¹ OR of being U.S. born adjusted for age, childhood SES and acculturation. Acculturation model² OR of Anglo orientation adjusted for age, childhood SES and nativity.
*Statistically significant at p=0.05.

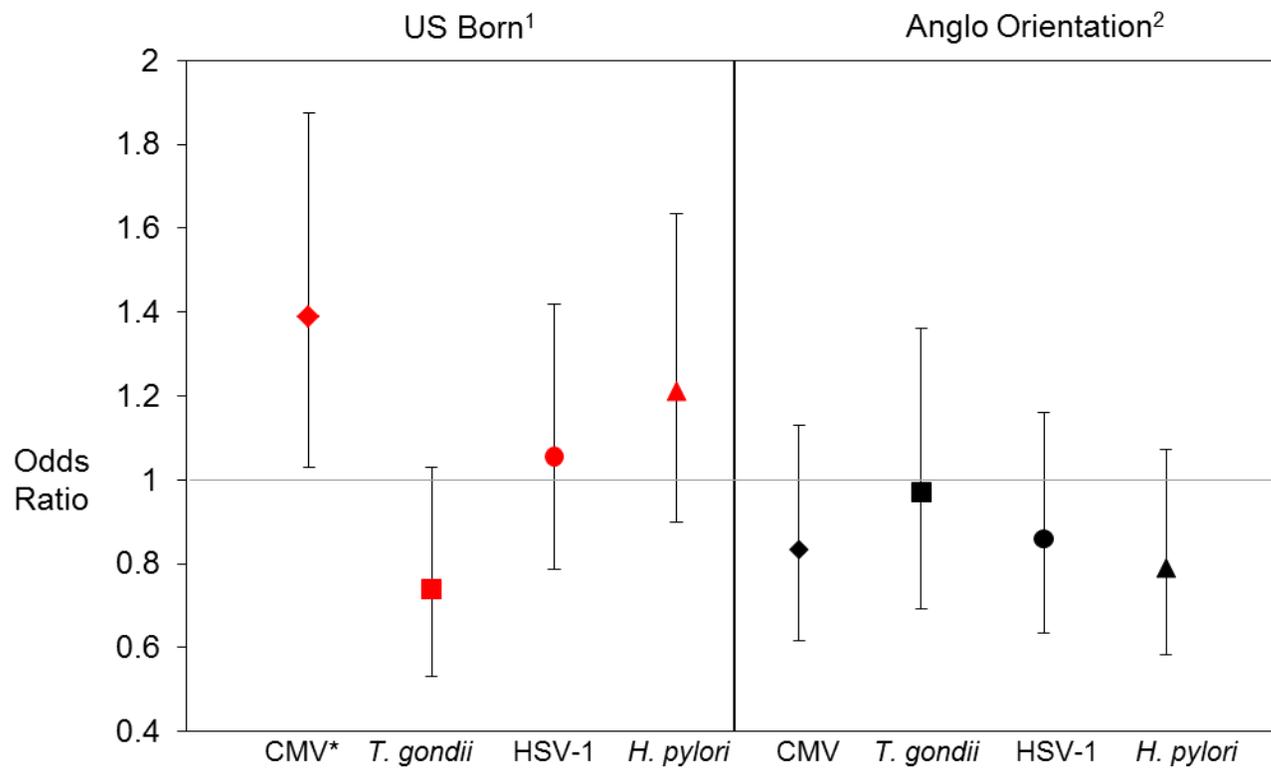


Table 4-2. Odds Ratios for higher antibody level or pathogen burden

Exposures	CMV		<i>T. gondii</i>		HSV-1		<i>H. pylori</i>		Total Pathogen Burden	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
U.S. born ¹	1.40	1.02, 1.86	0.74	0.53, 1.04	1.05	0.78, 1.41	1.20	0.90, 1.62	0.97	0.71, 1.33
Anglo oriented ²	0.84	0.62, 1.14	0.96	0.68, 1.34	0.87	0.64, 1.17	0.80	0.59, 1.08	0.83	0.61, 1.14
High lifetime SES ³	0.68	0.52, 90	1.23	0.83, 1.53	0.84	0.64, 1.10	0.85	0.64, 1.11	0.76	0.57, 1.01

¹Adjusted for age, gender, childhood SES and acculturation.

²Adjusted for age, gender, childhood SES and nativity.

³Adjusted for gender, age, nativity and acculturation.

Figure 4-2. Odds ratio of higher antibody level for high lifetime SES v. not high lifetime SES stratified by nativity and acculturation. Nativity model¹ adjusted for age, gender and acculturation. Acculturation model² adjusted for age, gender and nativity. P-value is for interaction term., * Statistically significant interaction term at alpha=0.05.

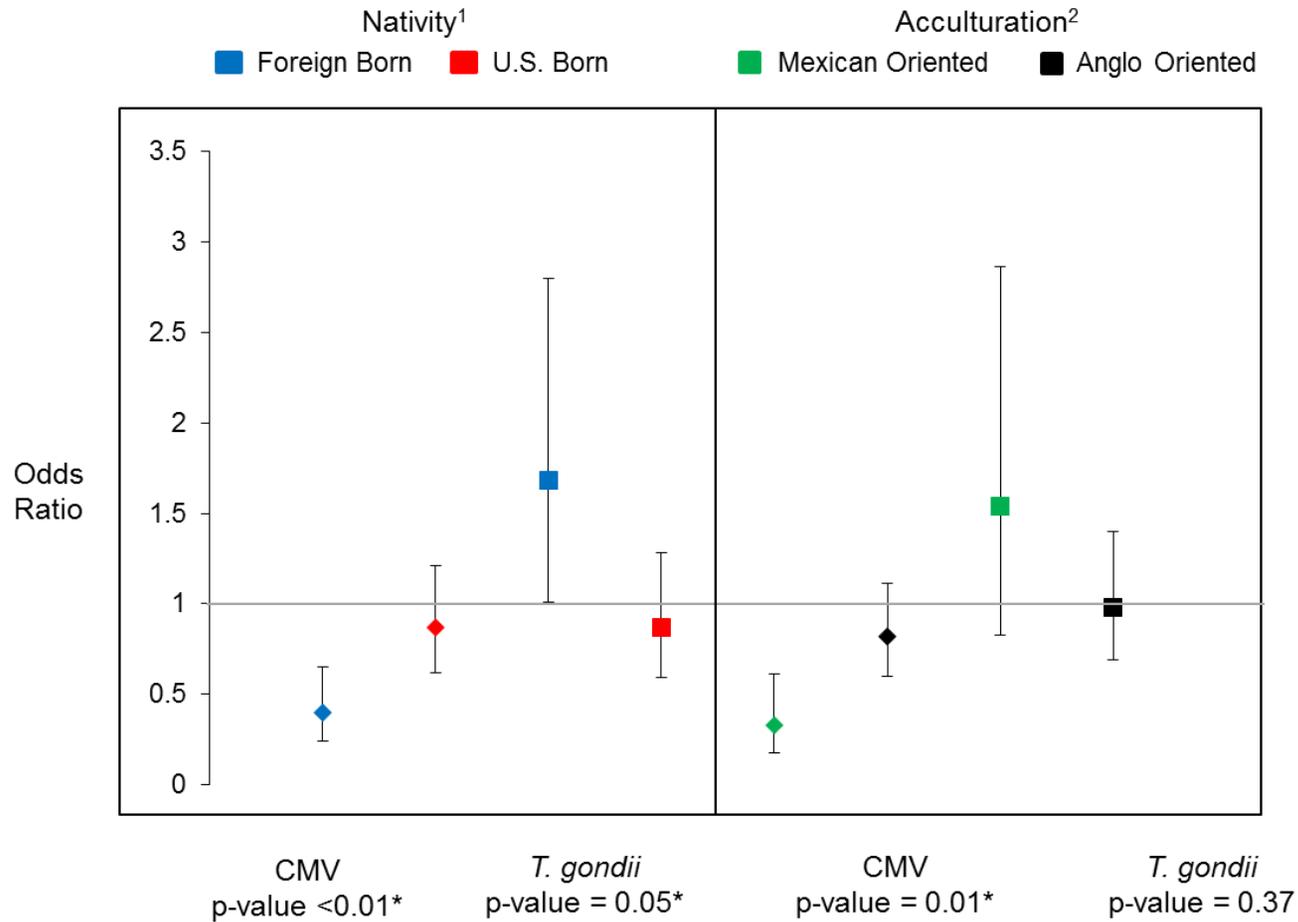


Figure 4-3. Odds ratio of higher antibody level for high lifetime SES v. not high lifetime SES stratified by nativity and acculturation. Nativity model¹ adjusted for age, gender and acculturation. Acculturation model² adjusted for age, gender and nativity. P-value is for interaction term., * Statistically significant interaction term at alpha=0.05.

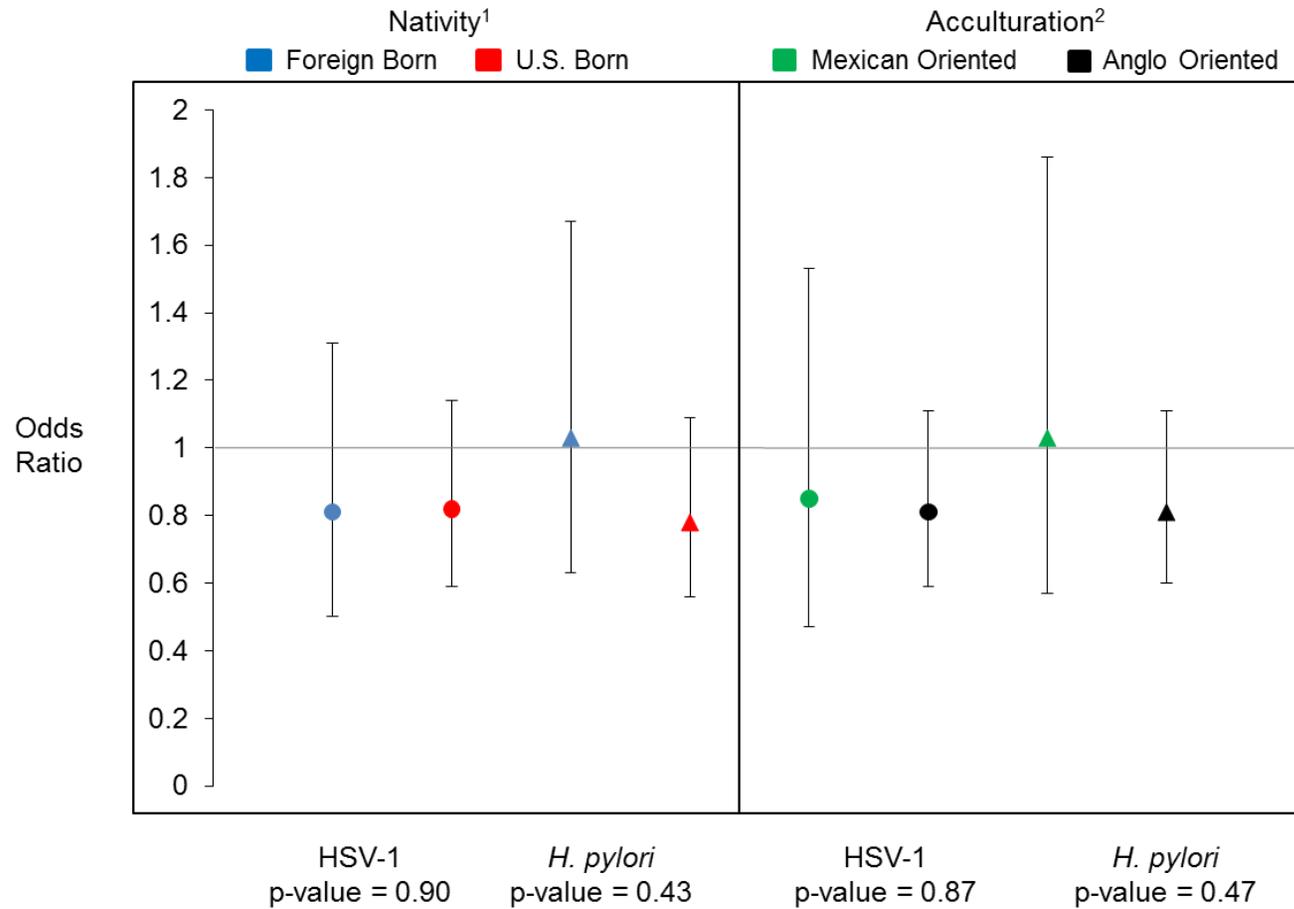


Figure 4-4. Odds ratio of pathogen burden for nativity and acculturation. Nativity model¹ OR of being U.S. born adjusted for age, childhood SES and acculturation. Acculturation model² OR of Anglo orientation adjusted for age, childhood SES and nativity. *Statistically significant at p=0.05. Odds ratio of higher pathogen burden for high lifetime SES stratified by nativity or acculturation. Nativity model³ adjusted for age, gender and acculturation. Acculturation model⁴ adjusted for age, gender and nativity. P-value is for interaction term., * Statistically significant interaction term at alpha=0.05.

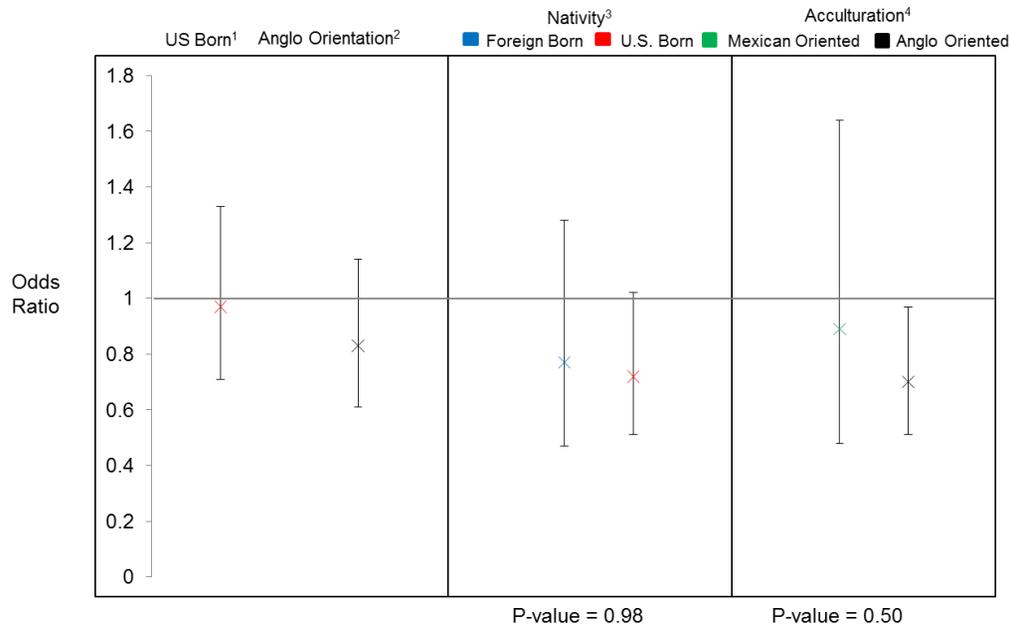


Table 4-3. Stratified ordered logit models: Odds ratio for being in a higher group for high lifetime SES stratified by nativity or acculturation

Covariate	Nativity ¹					Acculturation ²				
	Foreign Born		U.S. Born		p-value [#]	Mexican Oriented		Anglo Oriented		p-value [#]
	OR	95% CI	OR	95% CI		OR	95% CI	OR	95% CI	
CMV										
High lifetime SES	0.40	0.24, 0.65	0.87	0.62, 1.21	<0.01	0.33	0.18, 0.61	0.82	0.60, 1.11	0.01
<i>T. gondii</i>										
High lifetime SES	1.68	1.01, 2.81	0.87	0.59, 1.28	0.05	1.54	0.83, 2.86	0.98	0.69, 1.40	0.20
HSV-1										
High lifetime SES	0.81	0.50, 1.31	0.82	0.59, 1.14	0.90	0.85	0.47, 1.53	0.81	0.59, 1.10	0.87
<i>H. pylori</i>										
High lifetime SES	1.03	0.63, 1.67	0.78	0.56, 1.09	0.43	1.03	0.57, 1.86	0.81	0.60, 1.11	0.47
Total Pathogen Burden										
High lifetime SES	0.77	0.47, 1.28	0.72	0.51, 1.02	0.98	0.89	0.48, 1.64	0.70	0.51, 0.97	0.50

All models adjusted for age and gender. All nativity¹ models adjusted for acculturation. All acculturation² models adjusted for nativity.

#: p-value for interaction, **Bold** is significant at p=0.05

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Chapter 5. Discussion

5.1 Summary of Findings

This dissertation examined 1) the life course mechanisms by which early life SES acts to influence immune response to persistent pathogens and pathogen burden later in life, 2) the affect of nativity and acculturation on immune response to persistent pathogens and pathogen burden, independent of social conditions, and 3) whether nativity or acculturation interact with life course SES to influence immune response to pathogens and overall pathogen burden. It is now well established that many persistent pathogens are socially patterned, but this work was the first to use a life course approach to determine how the early life social environment influences immune response and pathogen burden later in life. This dissertation found evidence that early life SES may be operating through a chain of risk mechanism where the sequence of SES exposures over the life course are linked and ultimately impact immune response and pathogen burden later in life. Further, this dissertation was one of few studies to examine the independent effects of nativity and the first to look at the independent effect of acculturation on immune response to persistent pathogens and pathogen burden later in life. Though nativity was only associated with immune response to one persistent infection (CMV), nativity and acculturation were found to modify the life course social patterning of immune response to CMV and *T. gondii*.

5.2 Chapter 2 – Aim 1

This was the first study, to our knowledge, to examine the association between life course SES and immune response to persistent infections. Two potential life course mechanisms, the critical period model and the chain of risk model, were evaluated to determine how life course SES impacts immune response to several persistent infections associated with chronic health conditions later in life. Early life SES was not independently associated with immune response to any of the persistent infections included in this study. Later life SES, as measured by education and lifetime occupation, mediated the effect of early life SES on immune response. This finding supports a chain of risk life course mechanism, where the sequence of high SES exposures over the life course are linked to decrease risk of poor immune response later in life since high SES in childhood increases the likelihood of high SES in midlife and higher adult SES increases the likelihood of higher SES in late life. These findings have key public health implications because higher antibody levels to these infections in adulthood have been associated with chronic health conditions and mortality.¹⁻⁵ Moreover, these findings are especially pertinent for minority populations, such as Mexican Americans, are more likely to experience detrimental impacts of poor life course socioeconomic conditions on immune response, which may affect overall health and increase mortality. Findings from Aim 1 extend the current literature on social patterning of persistent infections, which often look at concurrent SES conditions, to consider the influence of early life social conditions.

5.3 Chapter 3 – Aim 2

Pathogen burden may be important for health because Mexican Americans demonstrate a higher pathogen burden and are more likely to suffer from chronic health conditions that have been associated with pathogen burden, such as cardiovascular disease.^{1,6,7} This study was the

first to investigate specific life course mechanisms, the critical period and the social chain of risk model, by which early life social factors may influence pathogen burden later in life. Early life SES was not directly associated with pathogen burden independent of later life SES measures. Instead, higher early life SES was associated with lower later life pathogen burden indirectly through the midlife SES (education) pathway. This study provides evidence for a socioeconomic chain of risk whereby early life SES acts through later life SES to influence later life pathogen burden.

Additionally, this study measured pathogen burden as a nominal variable derived from a latent profile analysis in an attempt to capture the specific clustering of persistent pathogens in this population. Though similar results were found using a measure of total pathogen burden, most likely due to high seroprevalences in this elderly population, the latent pathogen burden variable approach may be more informative about dynamics of co-infections in populations and their influence on health outcomes than a summary measure of pathogen burden.

Findings from this aim suggest that interventions focused on reducing early life socioeconomic disadvantage, including improving education, may help reduce exposure to persistent pathogens and consequently decrease pathogen burden, and associated chronic health outcomes, in Mexican Americans. In addition, future studies of pathogen burden should consider the specific combinations of co-infections and their biological implications to foster better cross-study comparisons.

5.4 Chapter 4 – Aim 3

Early life factors, such as geographic location and lifestyle, may affect immune response to persistent pathogens and pathogen burden in Mexican Americans. This study, to our knowledge, was the first to investigate the role of acculturation, and one of few to explore

nativity, as predictors of immune response to persistent pathogens and pathogen burden later in life independent of early life social conditions. Nativity was only associated with higher CMV such that those born in the U.S. had higher risk of higher CMV antibody levels than those born outside the U.S. Acculturation, independent of nativity, was not associated with any of the persistent infections in this study. Further, the effect of high lifetime SES on immune response to CMV and *T. gondii* was modified by both nativity and acculturation. The effect of high lifetime SES was different for each infection, as they have different routes of transmission, sites of latency and immune evasion strategies. These findings extend previous work on the social patterning of persistent infections to show that cultural exposures, such as place of birth and acculturation, matter for our health. Nativity and acculturation are critical components of early life racial/ethnic and social disparities in health, and further investigation of nativity, acculturation and life course social differences in immune response to persistent pathogens in other populations is warranted.⁸

5.5 Conclusion

It is a public health priority to identify, target and eliminate social and race/ethnic disparities in health. An explicit goal of Health People 2020 is to “achieve health equity, eliminate disparities, and improve the health of all groups.”⁹ Reducing disparities in persistent pathogens may be one step towards reaching this goal. Minorities, particularly Mexican Americans, are more likely to acquire persistent pathogens earlier in life, have higher seroprevalences, and have higher immune responses. Persistent pathogens do not have a mutualistic or commensal relationship with the host and instead may cause damage through direct and indirect pathways. Due to disparities in acquiring and controlling persistent pathogens, this harm is not born equally across the population, justifying research into prevention and

treatment of these agents. Furthermore, persistent pathogens are also associated with poorer chronic health and mortality. Again, the risk of these chronic health conditions and mortality is not equally distributed across the U.S. population, further heightening the need for elimination of disparities in persistent pathogens, and placing an even greater emphasis on the prevention and treatment of persistent pathogens. This dissertation sought to determine if early life social and cultural factors play a role in later life immunological control of persistent infections because 1) persistent pathogens are often acquired early in life, and 2) social and racial differences in seroprevalences of these pathogens have been detected at an early age. The ultimate goal of this work was to elucidate the best intervention point during the life course for improving immune control later in life, which would potentially translate into reduced chronic disease burden later in life.

This dissertation contributes new knowledge and understanding of the life course mechanisms by which early life social conditions act to influence later life immune response to persistent infections and the cultural factors that may modify these social exposures. The major findings from this work suggest that early life social conditions affect immune response to persistent infections through later life social conditions via a chain of risk mechanism. In addition, variation in early life cultural exposures may modify the social chain of risk differently for separate infections, though this was not unexpected since the pathogens evaluated in this dissertation are unique microorganisms with specific agent-host-environment dynamics. Interesting dynamics for individual persistent pathogens, CMV and *T. gondii* in particular, were observed in this population of Mexican Americans. As such, this work may be elucidating important biological pathways for each of these persistent infections. Place of birth represents geographical exposures outside of social conditions that influence transmission and susceptibility

to these pathogen, which are also not captured by acculturation. U.S. born Mexican Americans had higher risk of CMV than foreign born Mexican Americans. This is contrary to the limited evidence in the literature that shows higher risk of CMV for foreign born individuals. Moreover, foreign born participants were more likely to be seronegative to CMV than U.S. born participants, and among the seropositive, foreign born participants exhibited lower immune response (better immune control) of CMV than U.S. born participants. These findings may be evidence of a healthy migrant effect, where foreign born individuals are on average healthier than the population to which they migrate, or a reverse migration of elderly CMV seropositive individuals back to their country of birth, perhaps due to other health conditions. These results were not replicated when acculturation was the main exposure, suggesting that place of birth may be a unique risk factor for acquiring and controlling CMV later in life. In addition, higher lifetime SES was more protective for foreign born individuals than U.S. born individuals, again, likely evidence for a healthy migrant effect or salmon bias influencing CMV risk in this population. As a result, one would expect chronic diseases commonly associated with CMV to be less prevalent among elderly foreign born Mexican Americans with high lifetime SES than those without high lifetime SES. Indeed, other research has shown that among foreign born Latinos residing in California, a higher educational attainment was associated with better cardiovascular health outcomes.¹⁰

T. gondii had very different results than CMV. Though no independent effect of nativity or acculturation on immune response to *T. gondii* was observed, unique interactions between place of birth and SES were found. High lifetime SES resulted in higher risk of *T. gondii* infection among foreign born individuals than those without high lifetime SES. *T. gondii* transmission is most likely due to eating infected meat products. In a developing country pre-

nutrition transition, only individuals with high SES would be able to afford meat regularly. Thus, meat would not be a regular component in the diet of individuals with low SES, reducing exposure to *T. gondii* in this group. The findings from CMV and *T. gondii* reinforce to the importance of the historical context of study populations and what that implies for risk for persistent infections in life course research.

Results from this dissertation may also be generalizable to other biomarkers commonly used in social science as markers of inflammation and disease processes. Persistent pathogens may influence chronic disease progression through inflammatory pathways. Persistent pathogens have been implicated as having a pro-inflammatory role, inducing cytokines and elevated CRP. Other life course studies looking SES and inflammatory markers in adulthood, including CRP and IL-6, have found inverse relationships such that lower cumulative SES is associated with higher chronic inflammation in adulthood.^{11,12} This suggests a biological pathway, through more frequent reactivations of persistent pathogens and higher chronic inflammation, by which low socioeconomic status early in life may operate to influence disease processes in adulthood and later life.

The conclusions from this dissertation suggest that education may be particularly important as a driver of the life course SES effect on later life immune response to persistent pathogens and pathogen burden. Early life SES was frequently associated with these outcomes through the education pathway and education was often directly associated with the immune response as well. Educational attainment may be the best link for public health interventions to target on the life course social chain of risk. Educational attainment affects health through multiple pathways.¹³ Educational attainment improves health knowledge, literacy and behaviors, which leads to better nutrition and exercise, as well as better health and disease management.¹³

Higher educational attainment also translates into occupations with higher incomes and better working conditions, health insurance and other benefits, all which affect health.¹³ Educational attainment also increases one's sense of control, social standing and social support, reducing stress and increasing social and economic resources, resulting in better health.¹³ Raising educational attainment may break the social chain of risk, especially among minorities who are more likely to have lower SES, reducing exposure to persistent pathogens and improving immunological control over the life course.

Though evidence shows that social exposures are operating in a chain of risk, the importance of the early life social environment is not diminished by these findings. Educational attainment is highly correlated with early life social conditions and early life social conditions are the first link in the life course SES chain. To improve later life health in the U.S., emphasis should be placed on giving every child an adequate early life socioeconomic environment. The need for attention to and improvement of the early life environment is extremely timely as the wealth gap between the rich and poor widens and schools face funding challenges.^{14,15}

To improve lifetime educational attainment, efforts must be started in childhood. Studies show that children from low SES households and communities develop academic skills, such as language, letter recognition and phonological awareness, more slowly compared to children from higher SES households and communities.^{16,17} Among children starting kindergarten, those classified as disadvantaged have significantly lower cognitive skills than those who were classified as advantaged.¹⁸ Inequalities in the pre-academic environment cannot be overcome when disadvantaged children subsequently attend schools that are also resource-poor.¹⁸ School systems in low SES communities are usually financially challenged and lack experienced personnel when compared to school systems in high SES communities, which influences the

academic achievement of the students that attend these schools, and perpetuates the low SES of the community.^{18,19} Education cannot be the “great equalizer” when social disparities infiltrate the educational system.¹⁸ Early life social disadvantage and less educational resources, compounded with more exposure to persistent pathogens as a child, are likely to interact over the life course to influence both SES attainment and immune response later life. Though we were not able to measure these dynamic interactions over the life course in this study, they are likely to play a very important role. Education, however, appears to be the fulcrum for these dynamic interactions. This may be due to the far-reaching influence of higher educational attainment on the potential for subsequent higher SES exposures, such as better occupation grade, higher income level and increased wealth. Higher education also contributes to the development of health capital and better health behaviors, potentially reducing individual susceptibility or improving immunological function through, for example, better nutrition. In addition, higher educational attainment and higher later life SES may act as buffers by reducing the number and severity of stressors, which may impact the frequency of reactivation to persistent pathogens. Therefore, early life conditions may set the stage to enhance or prevent educational achievement, which has life-long consequences for social advantage or disadvantage, influences disparities in immune response to persistent pathogens, and general health overall.

Some may argue that persistent pathogens (“old friends”) may be beneficial for health.²⁰ The hygiene hypothesis highlights the role of certain microbes, which persisted in isolated hunter-gather groups with latent states or subclinical disease, in the development and regulation of the immune system.²⁰ These old friends co-evolved with humans to modulate the immune system.²⁰ Exposure to these microbes is diminished in higher SES settings leading to a loss of immunological education and more chronic inflammatory.²⁰ However, in low SES settings,

negative early life events may also lead to immunoregulatory disorders, such as chronic inflammation, acting synergistically with the lack exposure to persistent pathogens.²⁰ While there may be immunological benefits imparted by these pathogens early in life, co-evolution of persistent infections with humans occurred at a time when life expectancy was much shorter. The objective of the pathogen was to keep the host alive until transmission to the next generation could be achieved. Any health advantage in maintaining low-level inflammatory states due to the latency and reactivation of persistent pathogens may be lost in older ages after fecundity expires. For example, chronic inflammation generated by persistent infections may contribute to the development of chronic disease.^{11,21,22} In addition, clonal expansion of effector and effector memory T cells specific to herpesviruses reduces the immunological space for naïve T cells, a state known as immunosenescence, which are crucial for mounting a proper immune responses to novel pathogens.²³ Immunological control of persistent pathogens over the life course may contribute to morbidity and pre-mature mortality later in life, consequently, these “old friends,” that may be beneficial in childhood, are far from harmless as we age.

In summary, this dissertation was comprised of novel work on the contribution of life course socioeconomic status and other early life exposures to immune response to persistent infections and pathogen burden later in life. Better early life social conditions may reduce individual susceptibility and exposure to persistent pathogens, therefore it was hypothesized that early life was a critical period for SES, producing lasting effects which would be evident in better immune control of persistent pathogens later in life. Those with low early life SES would likely acquire these pathogens at an earlier age, increasing the opportunity for more reactivations over the life course. Individuals with low SES might also experience higher levels of stress, increasing the likelihood of more frequent reactivations. Infection at an earlier age combined

with more frequent reactivations over the life course would result in higher levels of immune response later in life. Instead, evidence from this dissertation suggests that later life immune response to persistent infections is indirectly influenced by early life SES exposures through a chain of risk mechanism. It is possible that individuals with low early life SES may still acquire persistent pathogens early in life, but that subsequent low SES exposure during adulthood, reduced access to resources, and higher levels of stress, may drive the frequency of reactivation. As a result of these social chains of risk, adult SES exposure may have a greater impact on later life immune response than early life SES. Therefore, reducing early life social disadvantage will result in higher educational attainment and may lead to better immunological control of persistent infections, and consequently reduced risk for diseases associated with persistent pathogens, later in life.

5.6 Strengths

This work was the first to use a life course approach to determine how the early life social environment influences immune response and pathogen burden later in life. Moreover, it was the first to examine independent associations between cultural factors and persistent infections and pathogen burden, as well as how cultural differences may modify the life course social patterning of persistent infections. Very few studies have looked at life course influences on biological indicators of immunity later in life. These important questions were addressed using the SALSA study, well-characterized cohort of community dwelling Mexican Americans from the Sacramento metropolitan area, limiting the influences of significant heterogeneity present among Latino populations. Though some might argue that only analyzing a subpopulation of Latinos is a limitation, researchers in minority health have specifically called for Latino subpopulations to be analyzed separately to promote proper inference and implement effective policy solutions in

this diverse ethnic population.^{8,24} SALSA is a large cohort with rich data both on life course SES and immune response to persistent pathogens. Samples were tested for persistent pathogens at a reliable laboratory using validated methods. In addition, the SALSA participants are diverse culturally with respect to nativity and acculturation, which is advantageous for examining these factors in relation to persistent pathogens.

. Almost no studies have used structural equation modeling (SEM) to address complex life course mediation analyses, which was another major strength of this dissertation. In contrast to regular regression, which minimizes the residuals of individual observations between predicted and observed values, SEM minimizes the difference between the sample co-variances and model predicted co-variances. The observed covariance matrix is a function of a set of model parameters, thus if the model is correctly specified, the population covariance matrix is reproduced and the differences between the observed and population covariance matrix is minimized.

The SEM approach is advantageous for life course analyses over traditional regression methods for several reasons. First, modeling childhood SES as a latent variable uses multiple indicators and allows measurement error to be incorporated into the model, strengthening predictive power over OLS regression, which assumes no measurement error. Second, SEM provides estimates and standard errors for specific mediation pathways. This is an improvement over traditional mediation techniques that only proved evidence for the attenuation of relationships by mediators without explicitly modeling hypothesized pathways. Third, creating a latent variable for childhood SES and pathogen burden is an improvement over more common summary measures described in the literature. Other methods would dichotomize each childhood indicator into low and high SES and then create a summary score, however, this process makes

many assumptions, including deciding the proper thresholds for low and high SES and that a summary SES score is a meaningful representation. Pathogen burden is often characterized as a sum of the number of persistent infections to which one is seropositive. There is little consistency across studies of the infections making up this score. The summation also ignores the specific combinations of co-infections and their biological implications. This dissertation used a latent profile analysis to determine groupings of pathogen burden by the clustering of infections to improve upon the traditional summary score. Modeling clusters of infections instead of a simple summary measure may provide more resolution about the dynamics of co-infections in populations and their influence on health outcomes. It may also improve cross-study inferences because the pathogens composing each cluster and the mean immune response to each infection within a grouping is identified.

5.7 Limitations

There are several limitations to this dissertation. Immune response to infection is measured by IgG level, a biological marker isolated from serum. IgG levels provide evidence that an individual received sufficient exposure to a particular pathogen to activate the adaptive immune system and trigger a humoral response, however, these biomarkers do not give an indication as to when the individual was exposed. IgM is the biomarker that would provide this information. It is possible high IgG level may represent recent primary infection, though this is unlikely in this elderly study population because infection commonly occurs during childhood, or that the primary infection elicited a very strong immune response.²⁵

Limited by data available, only four persistent pathogens were used in these analyses. Other pathogens of interest include *Chlamydia pneumonia*, Epstein-Barr Virus, Herpes Simplex Virus -2, Human Herpes Virus-6, Varicella Zoster Virus, Hepatitis B and A, and periodontal

pathogens. The four pathogens for which we did have data (CMV, HSV-1, *T. gondii*, and *H. pylori*) have been linked with morbidity and mortality in the U.S., and Mexican Americans have been found to be disproportionately affected by these pathogens and the chronic health outcomes associated with their exposure.

The SALSA participants may be healthier than the average Mexican American population in California for several reasons. First, a large portion of the study population migrated to the U.S. and it is possible that these immigrants are healthier than the average population they left.⁸ Further, there could be a health-selective return migration of those who were sick (salmon bias).^{26,27} The SALSA study may also be subject to survivor bias because participants were at least 60 years of age at baseline. Therefore, SALSA participants may be healthier than other Mexican Americans, resulting in better control of latent infections.

The early life SES measures reported in the SALSA study are also prone to recall bias, though we do not expect reporting of early life SES to vary by immune response since individuals are not routinely diagnosed for these infections and consequently would be unlikely to know their infection status. It is possible that poor cognition may also influence the recall of early life SES, however, we expect this to be non-differential with respect to level of SES, again biasing the estimates towards the null. Additionally, the early life SES latent variable used in this dissertation was the result of six different indicators, making it unlikely that a participant would incorrectly recall all of the six questions, and minimizing the impact of recall bias in this study.

5.8 Public Health Significance and Future Directions

This dissertation fills several gaps in public health knowledge about how early life conditions influence later life health. This work was the first to use a life course approach to determine how the early life social environment influences immune response to persistent

pathogens and total pathogen burden later in life. Childhood is an important period in the life course for acquiring and establishing control of persistent infections. Understanding life course SES mechanisms may help to explain disparities in chronic diseases associated with these pathogens that appear by SES in the U.S. These infections are also patterned by race/ethnicity, indicating that minority populations are more likely to acquire these pathogens earlier in life and have poorer immunological control later in life as a consequence of lower life course socioeconomic condition. Few studies have looked at other independent early life factors important among Mexican Americans, such as nativity and acculturation, and their impact on immune response to persistent pathogens and pathogen burden. Results from this dissertation provide insight into early life physical and cultural differences in the social patterning of specific persistent infections and identified educational attainment as the best point of intervention in the life course to improve immunological response to persistent infections later in life.

Additional work is needed to evaluate life course mechanisms in other populations with more infections and additional indicators of early life factors or intergenerational exposures. Future life course analyses should use appropriate modeling techniques, such as SEM, which are able to better measure life course constructs with latent variables and provide specific estimates and statistical tests for pathways involving mediation. However, life course studies can only be conducted if the data sources with life course information exist. Epidemiologic studies should consider collecting information on life course measures of SES and infection starting at early ages so that we may move beyond “black box” epidemiology to evaluate and understand how social and biological exposures over the life course work to produce health or disease later in life.

5.9 References

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