Stress biomarkers and Latinos' exposure to the United States

by

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DEDICATION

For my family:

Tom Novak and Louise Wolf-Novak

Daniel Novak, Sheila Hager Novak, Bridget Novak and Kurt Novak Hager

Tom and Carol Novak

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...and Ethan Forsgren

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11β-HSD2:	11β-hydroxysteroid dehydrogenase 2
AUC:	Area under the curve
BMI:	Body mass index
CAR:	Cortisol awakening response
CES-D:	Center for Epidemiologic Studies Depression Scale
CVD:	Cardiovascular disease
DAG:	Directed acyclic graph
GA:	Gestational age
HPA axis:	Hypothalamic-pituitary-adrenocortical axis
ICE:	Immigration and Customs Enforcement
LBW:	Low birthweight
LMP:	Last menstrual period
LOESS:	Locally estimated scatterplot smoothing
LTL:	Leukocyte telomere length
MESA:	Multi-Ethnic Study of Atherosclerosis
MET:	Metabolic equivalent
PIR:	Poverty-income ratio
PTB:	Preterm birth
qPCR:	Quantitative polymerase chain reaction
RERI:	Relative excess risk due to interaction

RR:	Risk ratio
SES:	Socioeconomic status
T/S ratio:	Relative telomere to single copy gene ratio

ABSTRACT

Background: Latino immigrants to the United States (US) have better health and mortality outcomes than US-born Latinos, but this health advantage erodes with increasing duration of US residence. Public health scholars have theorized that chronic stress mediates the relationship between exposure to the US environment and poor health among Latinos, but there is little literature examining biological mechanisms by which this occurs.

Methods: Informed by literature on structural determinants of health and the racialization of Latinos in the US, I examine links between life history, stress biomarkers and risk of poor health among Latinos. First (Aim 1), I use data from Latino participants in an ancillary study to the Multi-Ethnic Study of Atherosclerosis (MESA Stress) to examine cross-sectional and longitudinal relationships between nativity/duration of US residence and diurnal patterns in salivary cortisol, a stress hormone. Second (Aim 2), I use MESA Stress data to examine cross-sectional and longitudinal relationships between nativity/duration of US residence and leukocyte telomere length (LTL), a marker of stress-mediated cellular aging. Lastly (Aim 3), I use birth-certificate data to evaluate population-level effects of a major immigration raid on risk of low birthweight (LBW, a stress-sensitive birth outcome) among infants born to Latina mothers in the state of Iowa.

Results: Among MESA Stress participants, US-born Latinos and Latino immigrants with longer US residence had higher waking cortisol (cross-sectionally) and slower flattening of the diurnal cortisol curve (longitudinally) than more recently-arrived immigrants. While there were no cross-sectional differences in LTL according to nativity or duration of US residence, US-born Latinos and Latino immigrants with longer US residence had faster 10-year LTL shortening than more recently-arrived immigrants. Lastly, in the 37 weeks following a major immigration raid, immigrant and US-born Latina mothers in Iowa were at higher risk of having a LBW infant than Latina mothers during the same period one year earlier, while White mothers did not exhibit an increase in risk of LBW.

Conclusions: These findings extend the literature about biological pathways by which the structural position of Latinos in the US may contribute to declines in health that accompany increasing exposure to the US environment.

CHAPTER 1. **Introduction**

Background

In 2001, Latinos[1] became the second-largest racial/ethnic group in the United States after non-Latino Whites (Clemetson, 2003). Latinos now comprise 17.3% of the nation's population (Patten, 2016) and are immensely diverse in terms of country of birth, race, socioeconomic background, and cultural orientation. The majority of Latinos in the US are of Mexican origin (64%), followed by individuals of Puerto Rican (10%), Salvadoran (4%), Cuban (4%) and Dominican (3%) origin. Although much of the public conversation in the US conflates Latino ethnicity and immigration, more than half (51%) of Latino adults are US-born. Of foreign-born Latinos, 33.5% are US citizens (Patten, 2016). The majority of the growth of the US Latino population now comes from births and not from immigration (Stepler and Brown, 2015).

Latino immigrants to the United States tend to have lower risk of mortality and morbidity than US-born Latinos, but this health advantage erodes with increasing duration of residence in the US, particularly among Mexican immigrants (Bates et al., 2008; Borrell and Crawford, 2009; Lariscy et al., 2015). The pattern of deteriorating health status with increasing length of

[1] *Latino* and *Hispanic* are demonyms (ethnic labels) with overlapping but distinct (and contested) definitions, each with their own set of political and historical connotations. Generally speaking, *Latino* is understood to refer to individuals with Latin American heritage, while *Hispanic* refers to Spain and the Spanish language and thus also includes individuals from Spain with no Latin American heritage (and may exclude peoples in Latin America who do not speak Spanish, such as Brazilians and some indigenous groups). The US government has used *Hispanic* as an ethnic category since the early 1970's, although some agencies have recently expanded the label to "Hispanic or Latino" (Office of Management and Budget) or "Spanish/Hispanic/Latino" (US Census) (Cresce et al., 2003). Latinos in the US report a diversity of preferences for terminology, with many preferring neither *Hispanic* nor *Latino* but rather a reference to their particular country of origin (Mexican, Ecuadorian, Puerto Rican, etc.) (Taylor et al., 2012). I use the term Latino as it is most relevant to my research questions and the theories that undergird them. For a recently published history of the "Hispanic" category, see (Mora, 2014). For an old but still highly relevant discussion directed at public health professionals, see (Hayes-Bautista and Chapa, 1987; Treviño, 1987).

residence in the US has been observed across a number of clinical and subclinical health outcomes, particularly markers of cardiovascular (Kershaw et al., 2016, 2012; Lutsey et al., 2008; Moon et al., 2012; Moran et al., 2007) and metabolic (Ahmed et al., 2009; Bates et al., 2008; Sánchez-Vaznaugh et al., 2008) disease, as well as a number of psychiatric conditions (Alegría et al., 2008; Cook et al., 2009).

The observation of good health and mortality outcomes among immigrant Latinos, and the decline in health with increasing duration of residence or generations of US nativity, is part of a cluster of phenomena termed the "Hispanic paradox", or sometimes simply the "epidemiologic paradox". The good health of immigrant Latinos (and of Latinos relative to the non-Hispanic White population) has been deemed paradoxical because it exists despite the low socioeconomic status of these populations (Acevedo-Garcia and Bates, 2008). Scholars have taken a number of approaches to understand the incongruity of these patterns with the socioeconomic gradients that seem to dictate so much of the variation in US population health. Some portion of the immigrant mortality advantage is likely an artifact of selective migration of healthy immigrants ("healthy migrant" bias) (Abraido-Lanza et al., 1999; Rubalcava et al., 2008), an undercount of Latino immigrant deaths, or selective out-migration of ailing immigrants ("salmon" bias) (Palloni and Arias, 2004; Patel et al., 2004). However, there is not sufficient evidence to suggest that these biases and selection effects fully explain the Latino/Hispanic immigrant mortality advantage (Markides and Eschbach, 2005; Turra and Elo, 2008). These artefactual explanations also do not explain the deterioration of immigrants' health with increasing duration of US residence.

Another body of scholarship examines cultural explanations for these patterns, including the decline of protective cultural resources and the adoption of unhealthful behaviors over time and generations of US residence. These studies theorize that the decline in health over time is due to “acculturation” or “negative assimilation” and evaluate whether US-born Latinos have fewer protective cultural resources such as social support (Almeida et al., 2011, 2009; Gallo et al., 2009), or are more likely to engage in risky health behaviors such as poor diet, sedentary behavior, smoking and substance abuse (Abraido-Lanza et al., 2005) than their immigrant counterparts. However, evidence about behavior change with increasing US residence or US nativity is mixed. There is strong evidence, for example, that, among Latinos, rates of smoking increase with increasing residence in the US, or with US nativity (Fenelon, 2013). Dietary habits also vary according to nativity and duration of residence, with Latinos with longer tenure in the US consuming more sugary drinks and less fruit. However, changes in diet are not purely negative; US-born Latinos consume more added dietary fats, but use less animal fat in cooking, leading to the same amount of total fat intake as immigrant Latinos (Ayala et al., 2008). Similarly, physical activity for work or errands decreases with increasing US residence or US nativity, while leisure time physical activity actually increases (Berrigan et al., 2006; Crespo et al., 2001). And counter to the idea of “negative assimilation,” access to health care and use of preventive services improves with increasing US residence, even as health outcomes deteriorate (Lara et al., 2005). A further weakness in culture-centered accounts for the “Hispanic paradox” is that they pay less attention to the ways that structural and contextual factors, such as neighborhood environments and low incomes, contribute to these changes in behavior and social support. Acknowledging and understanding the upstream influences on these behavior changes is important for effective intervention and prevention.

The argument that individual-level cultural and behavioral accounts are not sufficient to explain the "Hispanic paradox" is bolstered by the fact that the "paradox" is not observed equally across all immigrant groups, or even all Latino subgroups. The decline in health status over time and generations is strongest among Latinos of Mexican origin, which suggests that the decline in health is not the natural or necessary consequence of migration but rather something that is modifiable and varies across Latino subgroups, perhaps because of differences in the characteristics of people migrating from different countries, or differences in the social position of different groups of Latino immigrants upon arrival in the US (Acevedo-Garcia et al., 2007; Borrell and Crawford, 2008; Goel et al., 2004). Mexican immigrants are more likely to be of low SES, with 39.2% of Mexican immigrants having less than a 9th grade education (compared to 13.7% of Caribbean immigrants and 9.7% of South American immigrants) (Brown and Patten, 2014). Mexican immigrants are more likely to work in food preparation, cleaning and maintenance, manufacturing and construction, while South American and Caribbean immigrants have higher rates of employment in fields such as management, office and administrative support, and healthcare (Brown and Patten, 2014; Suro et al., 2007). Mexican immigrants have the highest poverty rate of all immigrant groups: 27.8% of Mexican immigrants live in poverty, compared to 20.6% of Caribbean immigrants and 14.2% of South American immigrants (Brown and Patten, 2014). Mexican immigrants have also been far more likely to come to the US under precarious immigration statuses; in 2008 it was estimated that 61.1% of Mexican immigrants living in the US were undocumented, compared to 30.3% of South American immigrants and 14.6% of Caribbean Latino immigrants (Passel et al., 2009). Mexican immigrants have the lowest naturalization rates of all Latino immigrant groups, with only 21.6% of immigrants naturalized (compared to 37.6% of South American immigrants, for example) (Suro et al., 2007).

Even among US-born Latinos, those of Mexican origin are more likely to live in poverty than US-born Latinos from other Latino subgroups (Acevedo-Garcia and Bates, 2008; Suro et al., 2007). The fact that the "Hispanic paradox," as well as the decline in health over time and generations of US residence, is strongest among the Latino subgroup that most consistently experiences precarious immigration status, low incomes, and low educational attainment is consistent with the idea that legal and socioeconomic marginalization play a role in the deterioration in health of this particular group.

A growing literature hypothesizes that the observed decline in health status with increasing residence in the United States may mediated by the chronic stressors associated with life in the US as an immigrant or a racialized minority. Among low-status Latino immigrants, for example, the stress associated with navigating immigration status (Reed et al., 2005), housing and occupational instability (Hall et al., 2010; Hall and Greenman, 2013), family separation and family conflict (Dreby, 2015; Letiecq et al., 2014; Viruell-Fuentes and Schulz, 2009), all while having very few economic or legal resources, may build up over time and result in poorer health (Acevedo-Garcia et al., 2012; Viruell-Fuentes et al., 2012). While US-born Latinos, citizens at birth, are spared some of the challenges of immigration status, they may have family and community connection to immigration-related stressors (Dreby, 2015; Viruell-Fuentes, 2007), and still face the challenges of socioeconomic disadvantage and lifetime experience as a racialized minority in the US (Viruell-Fuentes, 2007; Viruell-Fuentes et al., 2012). Over time, exposure to this range of social and environmental stressors may wear down bodily systems and leave Latino immigrants and US-born Latinos vulnerable to disease. Despite many authors theorizing that chronic stress mediates the relationship between a number of exposures and poor health in particular segments of the Latino population (Lopez et al., 2016; Martinez et al., 2013;

Torres and Young, 2016), the literature exploring a biological stress pathway in this population is limited.

This dissertation takes several approaches to understanding the links between life history, chronic stress, and risk of poor health among Latinos in the United States. I use data from Latino participants in an ancillary study to the Multi-Ethnic Study of Atherosclerosis (MESA Stress) to examine associations between nativity, duration of US residence, and two aspects of the biological response to stress. First (Aim 1), I examine cross-sectional and longitudinal relationships between nativity/duration of US residence and diurnal patterns in salivary cortisol, a stress hormone. Second (Aim 2), I examine cross-sectional and longitudinal relationships between nativity/duration of US residence and leukocyte telomere length, a marker of cellular aging. Lastly (Aim 3), I turn further upstream and use a quasi-experimental approach to examine the effects of a contextual stressor, a major immigration raid, on low birth weight (a stress-sensitive birth outcome) among infants born to immigrant and US-born Latina mothers.

Theoretical frame

Exposure to the United States

I borrow the concept of "exposure to the United States" from a 2009 paper by Benjamin Cook and colleagues (including Margarita Alegría) at the Harvard School of Public Health (Cook et al., 2009). Cook and colleagues used this phrase to interpret associations between nativity, duration of US residence and risk for a number of psychiatric conditions. I have adopted their framing for my dissertation title and I argue that the concept of "exposure to the United States" is an overarching framework that links the three analyses in this dissertation project.

Nativity and duration of US residence

Nativity (country of birth) and duration of US residence (also called length of residence, duration of stay) are commonly used exposure variables in population studies of Latinos and other ethnic groups in the United States (Cho and Hummer, 2001; Krieger et al., 2011; Ro and Bostean, 2015). The measures of nativity and duration of residence are sometimes interpreted as markers of "acculturation" and are used, alone or in conjunction with other variables such as language spoken or survey measures of cultural orientation (Lutsey et al., 2008; Moran et al., 2007; Peek et al., 2010). However, interpreting nativity and duration of residence as markers of acculturation (a shift in cultural orientation) requires a number of assumptions and may elide other contextual, psychosocial and behavioral mechanisms by which life in the US is linked to poor health (Acevedo-Garcia et al., 2012; Viruell-Fuentes et al., 2012). In order to leave room for consideration of other pathways, I conceptualize nativity and duration of US residence as measures of the duration of exposure to life in the US and the various exposures, both protective and harmful, that US residence confers.

The Postville raid

In my final Aim, I employ a quasi-experimental study design to examine the effects of a large immigration raid on the risk of low birthweight among immigrant and US-born Latina mothers. While the Postville raid was undoubtedly a stressful event, I would like to take some space in this introduction to discuss the particular ways the Postville raid fits in the framework of "exposure to the US". As I describe below, I theorize that the Postville raid exaggerated a range of structurally-rooted stressors that are regular feature of life for Latino communities in the US and particularly in the rural Midwest, including employment instability and economic marginalization, fear of immigration enforcement and its effects on family and community relationships, and experiences of discrimination, stereotype threat and racialized exclusion. In this sense, the final Aim of my dissertation provides another perspective on links between "exposure to the US" and health by examining changes in health after an acute event that exaggerated a number of chronic stressors endemic to the US environment for many Latinos.

As mentioned above, economic marginalization, immigration-related stress, and anticipation of racialized exclusion are disproportionately experienced by Latinos in the US. It is typically very difficult to operationalize these diffuse (and often covert) aspects of the social/structural environment in order to study their relationships with health. In contrast, the Postville raid occurred on a single day, allowing for a clear comparison before and after the raid. The Immigration and Customs Enforcement (ICE) raid on a meat processing plant in Postville, IA on May 12, 2008 was, at the time, the largest single-site immigration raid in U.S. history. Carried out with no advance warning to local or state officials, the raid deployed 900 ICE agents to arrest 389 employees at a rural meat processing plant, 297 of whom were eventually deported. Ninety-eight percent of the individuals arrested were Latino (Camayd-Freixas, 2008).

The effects of the Postville raid on the local community were dramatic, and it received international attention as a humanitarian crisis (Camayd-Freixas, 2008; "The Shame of Postville, Iowa," 2008). Hundreds of families were separated from their primary breadwinner, and fear of follow-up home raids led many families to sleep in a local church or leave town altogether. Arrested individuals were transported 80 miles to the National Cattle Congress in Waterloo, Iowa, where men were housed in an exhibition hall while women were detained in county jails. Detainees were "fast-tracked" through court proceedings, arraigned in groups of ten for felony charges of aggravated identity theft. Mothers of small children were allowed to return to

Postville with ankle monitors but, barred from working, had no way to support their families (Camayd-Freixas, 2008; Rigg, 2011).

The Postville raid had effects throughout the state of Iowa, particularly in other communities with a Latino meat-processing workforce. Meatpacking is common in Iowa and Latinos have made up a large portion of the meatpacking workforce since the 1990's.(Artz, 2012) There are strong networks of communication within and between Latino communities, including Spanish-language newspapers, radio stations, and Latino civil society groups, and informal networks to share information about employment opportunities, wages, and work conditions (Fink, 1998; Naples, 2000). Local newspapers reported rumors of follow-up raids in Latino communities throughout western, southern, central and eastern Iowa (Burns, 2008; Jackson, 2008; Jacobs and Perkins, 2008; Krogstad, 2008a; Saul, 2008; Toopes, 2008). Local churches and immigrant advocacy groups in Latino communities across the state hosted "Know Your Rights" events and encouraged immigrants to talk to their children about what to do in case of a raid, identify a lawyer to represent them in case they were detained in by ICE, and arrange power of attorney papers to assign guardianship for children (Christensen, 2008; Jacobs and Perkins, 2008; Lopez, 2008; Toopes, 2008).

Fears of more immigration raids also affected Latino businesses across the state as individuals avoided public space and reined in spending in case they needed funds to move on short notice ("90 miles away, Postville raid's impact is still being felt," 2008; Burns, 2008). The raid brought increased scrutiny on the employment practices of meat processors throughout the state, which may have affected employment prospects for immigrants and their families (Jackson, 2008; Larsen, 2008; Saul, 2008; Toopes, 2008). This scrutiny may have also affected willingness to employ any Latinos, as public conversations about immigration often conflated Latino/Hispanic phenotype with undocumented status (Krogstad, 2008b; Saul, 2008).

As described above, the Postville raid exaggerated a number of stressors that disproportionately affect Latinos: economic marginalization, systemic/political pressure on family relationships, and experiences of discrimination and racialized exclusion. For these reasons I argue that the Postville raid is an instrument by which we can examine certain features of "exposure to the US" and health for Latinos.

Stress and chronic disease risk

There is a robust literature on physiological sequelae of psychosocial stress and its origins in structural inequality, but few studies have examined patterns in biological markers of stress according to nativity and duration of US residence in Latinos. US-born Latinos have been observed to have higher levels of inflammatory markers such as interleukin-1, interleukin-6 and C-reactive protein when compared to Latino immigrants (Ranjit et al., 2007; Rodriguez et al., 2012). A number of studies have also evaluated the relationship between nativity, duration of US residence and composite measures of stress-related physiological functioning such as allostatic load or biological risk scores. Allostatic load studies in Latino samples have consistently found evidence for a relationship between US nativity, longer duration of US residence, and poorer global physiologic function, particularly among Mexican immigrants and Mexican Americans (Crimmins et al., 2007; Kaestner et al., 2009; Peek et al., 2010; Salazar et al., 2016). A small pilot study of allostatic load among Latino day laborers in Seattle also reported that higher allostatic load was associated with higher economic stress and with a greater number of years working as a day laborer (de Castro et al., 2010).

These studies are consistent with the hypothesis that chronic stress may mediate some portion of the deterioration in the health of Latinos over time in the US and over generations. However, all existing studies are cross-sectional, which requires making assumptions about temporal processes (deterioration) based on observations at a single point in time. Longitudinal evidence would allow the direct observation of changes in health within individual people.

Summary and specific aims

In Chapters 2 and 3 I examine cross-sectional and longitudinal relationships between nativity/duration of US residence and two different markers of the biological response to stress: diurnal cortisol, which is a marker of hypothalamic-pituitary-adrenocortical (HPA) function, and leukocyte telomere length, a marker of stress-mediated cellular aging. Chapter 4 evaluates the relationship between the US context and stress by examining changes in a stress-sensitive birth outcome, low birth weight, after a major immigration raid. In Chapter 5 I integrate and contextualize my findings and discuss potential implications for public health policy and practice, and directions for future research.

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CHAPTER 2. Aim 1: Diurnal salivary cortisol and nativity/duration of residence in Latinos: The Multi-Ethnic Study of Atherosclerosis

Introduction

Despite facing higher rates of poverty and the challenges of migrating to a new country, Latino immigrants to the US have better health and mortality outcomes than US-born Latinos (Riosmena et al., 2015). However, this health advantage erodes with increasing duration of residence in the US such that immigrants with longer tenure in the US have higher risk of mortality and poor health than immigrants who arrived more recently (Lariscy et al., 2015). These patterns have been observed across a number of health outcomes, including obesity (Sánchez-Vaznaugh et al., 2008), stroke (Moon et al., 2012), and depression/anxiety (Alegría et al., 2008; Cook et al., 2009), and are strongest among Latinos of Mexican origin and in middle age (approximately ages 45-65) (Alegria et al., 2007; Sánchez-Vaznaugh et al., 2008).

Scholars have hypothesized that chronic activation of the body's stress response system may mediate a number of US health disparities, including those observed among US Latinos according to place of birth and, among Latino immigrants, duration of US residence (Kaestner et al., 2009; Viruell-Fuentes, 2007). Chronic activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, a component of the body's response to stress, can have harmful metabolic effects, including higher risk for several conditions that disproportionately affect US-born Latinos and Latino immigrants with longer duration in the US (Champaneri et al., 2012; Hackett et al., 2014; Hajat et al., 2013; Kumari et al., 2010; Matthews et al., 2006). Despite these compelling hypotheses, few studies have examined links between HPA function and nativity/duration of US residence among Latinos (Mangold et al., 2012), and there are no studies examining these hypotheses in large cohorts.

Nativity/duration of residence and stress exposure

Although no existing studies examine the association between nativity/duration and diurnal cortisol among Latinos, a number of studies have identified nativity/duration differences in other stress-mediated physiological measures, including allostatic load (Salazar et al., 2016) and markers of inflammation (Ranjit et al., 2007; Rodriguez et al., 2012).

Although newly arrived Latino immigrants face a number of stressors, they also tend to be healthy, perhaps because healthier individuals are more likely to immigrate (Rubalcava et al., 2008). However, the cumulative burden of navigating the challenging context for employment, housing, legal status and political resources as an immigrant to the United States (Hall and Greenman, 2014, 2013; Laird, 2015; Torres and Young, 2016) could contribute to the observed declines in health with additional years in the US. Although some immigrants experience improvements in income as they spend more time in the US, these improvements in material circumstances may come at the cost of high-effort striving in adverse circumstances (Viruell-Fuentes, 2007). Furthermore, there is evidence that immigrants may become more attuned to experiences of discrimination and their constructed position within the US ethnoracial hierarchy as they spend more time in the US environment (Viruell-Fuentes, 2011).

While US-born Latinos have the advantage of citizenship and tend to have higher education and income than Latino immigrants, they still experience higher rates of poverty than the general US population, which affects their ability to live in healthy environments and access health-promoting resources (Acevedo-Garcia and Bates, 2008). Many US-born Latinos have family and community connections to the stresses of immigrant life, including acculturative stress and immigration status vulnerability of family, friends or coworkers (Castañeda and Melo, 2014; Quiroga et al., 2014; Viruell-Fuentes and Schulz, 2009). Furthermore, US-born Latinos with increased economic and social integration into the United States may be more conscious of and sensitive to their constructed position, both socioeconomically, and racially/ethnically, in US social hierarchies (Cook et al., 2009). Experiences of social marginalization may be particularly important for cumulative wear-and-tear on the HPA axis for US-born Latinos: threats to the "social self" are among the most powerful triggers of a HPA response in laboratory settings (Dickerson and Kemeny, 2004), and there is evidence that individuals have more acute reactions to inflammatory language in their first language than in languages acquired later in life (Harris, 2004). Experiences of discrimination while attending school, working, and raising families in settings where Latinos are racialized as "other" and "forever foreign" may be particularly stressful for US-born Latinos (Viruell-Fuentes, 2007). Over time, exposure to a range of social and environmental stressors may wear down bodily systems and leave both Latino immigrants and US-born Latinos vulnerable to disease. These findings have been framed as a "weathering" or "accelerated aging" effect among Latino immigrants with longer US residence and US-born Latinos (Kaestner et al., 2009).

Diurnal cortisol

The release of cortisol throughout the day (diurnal cortisol) represents a biological marker of the functioning of the HPA axis (Adam and Kumari, 2009; Miller et al., 2007). A typical diurnal cortisol curve consists of a relatively steep increase in salivary cortisol during the first half-hour after waking, followed by a gradual decline over the rest of the day (with some fluctuations after eating and in response to stressors throughout the day), reaching the lowest level in the evening. Long-term neuroendocrine arousal in response to psychosocial stress may result in chronic alterations of the HPA axis. These alterations can vary according to the type and chronicity of stress exposure, but generally individuals facing stressors related to social position and social evaluation tend to have higher morning cortisol and flatter declines in cortisol over the course of the day (Miller et al., 2007). The diurnal curve also changes in response to aging, with higher wakeup cortisol, a flatter decline throughout the day, and higher total cortisol output as individuals age (Wang et al., 2014). These aging- and stress-mediated dysregulations in the cortisol curve have been linked in turn to health and mortality risk; for example, a flatter decline in cortisol throughout the day has been associated with higher risk for obesity, diabetes, and cardiovascular disease and higher all-cause mortality (Champaneri et al., 2012; Hackett et al., 2014; Kumari et al., 2011, 2010).

The aim of this study is to examine both cross-sectional and longitudinal associations between diurnal cortisol and nativity/duration of US residence in a sample of adult Latinos. We hypothesize that US-born Latinos and Latino immigrants with a longer duration of US residence will face particular dysregulations in the diurnal cortisol curve relative to more recently arrived immigrants (a higher wake-up cortisol level, a smaller cortisol awakening response, flatter early and late declines in cortisol and a higher total cortisol output) (Miller et al., 2007; Wang et al., 2014). Similarly, we hypothesize that, over a 5-year period, the dysregulation of diurnal cortisol among US-born Latinos and Latino immigrants with a longer duration of US residence will become more exaggerated (greater increase in wake-up cortisol level, greater decline in cortisol awakening response, greater blunting of early and late declines, and a greater increase in total cortisol output) relative to more recently arrived Latino immigrants.

Methods

Data

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal study designed to investigate risk factors for subclinical cardiovascular disease and its progression to clinical disease. From 2000-2002 MESA recruited adults ages 45-84 and free of cardiovascular disease at baseline from six sites across the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN). Latino participants were recruited from three sites: Los Angeles, CA; New York, NY; and St. Paul, MN.

As an ancillary study to MESA, the MESA Stress Studies (MESA Stress I and II) collected detailed measures of stress biomarkers, including diurnal salivary cortisol, at two follow-up visits approximately 6 years apart. The first wave of the MESA Stress ancillary study (Stress I) was conducted in two MESA sites: New York, NY and Los Angeles, CA from 2004 – 2006. The second wave (Stress II) was conducted from 2010-2012, and included the same two sites as MESA Stress I as well as a third study site, Baltimore, MD. Because the Baltimore site did not include Latino participants, this analysis is restricted to the New York and Los Angeles sites across both waves of the MESA Stress study.

Of MESA's 6814 original participants, 1002 (528 Latino) participated in MESA Stress I and 1082 (438 Latino) participated in MESA Stress II, including many follow-up participants from Stress I. There are 499 Latino participants with valid diurnal cortisol samples from MESA Stress I and 424 participants with valid diurnal cortisol samples from MESA Stress II, for a total of 613 unique individuals with valid cortisol samples at one or both wave. There were 309 Latino participants with valid diurnal cortisol samples from both waves of the study. The MESA

Stress Study was approved by institutional review boards at each study site and written informed consent was obtained from participants.

Cortisol

In the first MESA Stress exam participants were instructed to collect six saliva samples per day over 3 weekdays, resulting in a maximum of 18 samples per person. Participants were instructed not to eat, drink or brush their teeth 15 min before collecting the salivary samples. The first sample was to be taken immediately after waking (before getting out of bed), the second sample 30 min later, the third sample at around 10:00 AM, the fourth sample at around noon (or before lunch if lunch occurred before noon), the fifth sample at around 6 PM (or before dinner if dinner occurred before 6 PM), and the sixth sample right before bed. A time tracking device was embedded in the caps of the saliva collection tubes in order to automatically register the time at which cotton swabs were extracted to collect each sample. Participants were also asked to write down the times of sample collection for each sample on a daily questionnaire.

In the second MESA Stress Study participants were instructed to collect eight saliva samples per day over 2 weekdays, resulting in a maximum of 16 samples per person. The first sample was taken immediately after waking (and before getting out of bed), the second sample 30 min later, the third sample 1 hour after breakfast, the fourth sample around 10 am, the fifth sample at noon, the sixth sample around 4 pm, the seventh sample around 6 pm (or before dinner if dinner occurred before 6 PM), and the eighth sample right before bed. Time tracking caps were not used in MESA Stress II, but participants were provided with a digital clock to help them record the time of salivary sample collection, and, as in Stress I, they were asked to write down the times of sample collection for each sample on a daily questionnaire. A previous study found that lower adherence to the cortisol sampling schedule was associated with a lower CAR but not with any other cortisol features, and adjustment for compliance did not affect associations of socio-demographic characteristics with cortisol (Golden et al., 2014).

Saliva samples for diurnal cortisol were collected using Salivette collection tubes and stored at −20 C until analysis. Before biochemical analysis, samples were thawed and centrifuged at 3000 rpm for three minutes to obtain clear saliva with low viscosity. Salivary cortisol levels were determined employing a commercially available chemi-luminescence assay (CLIA) with high sensitivity of 0.16 ng/mL (IBL-Hamburg; Germany). Intra- and inter-assay coefficients of variation were below eight percent. Cortisol was measured in nmol per liter.

Nativity/duration of US residence

For this study place of birth (nativity) is categorized as US-born (born in the 50 US states or DC) or foreign-born/island-born (born outside of the US or in Puerto Rico). Among the foreign-born/island-born (for simplicity we will refer to this group as foreign-born), duration of US residence was dichotomized as <30 years or ≥30 years at the time of MESA Stress I. We calculated duration of residence at MESA Stress I by adding duration of residence collected at an earlier time (MESA Exam 1) to the amount of time elapsed before Stress I data collection. We chose 30 years as the cutoff based on the distribution of duration of residence in the MESA Stress Latino sample; approximately one-third of foreign-born participants had resided in the US for fewer than 30 years.

Covariates

We used a directed acyclic graph (DAG) to identify potential confounders of the association between nativity/duration of residence and diurnal cortisol (Figure 2-1).

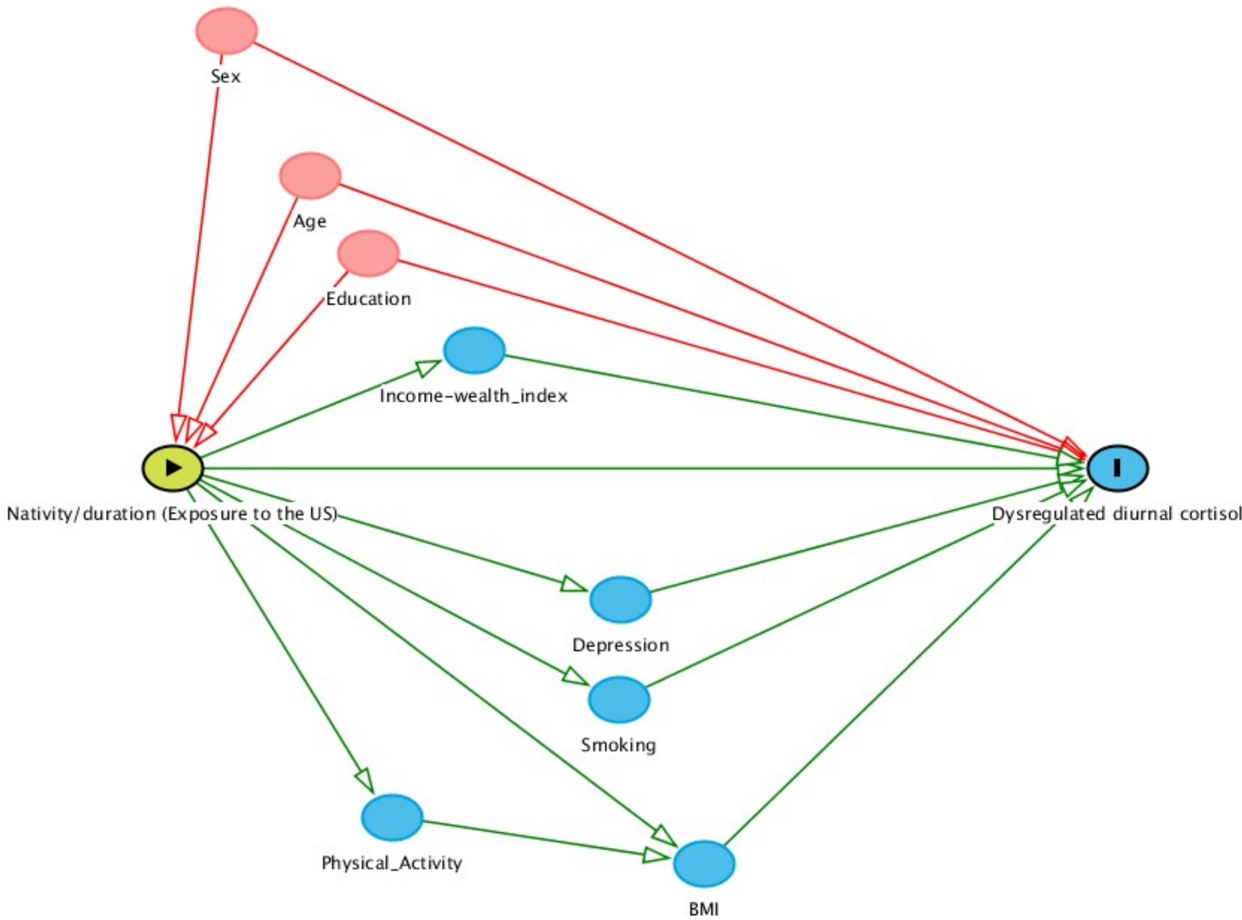

Figure 2-1 Directed Acyclic Graph (DAG) of the hypothesized relationships between nativity/duration of US residence, diurnal cortisol, and covariates of interest. Confounding variables, which precede both the exposure and the outcome in the causal pathway, are highlighted in red, while mediators, which do not precede the exposure in the causal pathway, are indicated by green arrows.

All models were adjusted for the following individual level covariates (obtained from a self-report questionnaire): age, sex, wake-up time (on the day of sampling), and sequential day the sample was collected (i.e. 1, 2 or 3). Age and sex were identified as potential antecedents of duration of residence and nativity because migration histories vary by age and sex.

In previous studies socioeconomic status (SES) has been considered a confounder of the relationship between diurnal cortisol and other social exposures, such as race/ethnicity and neighborhood environment (Hajat et al., 2015, 2010). However, in the relationship between nativity/duration and diurnal cortisol, SES may act as a confounder or as a mediator, depending on the measure and its relationship to the exposure and outcome. In our DAG we identified education as a confounder because it is completed prior to migration for most immigrants (the median age at arrival for immigrant Latinos in MESA is 28; only 25% arrived prior to age 21). However, income and wealth may depend on a participant's nativity/duration, making them more like mediators of the relationship between nativity/duration and cortisol, acting as a proxy for the participant's degree of integration and exposure to mainstream US contexts. For this reason we examine education as a confounder and add income-wealth in a later model. Education was categorized as less than high school, completed high school, and completed college. The income-wealth index combines information on asset ownership (car, home, land, and investments) and quintiles of income. It ranges from 0-8 points, where 0 represents lowest income-wealth (Hajat et al., 2010).

Behavioral and health-status covariates that may mediate the associations of interest include smoking status, body mass index (BMI), depressive symptoms, and physical activity. Smoking status (self-reported) was classified as current, former, and never smokers. BMI was calculated as weight (measured) in kilograms divided by height (measured) in meters squared. Depressive symptoms were assessed using the 20 item Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977). Physical activity questions were adapted from the Cross-Cultural Activity Participation Study (Ainsworth et al., 1999). Moderate and vigorous physical activity were measured in metabolic equivalent (MET)-minutes/week and categorized into quartiles for analysis. All covariates (age, sex, income-wealth index, years of education, smoking status, BMI, depressive symptoms and physical activity quartiles) were mean-centered for ease of interpretation. Wake-up time was centered at 7:00 AM, also for ease of interpretation.

We included a measure of time between Stress I and Stress II data collection in longitudinal models. Time between visits was standardized to 5 years.

Statistical Analysis

<u>Statistical model</u>

We use a piecewise linear mixed effects model to examine associations between our exposure of interest (nativity and duration of US residence) and features of the diurnal cortisol curve. Instead of calculating cortisol features and running separate models for each one (a less efficient two-step approach to calculating cortisol features), we include all cortisol samples (log-transformed to account for the skewed distribution of salivary cortisol (Wang et al., 2014)) in a single model. Piecewise splines capture the non-linearity of the cortisol curve across the day, with two knots fixed at 0.5 hours and 2 hours after wakeup (Hajat et al., 2010; Sánchez et al., 2012). Parameter estimates from the model are used to estimate the association of the exposure (nativity/duration) with the following cortisol features: wake-up cortisol level, cortisol awakening response (CAR, the rise in cortisol in the first 30 minutes after waking), early decline slope (the average hourly rate of decline in cortisol from 30 minutes to 2 hours after waking), late decline slope (the average hourly rate of decline in cortisol from 2 hours after waking to bedtime), wake-to-bed slope (the average hourly rate of decline in cortisol from waking to bedtime, excluding the peak after awakening), and standardized total area under the curve (AUC or total cortisol: the area under the linear spline, standardized to 16 hours of waking time, calculated by the trapezoid rule

(Yeh and Kwan, 1978)). See Figure 2-1 for a visual representation of features of the cortisol curve.

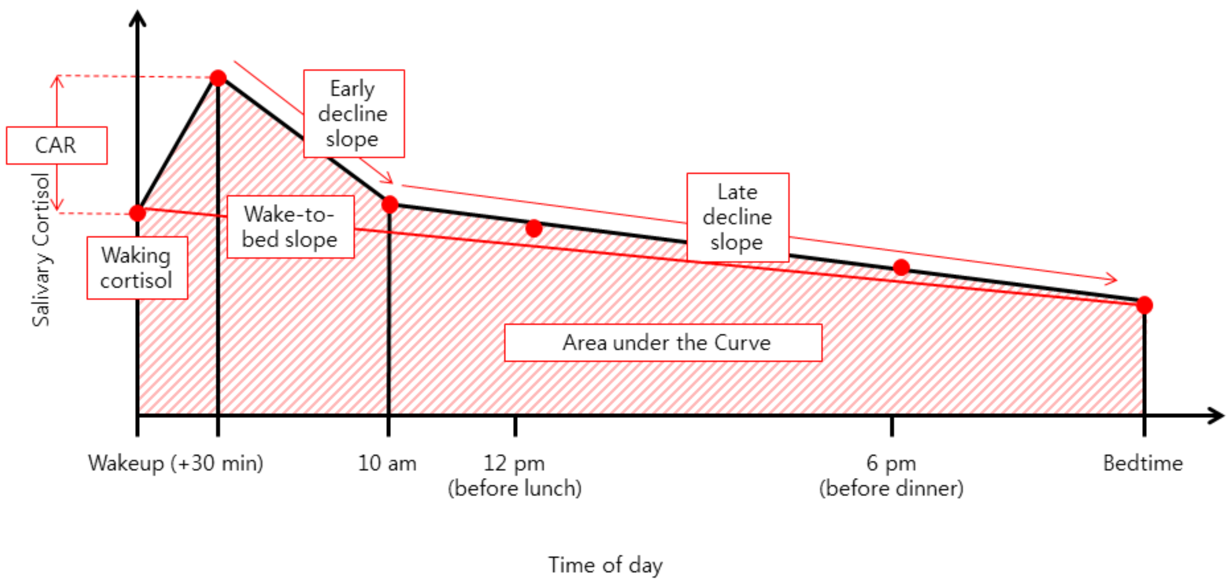

Figure 2-1. The diurnal cortisol curve and the various curve features.

For each hypothesis, we used a staged modeling approach, adding more variables to each subsequent model. Immigrants with fewer than 30 years of US residence were the reference group as we hypothesized they would have the least dysregulated cortisol. Model 1 adjusted for basic potential confounders of the relationship between nativity/duration and cortisol levels: age, sex, and time of wakeup. Model 2 adjusted for years of education, which we theorized was a confounder. Model 3 further adjusted for income-wealth index, which we theorized to be either a confounder or a mediator. Lastly, Model 4 was further adjusted for potential behavioral or health-status mediators of the nativity/duration-cortisol association: smoking status, BMI, depressive symptoms and reported physical activity. All covariates were included as main effects and as interactions with each spline term, the latter to enable estimation of the association of nativity/duration of US residence with each feature of the cortisol curve.

Descriptive analysis

We visually examined differences between cortisol curves across study wave and nativity/duration of residence using locally estimated scatterplot smoothing (LOESS) curves. We also use unadjusted piecewise models to estimate features of the cortisol curve at each level of nativity/duration and to estimate p-values for unadjusted differences in cortisol features by nativity/duration.

Cross-sectional analysis

To increase power, data from Stress Studies I and II (n=1458) were combined for cross-sectional analyses. After combining the two studies, we had 613 unique Latino individuals, 2292 days and 14,546 samples. We excluded samples that had missing or incomplete cortisol data (including time since wakeup), samples with cortisol values equal to 0 nmol/L or >100 nmol/L (generally considered to be outliers), persons on steroids or hormone replacement therapy, and those who had missing covariates and were left with 558 persons, 1983 days and 12,724 samples. Individuals excluded from the cross-sectional analysis were more likely to be immigrants, were more likely to be from the New York study site, had higher average CESD scores and had lower average income-wealth indices. There were no differences between included and excluded participants in age, sex, education, BMI, smoking, or physical activity.

The main effects of covariates and interactions of covariates with each spline piece were included to adjust the associations of nativity/duration for other variables. Within-person correlations of the repeated cortisol samples and between-person variation in the cortisol diurnal curve and in the difference in the curve across studies were modeled as individual-level random effects for the intercept and slopes of the cortisol curve for the first and third spline pieces as well as the study indicator and its interaction terms with the first and third spline pieces. Day-level and study-level variability were accounted for using fixed effects for day of sample.

Longitudinal analysis

Participants who attended both Stress studies (n=309 prior to exclusions) were included in the analyses of changes in cortisol features over time. We used the same exclusions described in the cross-sectional analysis above and were left with 248 persons, 1195 days and 7847 samples. Individuals excluded from the longitudinal analysis were more likely to be female, immigrants with 30 or more years of US residence, from the New York study site, and had lower average income-wealth indices and higher average physical activity. Nativity and duration of US residence and education were not time-varying and corresponded to the date participants were seen for Stress I. Some person-level characteristics (age, income-wealth index, BMI, smoking, depressive symptoms and physical activity) were time-varying. The main effects and interactions of nativity/duration categories with each spline term were included to calculate the cortisol features of interest. The interactions of time between visits with each of the spline terms were used to assess the average change in each of the features over time and three-way interactions between the exposure, spline terms, and time between visits were used to assess deviation in nativity/duration of US residence from overall change. Covariate main effects, interactions of covariates with each spline term, and three-way interactions of covariates with spline terms and time between visits were included to adjust for confounding. Person-to-person variation in the effect of time between visits on the diurnal cortisol curve was accounted for with the inclusion of random components for time between visits and interactions of time and the first and third spline terms. In addition, the model includes individual-level random intercept and slopes in the first and third spline terms to account for within-person correlations and between-person variation in cortisol curves. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Cross-sectional results

When we pooled samples for both Stress studies, the average age was 67.1 years and 49.3% of the cross-sectional sample was male. In terms of nativity and duration of US residence, 24.0% of the sample was foreign-born with less than 30 years of residence, while about half (51.2%) were foreign-born with 30 or more years of US residence, and 24.8% were US-born (Table 2-1). In visual observation of LOESS curves (Figure 2-2) as well as bivariate cross-sectional analysis (Table 2-2), US-born participants had higher wake-up cortisol (2.55 log nmol/L) and higher AUC (1.61 log nmol/L/hr) than foreign-born individuals with 30 or fewer years of residence (2.37 and 1.50 log nmol/L/hr, respectively). There were no bivariate nativity/duration differences in the cortisol awakening response, early or late declines, or wake-to-bed slope.

Table 2-1. Descriptive characteristics of participants included in the pooled cross-sectional and longitudinal analysis, Multi-Ethnic Study of Atherosclerosis (MESA) Stress Study.

	Stress study I	Stress study II	Sample in pooled cross-section	Sample in longitudinal analysis	
				At Stress I	At Stress II
N Persons	446	360	558	248	248
N Days	1280	703	1983	707	488
N Samples	7391	5333	12724	3867	3980
Age (mean (SD))	65.2 (9.5)	69.4 (9.3)	67.1 (9.6)	63.9 (9.5)	69.6 (9.4)
Male (%)	49.8	48.6	49.3	52.0	52.0
Income/wealth index (mean (SD))	3.2 (2.2)	3.5 (2.1)	3.3 (2.2)	3.5 (2.2)	3.7 (2.1)
Education (%)					

Less than high school	44.0	39.7	42.1	38.7	38.7
Completed high school	46.2	49.2	47.5	50.8	50.8
Completed college	9.9	11.1	10.4	10.5	10.5
Cigarette smoking status (%)					
Never	47.5	49.4	48.4	51.4	47.6
Former	46.2	46.4	46.3	42.9	48.4
Current	6.3	4.2	5.3	5.7	4.0
Body mass index (mean (SD))	29.4 (5.3)	29.1 (5.2)	29.3 (5.3)	28.9 (4.9)	29.1 (5.2)
Center for Epidemiologic Studies Depression Scale (mean (SD))	9.1 (9.2)	9.3 (8.6)	9.2 (8.9)	8.9 (9.3)	9.1 (8.6)
Total moderate or vigorous physical activity METS/week (mean (SD))	4636.0 (4476.6)	4443.4 (5149.2)	4550.0 (4786.6)	5059.1 (4893.7)	4370.1 (5391.2)
Study Site (%)					
New York, NY	40.1	45.8	42.7	40.3	40.3
Los Angeles, CA	59.9	54.2	57.3	59.7	59.7
Nativity/duration					
Foreign born <30 years	23.5	24.4	24.0	22.6	22.6
Foreign born 30+ years	50.9	51.7	51.2	53.6	53.6
US-born	25.6	23.9	24.8	23.8	23.8
Outcomes					
Cortisol nmol/L (mean(SD))	8.75 (8.82)	10.63 (10.50)	9.54 (9.61)	8.39 (8.61)	11.12 (10.74)
Log cortisol (mean (SD))	1.69 (1.07)	1.87 (1.14)	1.76 (1.10)	1.63 (1.09)	1.93 (1.12)
Wake-to-bed slope (mean (SE))	-0.96 (0.02)	-0.82 (0.02)	-0.90 (0.02)	-0.98 (0.02)	-0.86 (0.03)
Area under the curve (mean (SE))	1.47 (0.02)	1.65 (0.03)	1.53 (0.02)	1.45 (0.03)	1.67 (0.04)

Wake-to-bed slope and area under the curve were estimated using unadjusted piecewise models.

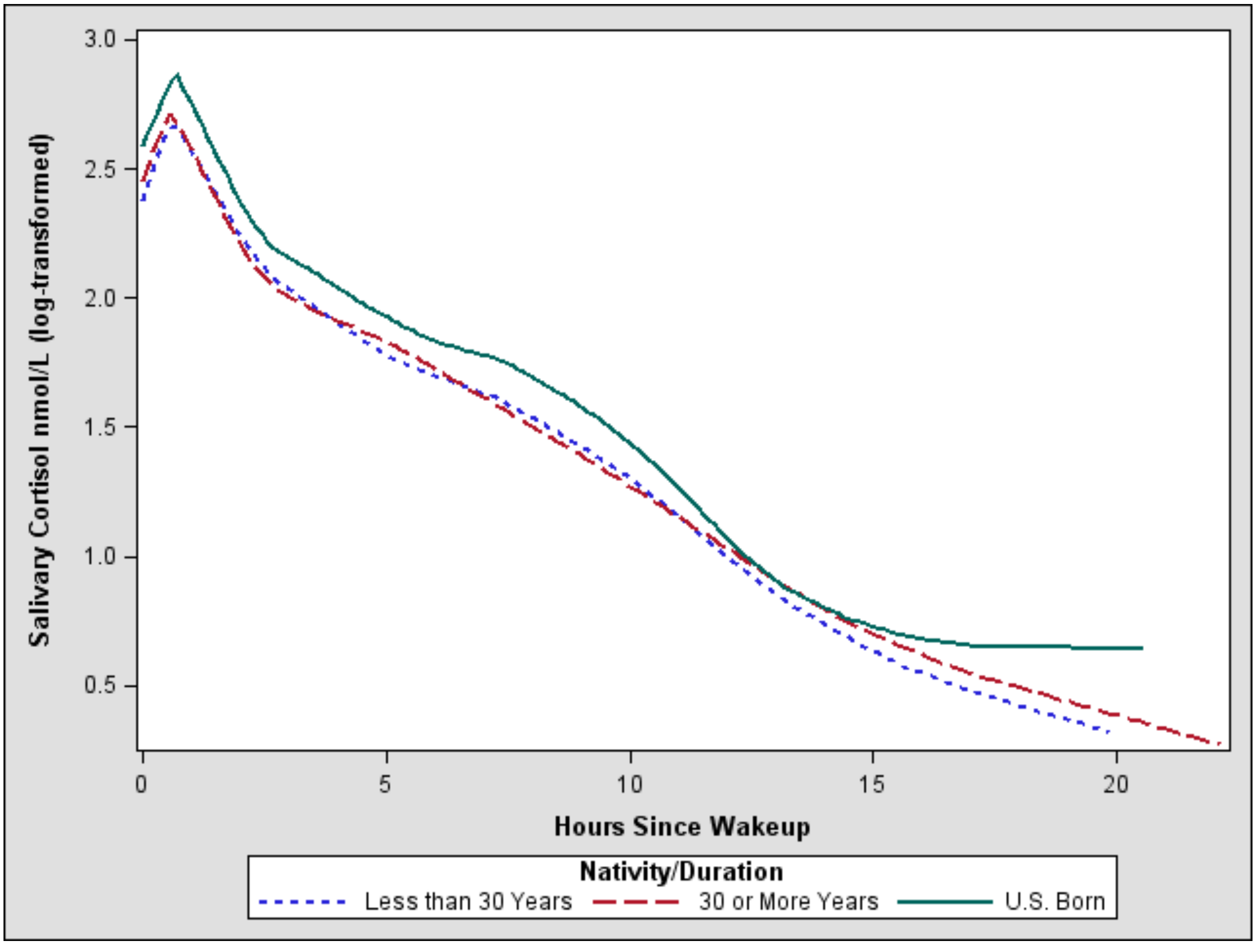

Figure 2-2. Locally estimated scatterplot smoothing (LOESS) curve of diurnal cortisol curves at either Stress I or Stress II, Latino MESA Stress participants included in cross-sectional analysis, by nativity/duration of US residence (n=558).

Table 2-2. Mean (SE) for features of the log cortisol curve by nativity/duration, pooled cross sectional analysis (N persons=558; N days=1983; N samples= 12,724)

	Wake-up level (nmol/L)	Cortisol awakening response (CAR) (nmol/L/hr)	Early decline (nmol/L/hr)	Late decline (nmol/L/8h)	Wake-to-bed slope (nmol/L/8h)	Area under the curve (AUC)
Foreign-born <30 years	2.37 (0.05)	0.71 (0.09)	-0.39 (0.03)	-0.88 (0.03)	-0.89 (0.03)	1.50 (0.04)
Foreign-born 30+ years	2.44 (0.03)	0.65 (0.07)	-0.42 (0.03)	-0.87 (0.03)	-0.90 (0.02)	1.51 (0.03)
US-born	2.55 (0.05)***	0.66 (0.08)	-0.42 (0.03)	-0.91 (0.04)	-0.93 (0.03)	1.61 (0.04)*

s indicate significant difference from foreign-born with <30 years of US residence. (*p<0.01, **p<0.05, * p<0.10)*

Estimates of cortisol features and p-values comparing cortisol features were calculated from unadjusted piecewise models.

We present results of regression models adjusting for all confounders (age, sex, wake-up time and education) in Table 2-3 and include results of other staged models in Table-2-4.

Table 2-3. Percent difference (95% confidence interval) in cortisol associated with nativity/duration for features of the cortisol curve in the pooled cross-section analysis, adjusted for age, sex, wake-up time and education (mean-centered) (*N* persons=558 *N* days=1983; *N* samples= 12724)

	Percent difference at wake-up	Percent difference in CAR (per 1 h)	Percent difference in early decline (per 1 h)	Percent difference in late decline (per 8 h)	Percent difference in wake-to-bed slope (per 8 h)	Percent difference in area under the curve (AUC)
Foreign-born <30 years	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Foreign-born 30+ years	3.88 (-6.96, 15.99)	2.83 (-17.54, 28.24)	0.52 (-7.53, 9.26)	-5.09 (-14.72, 3.74)	-3.43 (-11.29, 3.87)	2.12 (-6.35, 11.36)
US-born	12.56 (-1.69, 28.87)*	-2.65 (-32.8, 20.65)	0.78 (-7.95, 10.34)	-6.27 (-17.61, 3.98)	-5.14 (-14.83, 3.74)	7.21 (-3.7, 19.36)

**$p<0.05$, *$p<0.10$

Table 2-4. Percent difference (95% confidence interval) in cortisol associated with nativity/duration for features of the cortisol curve in the pooled cross-section analysis (*N* persons=558 *N* days=1983; *N* samples= 12724)

	MODEL	Percent difference at wake-up	Percent difference in CAR (per 1 h)	Percent difference in early decline (per 1 h)	Percent difference in late decline (per 8 h)	Percent difference in wake-to-bed slope (per 8 h)	Percent difference in area under the curve (AUC)
Foreign-born <30 years		(Ref.)	(Ref.)	(Ref.)	(Ref.)	(Ref.)	(Ref.)
Foreign-born 30+ years	1	3.82 (-6.92, 15.8)	6.08 (-15.17, 32.65)	-0.52 (-9.33, 7.58)	-5.05 (-14.63, 3.74)	-3.52 (-11.29, 3.71)	2.19 (-6.29, 11.44)
	2	3.88 (-6.96, 15.99)	2.83 (-17.54, 28.24)	0.52 (-7.53, 9.26)	-5.09 (-14.72, 3.74)	-3.43 (-11.29, 3.87)	2.12 (-6.35, 11.36)
	3	2.46 (-8.65, 14.93)	1.33 (-18.97, 26.73)	2.37 (-5.84, 11.29)	-4.86 (-14.59, 4.05)	-2.32 (-10.22, 5.02)	2.73 (-5.88, 12.12)
	4	2.31 (-8.72, 14.67)	-0.44 (-25.76, 19.78)	2.92 (-5.36, 11.91)	-5.09 (-14.77, 3.78)	-2.59 (-10.45, 4.71)	2.27 (-6.16, 11.45)
US-born	1	13.71 (0.29, 28.92)**	4.95 (-18.32, 34.84)	-3.3 (-12.78, 5.38)	-4.91 (-15.47, 4.69)	-5.17 (-14.3, 3.23)	7.32 (-3.09, 18.84)
	2	12.56 (-1.69, 28.87)*	-2.65 (-32.8, 20.65)	0.78 (-7.95, 10.34)	-6.27 (-17.61, 3.98)	-5.14 (-14.83, 3.74)	7.21 (-3.7, 19.36)
	3	8.67 (-6.08, 25.73)	-5.39 (-38.56, 19.83)	5.08 (-4.34, 15.43)	-5.6 (-17.61, 5.17)	-2.34 (-12.51, 6.9)	8.77 (-2.53, 21.38)
	4	10.01 (-4.88, 27.23)	-7.26 (-42.19, 19.09)	5.19 (-4.47, 15.83)	-6.44 (-18.77, 4.61)	-3.34 (-13.73, 6.11)	8.67 (-2.62, 21.27)

**$p<0.05$, *$p<0.10$

MODEL 1: adjusted for age, sex, wake-up time (mean-centered covariates)
MODEL 2: adjusted for covariates in Model 1 as well as education (mean-centered)
MODEL 3: adjusted for covariates in Model 2 as well as income-wealth index (mean-centered)
MODEL 4: adjusted for covariates in Model 3 as well as smoking status, BMI, CESD and physical activity (mean-centered)

Longitudinal results

In the longitudinal analysis (n=248) 52.0% of the sample were male. At Stress 1, 22.6% of the longitudinal sample were foreign born with less than 30 years of US residence, 53.6% were foreign-born with 30 or more years of US residence and 23.8% were US born (Table 2-1). The average time between visits was 6.2 years (SD: 0.7).

For the sample overall, the AUC became larger (1.45 to 1.67 log nmol/L/hr) and the wake-to-bed slope became flatter (–0.98 to –0.86 log nmol/L/8hr) over time (Table 2-5). Participants at Stress II tended to have flatter curves with higher cortisol at every time point (See Figure 2-3 for Stress I and Stress II LOESS curves).

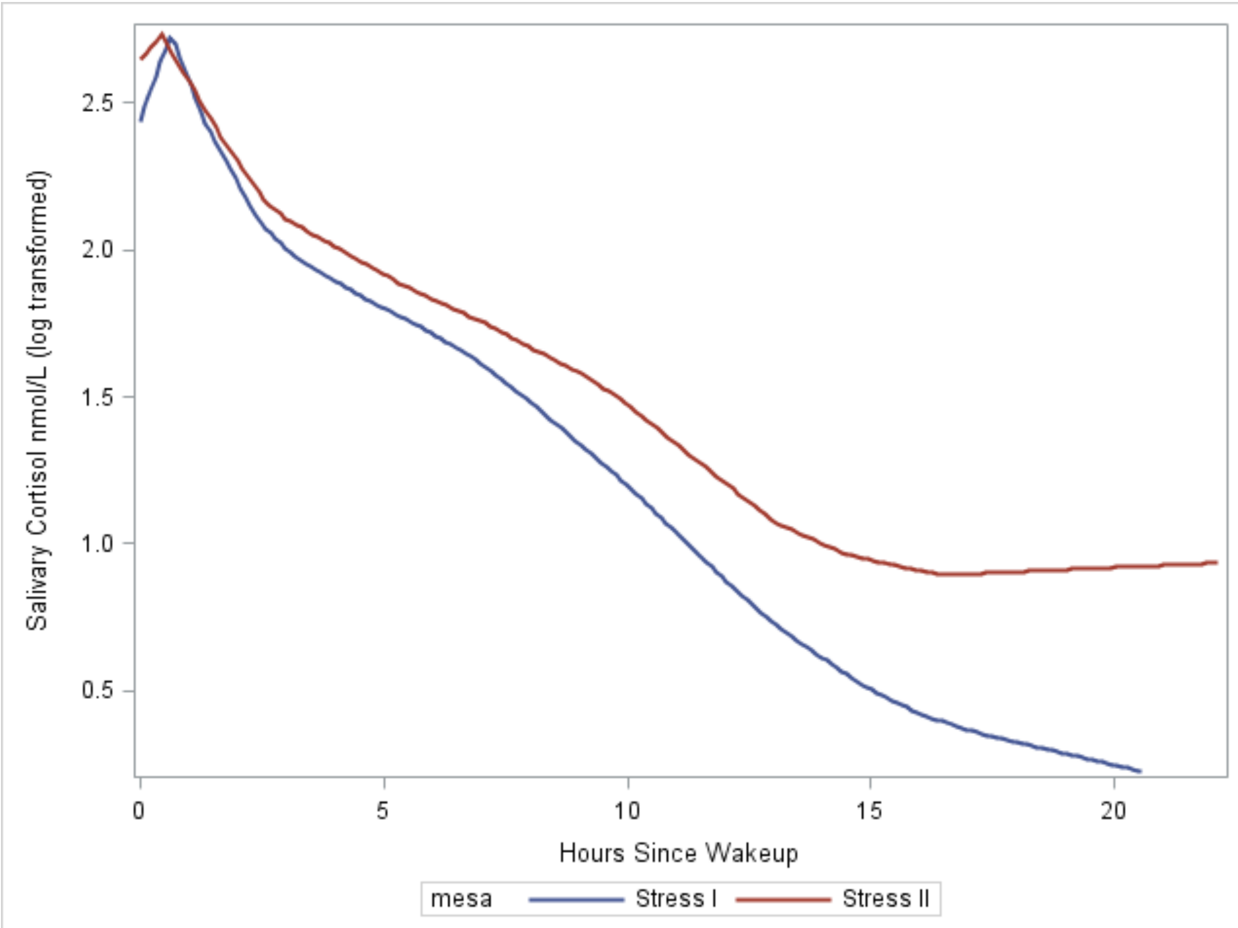

Figure 2-3. Locally estimated scatterplot smoothing (LOESS) curve of log-transformed diurnal cortisol curves at Stress I and Stress II, Latino MESA Stress participants included in longitudinal analysis (n=248).

Descriptive statistics (Table 2-5) and visual examination of LOESS curves by study wave and nativity/duration category (Figure 2-4) indicate that, between Stress I and Stress II, the cortisol awakening response flattened over time but the flattening was smaller for US-born participants (--31.1% change) than for immigrants with fewer than 30 years of US residence (-132.1% change) (Table 2-5). The early decline steepened slightly for US-born participants (-3.9% change) while it became substantially flatter for immigrants with fewer than 30 years of US residence (34.7% change). Similarly, the wake-to-bed slope flattened only slightly for US-born participants (6.3% change) while new immigrants had a more pronounced flattening (17.2%).

Table 2-5. Selected log cortisol features for both waves of the study and percent change in features between waves for the full sample and by categories of nativity/duration (*N* persons=248; *N* days=1195; *N* samples=7847)

Category	No. subj	Study wave	Wake-up level (nmol/L)	Cortisol awakening response (CAR) (nmol/L/hr)	Early decline (nmol/L/hr)	Late decline (nmol/L/8h)	Wake-to-bed slope (nmol/L/8h)	Area under the curve (AUC)
Entire Sample	248	1	2.38	0.92	-0.45	-0.98	-0.98	1.45
	248	2	2.64	0.27	-0.38	-0.77	-0.86	1.67
		% change	30.9%	-91.6%	8.2%	24.1%	12.0%	25.1%
Foreign-born <30 years	56	1	2.25	1.16	-0.52	-0.99	-0.98	1.34
	56	2	2.46	0.32	-0.22	-0.84	-0.82	1.66
		% change	23.5%	-132.1%	34.7%	17.1%	17.2%	39.0%
Foreign-born 30+ years	133	1	2.38	0.94	-0.44	-0.99	-0.98	1.47
	133	2	2.61	0.20	-0.40	-0.72	-0.86	1.60
		% change	26.4%	-109.4%	4.0%	30.7%	12.4%	13.8%
US-born	59	1	2.49	0.67	-0.42	-0.96	-0.97	1.51
	59	2	2.89	0.40	-0.46	-0.80	-0.91	1.85
		% change	49.8%	-31.1%	-3.9%	16.8%	6.3%	40.0%

Cortisol features were calculated from unadjusted piecewise models. Percent change in cortisol features was calculated by including a term for study wave in the piecewise model and converting the coefficient to percent differences.

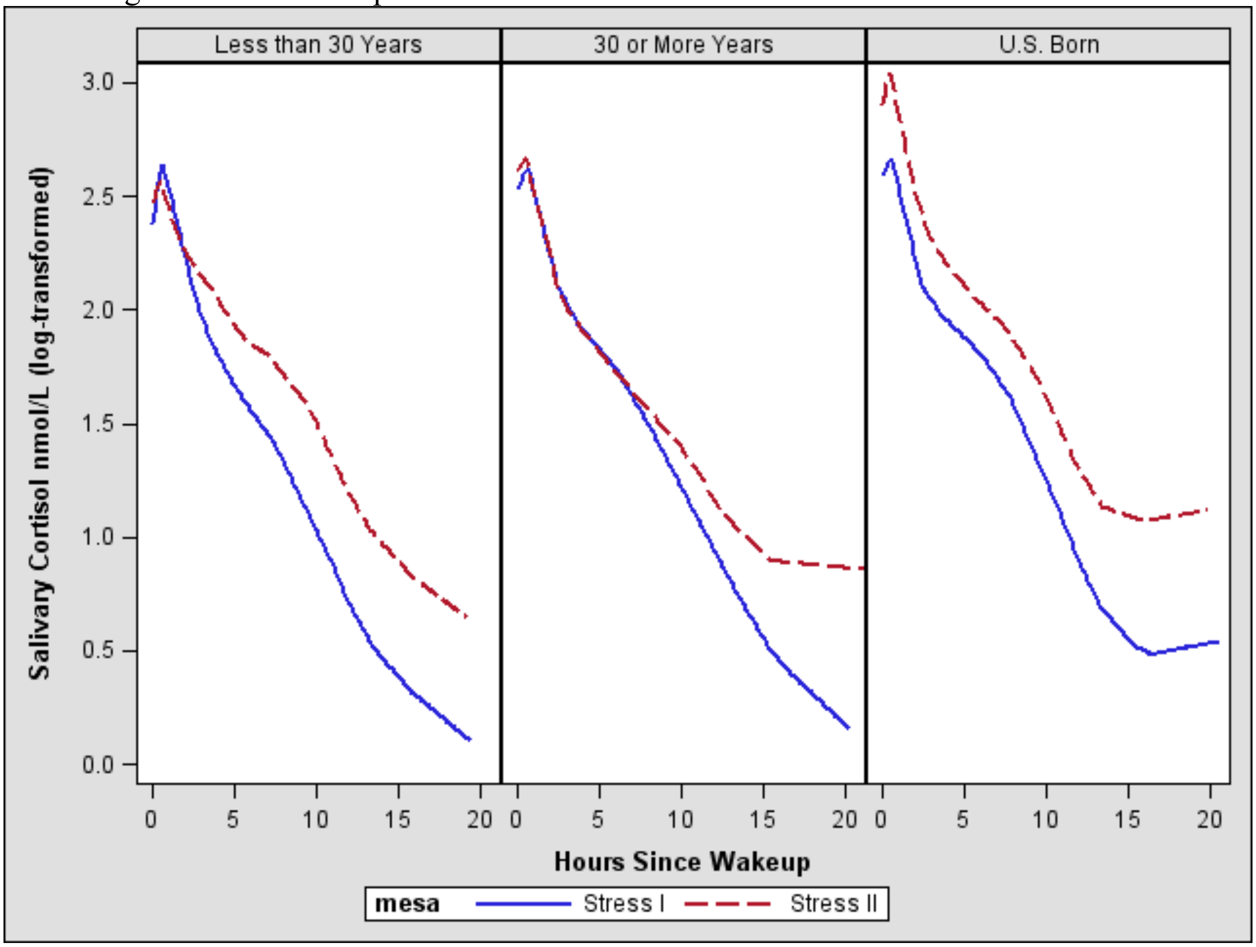

Figure 2-4. Locally estimated scatterplot smoothing (LOESS) curves of logged diurnal cortisol at Stress I and Stress II, by nativity/duration of US residence, among Latino MESA Stress participants included in longitudinal analysis (n=248).

Table 2-6 presents the estimates for the mean 5-year change and the mean differences in 5-year change by nativity/duration for each feature of the log cortisol curve, adjusted for age, sex, wakeup time and education. Other staged models are listed in Table 2-7. The mean differences in 5 year change reflect the deviation from the average 5 year change associated with each nativity/duration category (relative to immigrants with fewer than 30 years of US residence). Overall, the cortisol awakening response flattened between Stress Studies I and II (mean 5 year change: -0.55 log nmol/L/hr, 95% CI -0.95, -0.16), the early decline became flatter (0.23 log nmol/L/8hr, 0.11, 0.35) and total AUC increased (0.20 log nmol/L/8hr, 0.08, 0.32). US-born participants had a greater increase in wake-up cortisol than immigrants with fewer than 30 years of US residence (0.23 nmo/L, -0.03, 0.49). Immigrants with 30 or more years of US tenure and US-born participants had far less flattening of the early decline slope than new immigrants (mean difference in 5 year change: (-0.20 log nmol/L/8hr (95% CI -0.35, -0.05) and -0.24 log nmol/L/8hr (95% CI -0.42, -0.06), respectively) than new immigrants. Immigrants with 30 or more years of US residence had a less pronounced increase in the AUC than new immigrants (mean difference in 5-year change: -0.15 log nmol/L/hr cortisol, (95% CI -0.31, 0.01)).

Adjusting for income-wealth (a mediator) attenuated the increase in wake-up cortisol among the US-born but did not affect any other estimates (Table 2-7). Adjusting for behavioral mediators slightly attenuated the association between US nativity and change in the early decline slope (Table 2-7).

Table 2-6. 5-year changes in selected features of the log cortisol curve and mean differences in 5 year changes by nativity/duration, adjusted for age, sex, wake-up time and education (N persons=248; N days=1195; N samples=7847)

	Wake-up	Cortisol awakening response (CAR) (1 h)	Early decline (1 h)	Late decline (8 h)	Wake-to-bed slope (8 h)	Area under the curve (AUC)
Mean 5-year change	0.10 (-0.09, 0.29)	-0.55 (-0.95, -0.16)**	0.23 (0.11, 0.35)**	0.07 (-0.04, 0.18)	0.09 (-0.02, 0.20)	0.20 (0.08, 0.32)**
Mean differences in 5-year change by nativity/duration						
Foreign-born <30 years	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
Foreign-born 30+ years	0.03 (-0.20, 0.26)	0.03 (-0.45, 0.51)	-0.20 (-0.35, -0.05)**	0.11 (-0.03, 0.24)	-0.03 (-0.15, 0.1)	-0.15 (-0.31, 0.01)*
US-born	0.23 (-0.03, 0.49)*	0.20 (-0.35, 0.75)	-0.24 (-0.42, -0.06)**	0.03 (-0.13, 0.2)	-0.07 (-0.22, 0.07)	0.02 (-0.18, 0.22)

**$p<0.05$, *$p<0.10$

Table 2-7. 5-year changes in selected features of the log cortisol curve and mean differences in 5 year changes by nativity/duration (*N* persons=248; *N* days=1195; *N* samples=7847)

	MODEL	Wake-up	Cortisol awakening response (CAR) (1 h)	Early decline (1 h)	Late decline (8 h)	Wake-to-bed slope (8 h)	Area under the curve (AUC)
5-year change in cortisol features	1	0.10 (-0.08, 0.29)	-0.59 (-0.99, -0.18)**	0.23 (0.11, 0.35)**	0.08 (-0.04, 0.19)	0.09 (-0.02, 0.20)*	0.19 (0.07, 0.31)**
	2	0.10 (-0.09, 0.29)	-0.55 (-0.95, -0.16)**	0.23 (0.11, 0.35)**	0.07 (-0.04, 0.18)	0.09 (-0.02, 0.20)	0.20 (0.08, 0.32)**
	3	0.12 (-0.08, 0.32)	-0.55 (-0.97, -0.13)**	0.23 (0.10, 0.35)**	0.07 (-0.04, 0.18)	0.09 (-0.02, 0.21)	0.22 (0.10, 0.34)**
	4	0.11 (-0.09, 0.31)	-0.52 (-0.94, -0.11)**	0.22 (0.09, 0.35)**	0.06 (-0.06, 0.18)	0.08 (-0.03, 0.2)	0.20 (0.08, 0.32)**
Differences in 5-year change by nativity/duration							
Foreign-born <30 years	1	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)	(Ref)
	2						
	3						
	4						
Foreign-born 30+ years	1	0.02 (-0.21, 0.25)	0.08 (-0.40, 0.57)	-0.2 (-0.35, -0.05)**	0.1 (-0.04, 0.23)	-0.03 (-0.15, 0.09)	-0.14 (-0.3, 0.02)*
	2	0.03 (-0.20, 0.26)	0.03 (-0.45, 0.51)	-0.20 (-0.35, -0.05)**	0.11 (-0.03, 0.24)	-0.03 (-0.15, 0.1)	-0.15 (-0.31, 0.01)*
	3	0.00 (-0.25, 0.24)	0.03 (-0.48, 0.54)	-0.19 (-0.35, -0.04)**	0.11 (-0.03, 0.25)	-0.02 (-0.15, 0.10)	-0.17 (-0.33, -0.01)**
	4	0.01 (-0.24, 0.26)	0.01 (-0.51, 0.52)	-0.17 (-0.33, -0.02)**	0.10 (-0.04, 0.25)	-0.02 (-0.15, 0.11)	-0.15 (-0.32, 0.03)*
US-born	1	0.19 (-0.05, 0.43)	0.37 (-0.16, 0.90)	-0.26 (-0.44, -0.09)**	0.01 (-0.15, 0.17)	-0.08 (-0.21, 0.06)	0.02 (-0.16, 0.2)
	2	0.23 (-0.03, 0.49)*	0.20 (-0.35, 0.75)	-0.24 (-0.42, -0.06)**	0.03 (-0.13, 0.2)	-0.07 (-0.22, 0.07)	0.02 (-0.18, 0.22)
	3	0.15 (-0.16, 0.47)	0.19 (-0.45, 0.83)	-0.23 (-0.42, -0.03)**	0.03 (-0.16, 0.22)	-0.08 (-0.24, 0.09)	-0.04 (-0.25, 0.17)
	4	0.14 (-0.17, 0.45)	0.12 (-0.5, 0.75)	-0.18 (-0.39, 0.02)*	0.02 (-0.17, 0.21)	-0.07 (-0.24, 0.09)	-0.04 (-0.25, 0.17)

MODEL 1: adjusted for age, sex and wake-up time (mean-centered covariates)
MODEL 2: adjusted for covariates in Model 1 as well as education (mean-centered)
MODEL 3: adjusted for covariates in Model 2 as well as income-wealth (mean-centered)
MODEL 4: adjusted for covariates in Model 3 as well as smoking status, BMI, CESD and physical activity (mean-centered covariates)

Discussion

In this study we examined cross-sectional and longitudinal associations between diurnal cortisol and nativity/duration of residence in a sample of US Latinos. We sought to evaluate the hypothesis that chronic alterations to the HPA axis are implicated in the association of US nativity and duration of residence with risk of poor health among Latinos.

Cross-sectional findings

In cross-sectional analysis adjusted for confounders, we found that US-born participants and immigrants with a longer duration of US residence had higher wake-up cortisol than more recently-arrived immigrants. We did not observe significant nativity/duration differences in the cortisol awakening response, the early or late decline, the wake-to-bed slope or the AUC.

Our finding of higher wake-up cortisol among US-born participants was consistent with our hypothesis that we would observe more dysregulated cortisol in this group. Higher wake-up cortisol is generally associated with older age (Karlamangla et al., 2013; Wang et al., 2014) and higher cortisol output throughout the day (Golden et al., 2013), and is also associated with higher risk of depression (Bhagwagar et al., 2005), a condition that affects US-born Latinos at higher rates than immigrant Latinos (Alegria et al., 2007).

However, it is notable that we did not observe any nativity/duration differences in the early or late diurnal decline in cortisol; a flatter decline in cortisol throughout the day has consistently been found to be associated with other stressful exposures such as racial/ethnic minority status (Hajat et al., 2010), low socioeconomic status (Karlamangla et al., 2013), and residence in a stressful neighborhood environment (Do et al., 2011).

Adjusting for income-wealth attenuated the relationship between US nativity and wake-up cortisol because individuals with high income-wealth also tend to have higher wake-up cortisol. A substantial literature has examined income and other SES gradients in health within Latino samples and has typically found smaller health-SES gradients than are found in other racial/ethnic groups (Ranjit et al., 2007; Sánchez-Vaznaugh et al., 2009), and sometimes found nonexistent (Angel et al., 2001) or reversed (Collins et al., 2001; Geronimus et al., 2015) gradients. It has been theorized that the potential health advantages of increasing income are not as beneficial to Latinos (or at least some Latino subgroups) because increasing income comes at the cost of high-effort striving and coping that is in itself detrimental to health (Geronimus et al., 2016; Pearson, 2008) or comes with exposure to a range of other social and racialized stressors that counteract potential health benefits (Gallo et al., 2013).

Longitudinal findings

In our longitudinal analysis we found that participants generally tended to exhibit a decrease in the cortisol awakening response, a flattening of the diurnal decline, and an increase in the AUC, which is consistent with longitudinal patterns observed in the full MESA sample (Wang et al., 2014), although a longitudinal study in a different sample observed no consistent pattern of change in diurnal cortisol curves (DeSantis et al., 2015). Our hypothesis of greater dysregulation of diurnal cortisol among the US-born was confirmed for one cortisol feature: US-born participants had a greater increase in the cortisol awakening response than immigrants with fewer than 30 years of US residence. Contrary to our hypotheses, we generally found that change in diurnal cortisol was less exaggerated among US-born participants and immigrants with longer tenure in the US. US-born participants had a smaller flattening of the early decline relative to more recently-arrived immigrants. Immigrants with longer US residence also had a smaller flattening of the early decline and a smaller increase in the AUC relative to more recent immigrants. Adjusting for the income-wealth index attenuated the association between US nativity and a larger increase in wake-up cortisol, but did not affect either nativity/duration group's estimates for change in the early decline or the AUC.

Although our findings for nativity/duration differences in change in the early decline and AUC were counter to hypothesis that we would observe greater dysregulation over time among US-born participants and immigrants with longer US residence, they do mirror longitudinal findings for Black-White disparities in change in diurnal cortisol. Wang and colleagues found that, like US-born participants in our study, Black adults in MESA had smaller flattening in the CAR over time, and a slower flattening of the early decline when compared to White adults (Wang et al., 2014). Similarly, Latino adults in MESA also had a greater increase in wake-up cortisol (relative to Whites) but Latinos had a faster flattening of the early decline and no difference in the flattening of the CAR (Wang et al., 2014). In the full MESA Stress sample there were no differences in change in the diurnal cortisol curve according to income-wealth index (Wang et al., 2014), but a different study observed a faster flattening of the diurnal cortisol curve for low-income individuals relative to high-income individuals (DeSantis et al., 2015).

A recent study of neighborhood environments and longitudinal change in diurnal cortisol in MESA also encountered counter-intuitive findings, in which individuals exposed to higher neighborhood poverty and lower social cohesion had less pronounced change in the diurnal cortisol curve relative to individuals in more advantaged neighborhoods (Hajat et al., 2015). Given that both of these analyses of MESA data found less pronounced dysregulation in the cortisol curve over time among groups typically found to be at higher risk of poor health, we might speculate that this is because the groups at higher risk experienced substantial dysregulation of the cortisol curve prior to the period of observation in the longitudinal study of a late-middle-age sample. It may be that individuals in the group at lowest risk of poor health (in our study), foreign-born adults with <30 years of US residence, exhibit faster changes in the diurnal cortisol curve because they had less dysregulated curves at the initial data collection, and thus, more room for change.

Limitations

Our sample had very few recently arrived immigrants, which led us to dichotomize duration of residence at 30 years, a higher cutoff than most studies of duration of US residence, many of which have multiple categories of duration of residence and use 10 or 15 years as the highest cutoff (Albrecht et al., 2013; Creighton et al., 2012). We would have chosen a duration of residence cutoff more comparable to other studies of nativity/duration and health if we had a larger sample of recently arrived immigrants. However, studies that examine health gradients at longer durations of US residence continue to observe associations with duration of residence and health outcomes even after 25 (Park et al., 2008) or 30 years of US residence (Moran et al., 2007).

The distribution of Hispanic subgroups included in MESA's Latino sample differs from that of many other studies of US Latinos—it includes more Caribbean Latinos and has a lower proportion of participants from Mexico (although Latinos of Mexican descent still make up over half the sample). Studies have found that many nativity/duration effects are strongest among Latinos of Mexican origin and that nativity/duration gradients can be flatter or reversed in other Hispanic subgroups (Acevedo-Garcia et al., 2007; Borrell and Crawford, 2008). However, other studies have documented nativity/duration effects in the MESA Latino sample (Lutsey et al., 2008), and MESA is currently the richest source of data about diurnal cortisol among US Latinos (Wang et al., 2014).

Salivary cortisol has high random variance over the course of the day and between days. Although MESA's salivary cortisol collection protocol is far richer than other longitudinal studies of diurnal cortisol in adults, which collect fewer samples per day (DeSantis et al., 2015) or collect only one day of cortisol per study wave (Singh-Manoux et al., 2014), the random variation in cortisol becomes even more challenging when examining change in cortisol over time. The early and late decline in cortisol have been found to be relatively stable cortisol features that may provide more useful information about long-term HPA-axis function (trait variation), as opposed to the CAR, which may provide more information about day-to-day changes in HPA axis activity (state variation) (Golden et al., 2013; Ross et al., 2014).

Strengths

MESA's large longitudinal sample provides a unique and rich source of data on diurnal cortisol, both cross-sectionally and longitudinally. Longitudinal data allows us to examine change in HPA function over time, which lends more insight into cumulative aging processes linked to HPA function. Our use of piecewise linear mixed models maximizes efficiency relative to other studies that estimate cortisol features and model each one separately. A recent study illustrated ways that the two-step model used in many other studies of diurnal cortisol artificially deflates confidence intervals by not factoring in the error in estimating each cortisol feature (Rudolph et al., 2016).

Conclusions

Ours is the first study to examine cross-sectional or longitudinal variation in diurnal cortisol according to nativity and duration of US residence in a sample US Latinos in late-middle-age. Although we found some evidence that diurnal cortisol varies by nativity and duration of US-residence, future studies should examine more recently-arrived Latino immigrants and examine changes in diurnal cortisol throughout the life course. We hope to contribute to the growing literature that evaluates the role of chronic stress and its physiological sequelae for US-born and immigrant Latinos.

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CHAPTER 3. **Aim 2: Leukocyte telomere length and nativity/duration of residence in Latinos: The Multi-Ethnic Study of Atherosclerosis**

Introduction

Latino immigrants to the United States (US) tend to have lower risk of mortality and morbidity than US-born Latinos, but this health advantage erodes with increasing duration of residence in the US (Borrell and Crawford, 2009; Lariscy et al., 2015). The pattern of deteriorating health status with increasing length of US residence has been observed across a number of clinical and subclinical indicators of health, particularly markers of cardiovascular (Kershaw et al., 2016, 2012; Lutsey et al., 2008; Moon et al., 2012; Moran et al., 2007) and metabolic (Ahmed et al., 2009; Bates et al., 2008; Sánchez-Vaznaugh et al., 2008) disease. A growing literature hypothesizes that the observed decline in health status with increasing residence in the United States is mediated by chronic stress associated with migration and the cumulative burden of exposure to occupational/economic strain and discrimination faced by many Latino immigrants to the US (Viruell-Fuentes, 2007). The poor health observed among US-born Latinos may be related to family and community connection to the stresses of immigrant life, as well as socioeconomic disadvantage and lifetime experience as a racialized minority in the US (Acevedo-Garcia et al., 2012; Viruell-Fuentes et al., 2012). Over time, exposure to this range of structurally-rooted social and environmental stressors may wear down bodily systems and leave Latino immigrants and US-born Latinos vulnerable to disease.

Nativity- and duration-of-residence-related patterns in Latino health, whereby US-born Latinos have poorer health than immigrant Latinos, and immigrant Latinos with longer tenure in the US have poorer health than new arrivals, are consistent across a wide range of chronic conditions and organ systems (Acevedo-Garcia and Bates, 2008; Kaestner et al., 2009; Peek et al., 2010). The allostatic load model frames this type of multi-system deterioration in health as cumulative "stress-mediated wear-and-tear" resulting from chronic activation of a stress response, which can, over time, have harmful physiologic effects (McEwen, 1998). The weathering hypothesis further roots this concept of the cumulative physiological toll of stress in a broader framework that addresses the dynamic historical and social structural origins of stressors faced by marginalized social groups (Collins et al., 2012; Geronimus et al., 2006; Kaestner et al., 2009; Pearson and Geronimus, 2011). In this framework, advanced "biological age" observed among US-born Latinos and immigrant Latinos with longer duration of US residence may result not only from exposure to material or economic stressors (lower socioeconomic position), but also from stressors related to ethnic identity and experience as a racialized minority in the US (Geronimus et al., 2006; McEwen, 1998; Viruell-Fuentes et al., 2012). These identity-related stressors are identified, appraised, negotiated and coped with not only on an individual level, but also on a community level, and the health implications of exposure these stressors may vary by a person's orientation to the US context and their access to alternative cultural frameworks to interpret experiences of marginalization, discrimination, and "identity threat".

The weathering framework is helpful lens to understand patterns in health among US Latinos, which are often framed as "paradoxical" because the group with the lowest income and occupational status (newly arrived immigrants) tends to have better health outcomes (Acevedo-Garcia and Bates, 2008). From the perspective of weathering, this may not be so surprising: US-born Latinos and Latino immigrants with longer histories in the US not only have a longer lifetime experience of navigating day-to-day stresses of life as a racialized minority in the US, but they also have a greater attunement to the US ethno-racial hierarchy, which may result in greater racism-related vigilance (Hicken et al., 2013), and high-effort coping to navigate these stressors (Viruell-Fuentes, 2011). For example, US-born Latinos and Latino immigrants with longer duration of US residence report higher rates of discrimination than immigrant Latinos, and in a wide range of domains (exclusion/rejection, stigmatization devaluation, discrimination at work or school, threat/aggression and total discrimination) (Arellano-Morales et al., 2015). Furthermore, while US-born Latinos and Latino immigrants may have higher incomes than some new immigrants, they still experience high rates of poverty relative to the rest of the US population (Stepler and Brown, 2015); evidence indicates that an individual's assessment of their low income (as evaluated by subjective social status) varies between immigrant and US-born Latinos, suggesting US-born Latinos may be sensitive to low relative incomes in ways that are not as psychosocially salient for immigrant Latinos (or at least recently arrived immigrant Latinos) (Franzini and Fernandez-Esquer, 2006; Garza et al., 2016).

A number of studies have explored allostatic load or weathering models in Latino samples by using composite indices of physiologic function (biological risk or allostatic load scores) to compare markers of aging according to nativity and duration of US residence (Crimmins et al., 2007; de Castro et al., 2010; Kaestner et al., 2009; Peek et al., 2010; Salazar et al., 2016). Findings from these studies are consistent with theory about a cumulative and multi-system acceleration of aging among US-born Latinos and Latinos with longer duration of US residence; US-born Latinos consistently have the highest (most "aged") allostatic load or biological risk scores, and among immigrant Latinos there is a graded, positive relationship between duration of US residence and allostatic load.

Leukocyte telomere length (LTL), which has been proposed as a biological marker of cellular aging (Der et al., 2012) and exposure to chronic stress (Blackburn and Epel, 2012; Shalev et al., 2013), may serve as a parsimonious marker of patterns of stress-mediated wear and tear on the body for Latino immigrants and US-born Latinos. Telomeres are caps of DNA at the end of chromosomes that protect the chromosome during cellular replication. Telomeres tend to shorten with increasing chronological age (Aubert and Lansdorp, 2008; Frenck et al., 1998), which leads to cellular dysfunction when telomeres become critically short (Effros, 2004; Effros et al., 2005). Shorter LTL has been linked with a number of measures of morbidity (Demissie et al., 2006; Zee et al., 2010) and mortality (Bakaysa et al., 2007; Weischer et al., 2012) even after adjusting for age. Studies have provided some evidence for links between stressful social exposures and shorter LTL (Geronimus et al., 2015; Needham et al., 2013; Puterman et al., 2015), but no study has examined the links between LTL and nativity or duration of residence among Latinos.

This paper uses cross-sectional and longitudinal-data on Latino participants in the Multi-Ethnic Study of Atherosclerosis (MESA) to evaluate LTL as a possible biological mechanism for the declines in health observed among US-born Latinos and Latino immigrants with increasing duration of US residence.

The telomere hypothesis of aging

Shortened LTL is hypothesized to mediate the relationship between stressful exposures and poor health. Telomeres are repeating sequences of noncoding DNA at the end of each chromosome (repeating nucleotides TTAGGG) and serve as buffers to protect genetic material during cell replication. They consist of about 5,000-15,000 base pairs of DNA at the time of birth, but shorten with each successive cell replication (Sanders and Newman, 2013). Although telomere shortening is a normal part of cell replication, when telomeres become critically short the cell becomes senescent, or incapable of replication. Studies have shown that cells in connective tissue (fibroblasts) release pro-inflammatory cytokines as telomeres become critically short, which can in turn cause further cell and tissue damage (Rodier et al., 2009).

Leukocyte telomere length is often used in epidemiologic studies because leukocytes (blood cells) are easier to collect than cells from other tissues. Telomere length in circulating leukocytes reflects telomere length in hematopoietic stem cells, which produce all blood cells (Kimura et al., 2010). Telomere lengths in different tissues are correlated, so leukocyte telomere length provides information about cellular aging in tissues throughout the body (Daniali et al., 2013; Friedrich et al., 2000).

Telomere shortening can be accelerated by biological processes associated with psychosocial stress. Chronic activation of the hypothalamic-pituitary adrenocortical (HPA) axis from psychosocial stress leads to increased secretion of cortisol, a stress hormone, which has been mechanistically linked to telomere shortening (Choi et al., 2008; Tomiyama et al., 2012). Cortisol also contributes to oxidative stress and DNA damage (Aschbacher et al., 2013; Joergensen et al., 2011), which can also lead to telomere shortening (Kawanishi and Oikawa, 2004). Stressful life conditions, such as a heavy caregiving burden or exposure to violence or other histories of trauma and abuse have also been associated with shorter telomere length (Kananen et al., 2010; Litzelman et al., 2014; Oliveira et al., 2016; Tyrka et al., 2010). As such, telomere length has been hypothesized to be a marker of cumulative stress, biologically responsive to both the duration and magnitude of stress an individual has experienced (Blackburn and Epel, 2012; Shalev et al., 2013).

Recent studies have examined change in LTL over time. As expected, LTL tends to shorten with age, although most studies also observe LTL lengthening among some portion of the sample (this is in part due to measurement error, but some telomere lengthening is a real phenomenon) (Steenstrup et al., 2013). Exposure to stressful life events (such as death of a loved one, loss of a job or major financial challenges) has been found to be prospectively associated with LTL shortening (Puterman et al., 2015; van Ockenburg et al., 2015). Studies also observed faster telomere shortening among Black Americans relative to White Americans from birth to middle age (Rewak et al., 2014) and over shorter time periods in adulthood (Aviv et al., 2009), which is consistent with a weathering framework (although some portion of the latter study's differences in LTL attrition were reduced with adjustment for baseline LTL (Aviv et al., 2009)). Longitudinal studies of LTL have highlighted the importance of DNA quality and the precision of LTL measurement. High measurement error in LTL measurement can artifactually exaggerate the appearance of telomere lengthening over time (Bendix et al., 2013; Steenstrup et al., 2013).

Nativity and duration of US residence, stress and LTL

As described above, observed patterns in the health of US Latinos suggest a cumulative deterioration, or "weathering" of health over time and across generations that may correspond to a model of aging consistent with the telomere hypothesis (Geronimus et al., 2006; Kaestner et al., 2009). In this framing, recently arrived Latino immigrants are at the lowest risk of poor health and would be hypothesized to have the longest LTL and slowest rate of LTL shortening, while Latino immigrants with longer duration of US residence and US-born Latinos would be hypothesized to have shorter telomeres and faster LTL shortening.

To date, no studies have specifically examined the relationship between telomere length and nativity or duration of US residence among Latinos. In a study of the relationship between socioeconomic status and LTL using data from the National Health and Nutrition Examination Survey (NHANES), there was no association between foreign-born status and LTL when comparing Mexican immigrants to US-born Mexican-Americans (the model was built to examine ethnicity-specific relationships between LTL and SES; in addition to nativity it adjusted for age, sex, marital status, education and poverty-income ratio) (Needham et al., 2013). However, that analysis did not examine differences in LTL according to duration of US residence among Mexican immigrants.

Nativity duration, socioeconomic status, and LTL

Both nativity/duration of residence and LTL have been linked to socioeconomic status. As mentioned above, among Latinos, US nativity and duration of residence are associated with higher levels of income and lower rates of poverty (Lariscy et al., 2015). The picture for educational attainment is slightly more complex; relative to immigrant Latinos, a higher proportion of US-born Latinos have 12 or more years of education, but a similar proportion of immigrant and US-born Latinos have college diplomas. However, in Latino samples higher SES is not always associated with better health outcomes. Studies in Latino samples typically have typically found smaller health-SES gradients than are found in other racial/ethnic groups (Ranjit et al., 2007; Sánchez-Vaznaugh et al., 2009), and have sometimes found nonexistent (Angel et al., 2001) or reversed (Collins et al., 2001; Geronimus et al., 2015) gradients.

In studies not restricted to Latinos, findings for the association between socioeconomic status and LTL have been mixed, whether using education (Adler et al., 2013; Carroll et al., 2013; Needham et al., 2013; Steptoe et al., 2011), income (Needham et al., 2013), or poverty (Geronimus et al., 2015; Needham et al., 2013; Oliveira et al., 2016). There is evidence that the relationship between SES and LTL varies by race/ethnicity (Geronimus et al., 2015; Needham et al., 2013). In the NHANES study described above, LTL was positively associated with education among White participants but there was no relationship between LTL and education among African Americans or among Mexican Americans (Needham et al., 2013). A recent study evaluating telomere length in a community-based sample in Detroit observed even stronger differences in the relationship between SES an LTL; it found that, among White individuals poverty was associated with shorter LTL, while there was no association between poverty and LTL for Black participants and the association was reversed for individuals of Mexican origin (poverty was associated with *longer* telomeres) (Geronimus et al., 2015).

Given the complex relationships between socioeconomic status, nativity/duration and LTL, we consider socioeconomic status as a potential mediator *or* confounder of the relationship between nativity/duration and LTL.

Nativity/duration, health behaviors and LTL

A number of studies have examined differences in health behavior according to nativity and duration of residence. Latino immigrants tend to have lower rates of smoking than US-born Latinos (Fenelon, 2013). Dietary habits also vary according to nativity and duration of residence, with Latinos with longer tenure in the US consuming more sugary drinks and less fruit. However, changes in diet with increasing US residence are not purely negative; US-born Latinos consume more added dietary fats, but use less animal fat in cooking, leading to the same amount of total fat intake as immigrant Latinos (Ayala et al., 2008). Similarly, physical activity for work or errands decreases with increasing US residence or US nativity, while leisure time physical activity actually increases (Berrigan et al., 2006; Crespo et al., 2001). BMI, which is related to (but not completely determined by) physical activity and diet, is strongly positively associated with duration of US residence and US nativity (Bates et al., 2008; Park et al., 2008; Sánchez-Vaznaugh et al., 2008).

Some health behaviors have been found to be cross-sectionally associated with telomere length, including smoking (Müezzinler et al., 2015; Needham et al., 2012; Strandberg et al., 2011), physical activity (Cherkas et al., 2008; Ludlow et al., 2008; Savela et al., 2013), and body mass index or obesity (which can be related to health behaviors such as diet and physical activity) (Kim et al., 2009; Strandberg et al., 2011; Valdes et al., 20). Findings for health behaviors and longitudinal change in LTL are more mixed, with some studies observing associations between LTL attrition and health behaviors such as smoking or alcohol consumption (Bendix et al., 2013; Huzen et al., 2014), while others do not observe these associations (Ehrlenbach et al., 2009; Müezzinler et al., 2015; Révész et al., 2016; Weischer et al., 2014). Another study found that health behaviors modified the association between exposure to stressful events and 1-year telomere attrition (Puterman et al., 2015).

Because health behaviors have been associated with both nativity/duration and LTL, we evaluate these factors as potential mediators of the relationship between nativity/duration and LTL.

Hypotheses

Given our theoretical frame and existing evidence about nativity/duration of US residence and other measures of stress-mediated biological aging such as allostatic load, we examined the following hypotheses:

Hypothesis 1. Among Latinos, US nativity and longer duration of US residence will be cross-sectionally associated with shorter telomeres relative to immigrants with shorter duration of US residence.

Hypothesis 2. Among Latinos, US nativity and longer duration of US residence will be longitudinally associated with faster telomere shortening relative to immigrants with shorter duration of US residence.

Methods

Data

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal study designed to investigate risk factors for subclinical cardiovascular disease and its progression to clinical disease. From 2000-2002 MESA recruited adults ages 45-84 and free of cardiovascular disease at baseline from six sites across the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN). Latino participants were recruited from three sites: Los Angeles, CA; New York, NY; and St. Paul, MN.

An ancillary study to MESA, the MESA Stress Study, examined the effects of stress on cardiovascular outcomes. Of MESA's 6814 original participants, 1295 MESA Stress participants (547 Latino) from three study sites (New York, Los Angeles and Baltimore) had blood samples analyzed for LTL. Latino participants in MESA Stress were from the New York and Los

Angeles sites. The first sample was collected at MESA Exam 1 (2000-2002) and the second sample was collected at Exam 5 (2010-2012). Twenty-four samples were missing a valid LTL measurement for Exam 1, and 6 participants were missing a LTL sample for Exam 5, leaving 517 participants with valid LTL measurements for both exams.

We excluded 59 samples that had missing data on one or more of: nativity/duration (n=37), poverty-income ratio (n=6) marital status (n=3), pack-years of smoking (n=12), and physical activity (n=6) and were left with 458 persons. Individuals excluded were slightly younger, had higher average physical activity, and more likely to be from the New York study site. There were no significant differences between included and excluded participants in nativity/duration, telomere length, sex, education, poverty-income ratio, BMI or pack-years of smoking. The MESA Stress Study received IRB approval from all participating sites.

LTL

DNA samples were purified from whole blood. LTL (LTL) was measured by quantitative polymerase chain reaction (Q-PCR) in the laboratory of Dr. Elizabeth Blackburn at University of California-San Francisco.(Cawthon, 2002) Telomere length was measured relative to standard reference DNA (T/S ratio), as described in detail elsewhere.(Cawthon, 2002; Lin et al., 2010) Each LTL sample was assayed three times on three different days. The samples were assayed on duplicate wells, resulting in six data points. Sample plates were assayed in groups of three plates, and no two plates were grouped together more than once. Each assay plate contained 96 control wells with eight control DNA. Assay runs with eight or more invalid control wells were excluded from further analysis. No run failed in the analysis of MESA Stress LTL data. Control DNA values were used to normalize between-run variability. The protocol specified that runs with more than 4 control DNAs falling outside 2.5 standard deviations from the mean for all assay runs be excluded from further analysis, but no runs met this criteria. For each sample, any potential outliers were identified and excluded from the calculations (0.2% of samples). The mean and standard deviation of T/S ratio were then calculated normally. The inter-assay coefficient of variation was 2.9% ± 2.1%. For brevity, I refer to T/S ratio and relative telomere length as telomere length or LTL, and change in T/S ratio as LTL shortening or telomere attrition.

Nativity/duration of US residence

For this study place of birth (nativity) is categorized as US-born (born in the 50 US states or DC) or foreign-born/island-born (born outside of the US or in Puerto Rico). Among the foreign-born/island-born (for simplicity we will refer to this group as foreign-born), duration of US residence was categorized as <20 years, 20-40 years, and 40 or more years at the time of MESA Exam I. We selected these cutoffs to capture the range of the duration of US residence variable.

Covariates

We used a directed acyclic graph (DAG) to identify potential confounders of the association between nativity/duration of residence and LTL or telomere attrition (Figure).

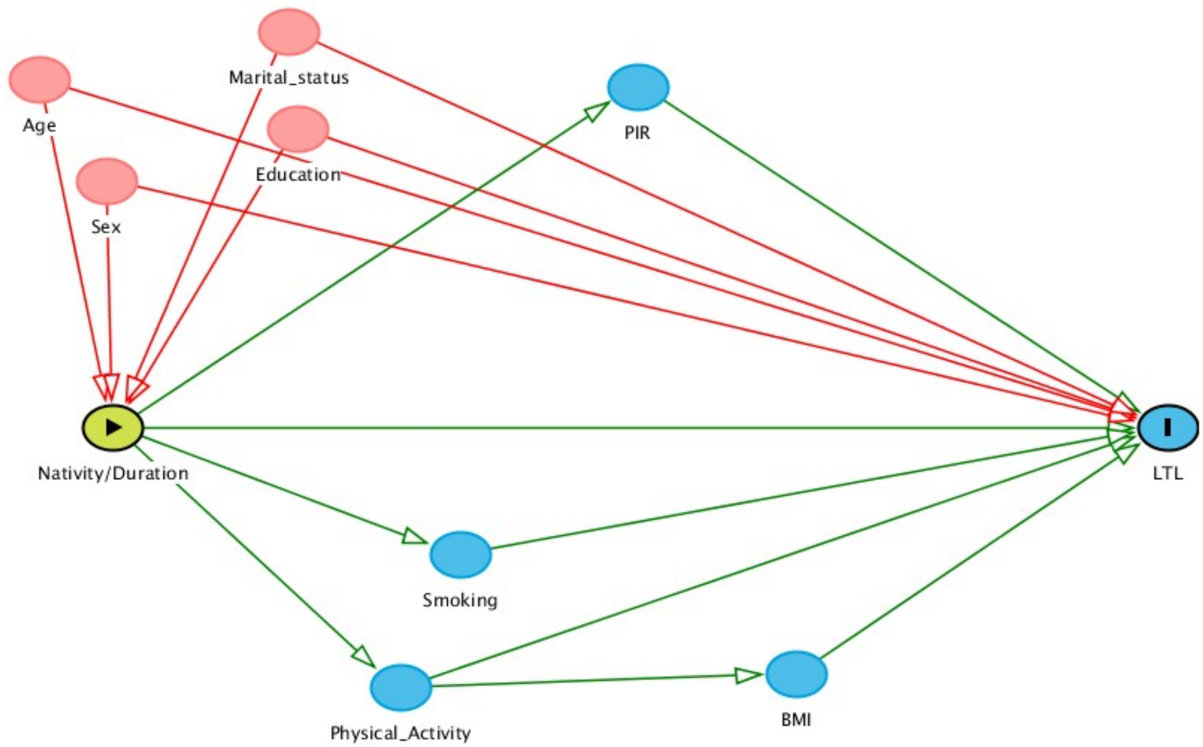

Figure 3-1. Directed Acyclic Graph (DAG) of the hypothesized relationships between nativity/duration of US residence, LTL, and covariates of interest. Confounding variables, which precede both the exposure and the outcome in the causal pathway, are highlighted in red, while mediators, which do not precede the exposure in the causal pathway, are indicated by green arrows.

All models were adjusted for sex and age, as well as an age-squared term to account for potential nonlinearities in the relationship between age and LTL. Age and sex were identified as potential antecedents of duration of residence and nativity because migration histories vary by age and sex.

Education and marital status were identified as potential sociodemographic confounders of the relationship between nativity/duration and LTL. Education is completed prior to migration for most immigrants in MESA (the median age at arrival for immigrant Latinos in MESA is 28; only 25% arrived prior to age 21). Education was categorized as less than 9th grade,

9^{th} grade but less than high school, completed high school, some college, and completed college. Marital status was categorized as married/not married at Exam 1.

The income measure was poverty-income ratio (PIR) which has been used in previous studies of social disparities in LTL (Geronimus et al., 2015; Needham et al., 2013). PIR is calculated as the ratio of income to the poverty threshold for a household of a given size. To calculate PIR we first created a continuous income variable by assigning the midpoint of a participant's income category as their income level, and then divided the continuous measure of income by the 2002 federal poverty threshold for the participant's household size (US Department of Health and Human Services, 2002). We examined PIR as a continuous measure and as a dichotomous measure (poor: PIR<1, nonpoor: PIR≥1) and did not see a difference in findings; we present results using the continuous variable. PIR may be a confounder: among immigrants, duration of residence may reflect membership in different arrival cohorts that have different pre-migration levels of income and wealth (Hamilton et al., 2015). However, it could also be a mediator of nativity/duration effects, whereby longer tenure in the US (or US nativity) is causally related to higher income and asset ownership.

Behavioral covariates include pack-years of smoking, body mass index (BMI), and physical activity. Pack-years of smoking was calculated by multiplying the number of cigarettes smoked per day by reported years of smoking, divided by 20, and categorized as 0 years (never smoked), <30 years, 30-59 years and ≥60 years. BMI was calculated as weight (measured) in kilograms divided by height (measured) in meters squared, and used continuously. Physical activity questions were adapted from the Cross-Cultural Activity Participation Study (Ainsworth et al., 1999). Moderate and vigorous physical activity were measured in metabolic equivalent (MET)-minutes/week and categorized into quartiles for analysis. All covariates (age and age-squared, sex, education category, PIR, pack-years of smoking, BMI, and physical activity quartiles) were mean-centered for ease of interpretation.

Analysis

We begin with descriptive analyses, using t-tests to examine bivariate associations between baseline measures of nativity/duration with telomere length at baseline and change in telomere length.

Cross-sectional analysis

We use data from Exam 1 (baseline) to model the cross-sectional relationship between LTL and nativity/duration of residence with linear models regressing LTL (T/S ratio) on categories of nativity and duration of residence. Immigrants with fewer than 20 years of US residence are the reference group as we hypothesized they would have the longest telomeres. All models adjust for age sex, age, and an age-squared term to account for nonlinear associations between age and LTL. We build nested models to compare the crude model (adjusting for age, age-squared, and sex only) to models that further adjusted for sociodemographic confounders (marital status, education), then income (PIR), and lastly for potential mediators of the relationship between nativity/duration and LTL: health behaviors (pack-years of smoking, BMI and physical activity quartiles).

Longitudinal analysis

We use a linear mixed effects regression model with a term for intra-individual time since Exam 1 (mean-centered and standardized to 10-year change) to examine nativity/duration differences in telomere shortening (change in LTL from Exam 1 to Exam 5). We mean-center each individual's time since Exam 1 to account for potential confounding by time elapsed between Exam 1 and Exam 5, and we use an individual-level random intercept to account for the within-person correlation in LTL. We include exposure categories (nativity/duration) as interactions with the mean-centered time since Exam 1 variable. Immigrants with fewer than 20 years of US residence are again the reference group as we hypothesize that they have the slowest rate of telomere shortening. Parameter estimates from the model are used to estimate the association of the exposure variables (nativity/duration) with change in telomere length between Exam 1 and Exam 5 (standardized to 10-year change). There is debate about whether to adjust for baseline LTL in longitudinal analyses of telomere attrition (Verhulst et al., 2013). We estimate models with and without adjustment for baseline LTL.

We use the same nested modeling approach as the cross-sectional analysis, adding more variables to each subsequent model, including all covariates as interactions with mean-centered time since Exam 1. Measures of education, marital status and PIR corresponded to Exam 1 (they were not time-varying), while behavioral covariates (pack-years of smoking, BMI and physical activity quartiles) were time-varying. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Cross-sectional results

Table 3-1 presents descriptive statistics for the full sample, and by nativity duration, corresponding to Exam 1. The average age at Exam 1 was 60.7 and 37% of the sample was male. About 24% of the sample was US-born, and 76% were foreign-born (13% with <20 years of US residence, 41% with 20-39 years in the US, and 22% with 40 or more years). There were no bivariate differences in LTL between nativity/duration groups at Exam 1 (Table 3-2).

Table 3-1. Descriptive statistics by nativity/duration of residence

	Foreign born <20 years (n=59)		Foreign born 20-39 years (n=189)		Foreign born 40+ years (n=102)		US Born (n=108)		Full sample (n=458)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Age (mean (SD))		58.2 (10.4)		58.6 (8.5)		64.5 (9.1)		62.0 (10.4)		60.7 (9.7)
Male (%)	32%		33%		42%		43%		37%	
Poverty-income ratio		1.63 (0.89)		2.05 (1.55)		2.42 (1.71)		3.22 (1.96)		2.35 (1.71)
PIR<1	29%		27%		15%		10%		21%	
Education (%)										
< 9th grade	49%		39%		25%		4%		29%	
> 9th grade, no diploma	8%		13%		17%		15%		14%	
High school	12%		22%		27%		23%		22%	
Some college	15%		19%		22%		43%		24%	
College	15%		7%		10%		16%		11%	
Married	58%		60%		64%		65%		62%	
Health behaviors at Exam 1										
Pack years smoking										
0 pack years	64%		61%		60%		65%		62%	
<30 pack years	31%		30%		33%		29%		31%	
30-59 pack years	5%		6%		5%		4%		5%	
60+ pack years	--		2%		2%		3%		2%	
Body mass index (mean (SD))		28.2 (3.4)		28.6 (5.1)		29.3 (4.7)		29.9 (6.2)		29.3 (5.7)
Total moderate or vigorous physical activity METS/week (mean (SD))		5662.0 (6113.7)		5149.4 (4401.7)		5268.1 (5283.6)		5890.5 (6255.8)		5416.6 (5304.9)
Study Site (%)										
New York, NY	58%		58%		58%		16%		48%	
Los Angeles, CA	42%		42%		42%		84%		52%	

Table 3-2. Mean (SE) for T/S ratio at Exam 1, by nativity/duration of US residence (n=458)

	Foreign born <20 years (n=59)	Foreign born 20-39 years (n=189)	Foreign born 40+ years (n=102)	US Born (n=108)	Full sample (n=458)
LTL (T/S ratio) at Exam 1	0.916 (0.207)	0.926 (0.209)	0.907 (0.224)	0.924 (0.193)	0.921 (0.207)

In regression models adjusting for age, sex and an age-squared term, we do not observe significant differences in LTL at Exam 1 according to participants' nativity or duration of US residence (Table 3-3, Model 1). After adjustment for sociodemographic confounders, education and marital status, US nativity was marginally associated with longer LTL relative to immigrants with <20 years of US residence (Model 2). Adjustment for poverty-income ratio (Model 3) and health behaviors (Model 4) did not further change the association between nativity/duration and LTL.

Table 3-3. Regression coefficients, association of LTL with nativity/duration at MESA Exam 1 (n=458)

	Model 1 (adjusted for age, age-squared, and sex)		Model 2 (further adjusted for education and marital status)		Model 3 (further adjusted for poverty-income ratio)		Model 4 (further adjusted for health behaviors)	
	Est. (SE)	*p*	Est. (SE)	*p*	Est. (SE)	*p*	Est. (SE)	*p*
Intercept	0.904*** (0.026)	<.001	0.895*** (0.026)	<.001	0.891*** (0.027)	<.001	0.890*** (0.027)	<.001
Nativity/duration (Foreign-born, <20 years)	(ref)		(ref)		(ref)		(ref)	
Foreign-born, 20-39 years	0.011 (0.030)	0.718	0.011 (0.030)	0.724	0.014 (0.030)	0.648	0.015 (0.030)	0.615
Foreign-born, ≥40 years	0.023 (0.034)	0.492	0.035 (0.034)	0.300	0.040 (0.034)	0.240	0.040 (0.034)	0.242
US born	0.031 (0.033)	0.350	0.059* (0.087)	0.087	0.067* (0.035)	0.058	0.065* (0.035)	0.068
Age	0.010 (0.013)	0.443	0.007 (0.073)	0.563	0.008 (0.013)	0.535	0.009 (0.013)	0.508
Age^2	-0.000 (0.000)	0.220	-0.000 (0.000)	0.278	-0.000 (0.000)	0.258	-0.000 (0.000)	0.248
Male (Female)	-0.021 (0.019)	0.276	-0.024 (0.020)	0.235	-0.024 (0.020)	0.240	-0.010 (0.021)	0.637
Married (Not married)			0.018 (0.020)	0.364	0.022 (0.021)	0.279	0.023 (0.021)	0.261
Education (High School)								
< 9^{th} grade			0.047* (0.027)	0.082	0.042 (0.027)	0.125	0.038 (0.028)	0.168
> 9^{th} grade, no diploma			-0.004 (0.032)	0.894	-0.007 (0.032)	0.817	-0.004 (0.032)	0.912
Some college			-0.018	0.525	-0.012	0.671	-0.013	0.651

			(0.028)		(0.028)		(0.028)		
College			-0.077** (0.035)	0.027	-0.065* (0.037)	0.080	-0.065* (0.037)	0.078	
PIR					-0.007 (0.007)	0.283	-0.009 (0.007)	0.204	
Pack years smoking (0 pack years)									
<30 pack years							-0.040 (0.021)	0.061	
30-59 pack years							-0.096 (0.043)	0.029	
60+ pack years							-0.066 (0.070)	0.348	
Physical activity (lowest quartile)									
2nd quartile							0.020 (0.027)	0.457	
3rd quartile							0.007 (0.027)	0.800	
4th quartile							-0.003 (0.028)	0.919	
BMI							-0.000 (0.002)	0.926	

*$p<0.10$; **$p<0.05$;***$p<0.01$;

Model 1 adjusts for age, age^2, and sex

Model 2 further adjusts for marital status, education

Model 3 further adjusts for poverty-income ratio

Model 4 further adjusts for pack-years smoking, physical activity and BMI

Longitudinal results

The mean time between Exam 1 and Exam 5 was 9.5 years (SD 0.4). Average time between exams was slightly longer for immigrants with <20 years of US residence (9.6 years, SD 0.5) and immigrants with 20-40 years of US residence (9.6 years, SD 0.5) relative to those with 40 or more years of residence (9.3 years, SD 0.3) and the US-born (9.4 years, SD 0.5). Relative LTL tended to shorten between Exam 1 and Exam 5 (standardized to 10-year change), by a mean of -0.24 in the full sample (Table 3-). Change in LTL was greater among the US-born (-0.26) relative to immigrants with <20 years of US residence (-0.20) (p=0.05).

Although the general pattern is for LTL to shorten over time, LTL measurements were longer at Exam 5 than at Exam 1 for 9.4% of the sample. LTL lengthening was marginally more common among immigrants with <20 years of US residence (15.3%) than among the US-born (6.5%) (p for chi-square test=0.07).

Table 3-4. Telomere length at Exam 1 and Exam 5 for full sample and by sex, age, and nativity/duration

			Exam 1		**Exam 5**		**10-year Change***		***p for difference***
		N	**MEAN**	**SD**	**MEAN**	**SD**	**MEAN**	**SD**	
All		458	0.92	0.21	0.70	0.14	-0.24	0.19	--
Sex	Female	288	0.93	0.21	0.70	0.14	-0.24	0.18	(ref)
	Male	170	0.91	0.20	0.69	0.14	-0.23	0.21	0.868
Age	45-54	149	0.97	0.21	0.74	0.14	-0.24	0.20	(ref)
	55-64	131	0.94	0.19	0.70	0.13	-0.25	0.18	0.617
	65-74	131	0.89	0.21	0.68	0.14	-0.23	0.20	0.536
	75-84	47	0.80	0.18	0.61	0.12	-0.20	0.19	0.263
Nativity/ duration	FB <20	59	0.92	0.21	0.72	0.14	-0.20	0.19	(ref)
	FB 20_39	189	0.93	0.21	0.71	0.15	-0.23	0.19	0.293
	FB 40+	102	0.90	0.22	0.67	0.13	-0.24	0.21	0.199

	US-Born	108	0.92	0.19	0.68	0.13	-0.26	0.18	0.051

10-year change = 10(TS5-TS1)/Follow-up Years
*follow-up years = Exam 5 visit date – Exam 1 visit date.

Table 3-5 presents estimates for the change between Exam 1 and Exam 5, standardized to change over 10 years. We report the mean 10-year change for immigrants with fewer than 20 years of US residence, and the mean differences in 10-year change according to category of nativity/duration (relative to immigrants with fewer than 20 years of US residence).

Relative to foreign-born participants with fewer than 20 years of US residence, US-born participants had a greater 10-year decrease in LTL (p=0.030) in models adjusting for age, age-squared, and sex (Model 1). These differences were exaggerated in models with adjustment for and education and marital status (Model 2). Further adjustment for PIR (Model 3) and health (Model 4) behaviors did not substantially change estimates. Telomere attrition among immigrants with 40+ years of US residence was slightly greater than attrition among immigrants with 20 or fewer years of residence, but this difference was only marginally significant in models adjusting for confounding by education and marital status (Model 2) (p=0.092).

In models adjusting for baseline telomere length, effect sizes for nativity/duration were slightly attenuated but still statistically significant. We present results adjusted for baseline LTL as a supplementary table (Table 3-6).

Table 3-5. Mean 10-year change in LTL from Exam 1 to Exam 5 and % differences in change by nativity duration (n=458)

		Model 1 (adjusted for age, age-squared and sex)		Model 2 (further adjusted for education and marital status)		Model 3 (further adjusted for poverty-income ratio)		Model 4 (further adjusted for health behaviors)	
		Est. (SE)	*P*	Est. (SE)	*p*	Est. (SE)	*p*	Est. (SE)	*p*
	Intercept	0.809 (0.007)	<0.0001	0.809 (0.007)	<0.0001	0.809 (0.007)	<0.0001	0.809 (0.007)	<0.0001
	10-year change for Foreign-born, <20 years	-0.196 (0.025)	<0.0001	-0.193 (0.025)	<0.0001	-0.192 (0.025)	<0.0001	-0.192 (0.025)	<0.0001
	Difference in LTL attrition by nativity/duration								
	Foreign-born, <20 years	(Ref)		(Ref)		(Ref)		(Ref)	
	Foreign-born, 20-39 years	-0.031 (0.028)	0.262	-0.030 (0.028)	0.292	-0.031 (0.028)	0.279	-0.030 (0.028)	0.277
	Foreign-born, ≥40 years	-0.057 (0.033)	0.088	-0.061 (0.033)	0.067	-0.063 (0.034)	0.063	-0.066 (0.033)	0.046
	US born	-0.065 (0.030)	0.032	-0.076 (0.031)	0.014	-0.078 (0.032)	0.014	-0.073 (0.032)	0.021
Association of covariates with *change* from Exam 1	Age	-0.004 (0.012)	0.735	-0.005 (0.012)	0.699	-0.005 (0.012)	0.687	-0.008 (0.012)	0.516
	Age^2	0.000 (0.000)	0.634	0.000 (0.000)	0.580	0.000 (0.000)	0.566	0.000 (0.000)	0.378
	Male (Female)	0.005 (0.019)	0.786	0.002 (0.019)	0.932	0.002 (0.019)	0.937	0.002 (0.020)	0.906
	Married (Not married)			0.007 (0.013)	0.617	0.005 (0.014)	0.703	0.005 (0.013)	0.724
	Education (High School)								

	< 9th grade			-0.004 (0.018)	0.837	-0.002 (0.018)	0.923	0.005 (0.018)	0.789
	> 9th grade, no diploma			0.038 (0.021)	0.074	0.039 (0.022)	0.069	0.043 (0.022)	0.046
	Some college			0.020 (0.018)	0.290	0.018 (0.019)	0.347	0.016 (0.018)	0.391
	College			0.054 (0.019)	0.004	0.050 (0.019)	0.010	0.041 (0.019)	0.030
	PIR					0.002 (0.004)	0.515	0.001 (0.004)	0.882
	Smoking (0 pack years)								
	<30 pack years							-0.014 (0.014)	0.350
	30-59 pack years							0.018 (0.019)	0.351
	60+ pack years							-0.027 (0.033)	0.419
	Physical activity (lowest quartile)								
	2nd quartile							0.010 (0.016)	0.531
	3rd quartile							0.016 (0.017)	0.375
	4th quartile							0.080 (0.018)	<0.0001
	BMI							0.000 (0.001)	0.973

Model 1 adjusts for age, age^2, and sex
Model 2 further adjusts for marital status, and education
Model 3 further adjusts for poverty-income ratio
Model 4 further adjusts for pack-years smoking, physical activity and BMI

Discussion

Cross-sectional findings

In this study we examined cross-sectional and longitudinal associations between LTL and nativity/duration of residence in a sample of US Latinos. In cross-sectional analysis, we did not observe significant differences in LTL according to nativity/duration, although the trend was in the opposite direction as hypothesized (US-born participants had marginally longer LTL than immigrants with fewer than 20 years of US residence). Adjustment for potential confounders and mediators exaggerated this association.

In this Latino sample we observed a strong cross-sectional inverse association between educational attainment and LTL. This is consistent with findings reported for a small sample of low-income Latina women, where education was inversely associated with LTL (Zota, 2013), and calls to mind Geronimus' finding of a positive association between poverty and LTL among Mexican Americans in Detroit (Geronimus et al., 2015). It is not consistent with findings among Mexican American participants in NHANES (Needham et al., 2013).

Longitudinal findings

In our longitudinal analysis we found that nearly all participants (90.6%) had shortening of telomeres over time. In multivariate regression models, LTL shortening was greater (β (SD)=-0.063 (0.030)) among US-born participants relative to immigrant participants with fewer than 20 years of US residence, which was consistent with our hypotheses. Adjustment for education and marital status exaggerated this association.

There is debate about whether studies of change in LTL over time should adjust for baseline telomere length. Change in telomere length has been strongly associated with baseline telomere length in other studies, although there is some evidence that some portion of this effect is artefactual and due to measurement error and regression to the mean (Verhulst et al., 2013). Furthermore, if an exposure is causally related to a baseline measure, analyses should not adjust for baseline because it is on the causal pathway between the exposure and outcome. However, because baseline LTL has been so strongly predictive of telomere attrition in other studies we did estimate these models as a check on our analyses. Adjustment for baseline telomere length reduced the magnitude of the difference by about one third (from -0.06 to -0.04), but it remained statistically significant (p=0.047). It makes sense that adjustment for baseline telomere length attenuated our longitudinal findings because the group with the largest telomere attrition had the longest telomeres at baseline. However, the fact that the direction of the coefficients remained significant after this adjustment gives us yet more confidence that we may be observing an effect independent of baseline telomere length.

Telomere length changes throughout the life course, and growing evidence suggests that telomere length is particularly affected by exposures in early life, or even in utero (Drury et al., 2012; Tyrka et al., 2010; Wojcicki et al., 2016). Telomere length typically shortens rapidly in the first several years of life, then plateaus until early adulthood, at which point it begins to decrease more steadily in adulthood (Frenck et al., 1998). This complicates our study of telomeres by nativity and history of migration because individuals migrating from different places may have dramatically different early-life exposures. The variety of factors shaping telomere length, especially with the added complication of migration, may explain why we did not observe any cross-sectional differences according to nativity/duration of residence.

Although a large part of variation in telomere length is determined in early life, exposure to stress and differences in health behavior can modify the rate of telomere attrition even in adult life (Puterman et al., 2015). It is possible that the differences we observed in ten-year change in LTL according to nativity/duration of US residence may reflect differences in exposure to stress or available resources to cope with stress.

We did not find that adjustment for health behaviors affected our estimates of the association between nativity/duration of US residence and LTL, longitudinally or cross-sectionally. We may need to consider other health behaviors that have been linked to LTL, such as sleep quality (Puterman et al., 2015) or particular components of diet such as sugar-sweetened beverage or processed meat consumption (Leung et al., 2014; Nettleton et al., 2008). However, it is not uncommon to find that associations between nativity/duration and health persist after adjustment for health behaviors (Crimmins et al., 2007; Kaestner et al., 2009; Salazar et al., 2016).

Limitations

MESA has relatively few recently arrived immigrants, which led us to create duration of residence categories at higher cutoffs than most studies of duration of US residence, many of which examine differences among immigrants with 10 or 15 years of residence (Albrecht et al., 2013; Creighton et al., 2012). We would have chosen a duration of residence cutoff more comparable to other studies of nativity/duration and health if we had a larger sample of recently arrived immigrants. However, studies that examine health gradients at longer durations of US residence continue to observe associations with duration of residence and health outcomes after 25 or 30 years of US residence (Moran et al., 2007; Park et al., 2008).

Strengths

MESA Stress's large longitudinal sample provides a unique source of data on telomere length, with a large sample of Latinos. The coefficient of variation for MESA's LTL assessment is lower than those observed in many longitudinal studies.

Conclusion

Ours is the first study to examine nativity/duration of US residence and LTL among Latinos. Our findings of faster telomere shortening among US-born Latinos and Latinos with longer residence in the US is consistent with a weathering framework, which posits that a range of structurally-rooted environmental and psychosocial stressors accumulate to take a toll on health.

Table 3-6. Mean 10-year change in LTL from Exam 1 to Exam 5 and % differences in change by nativity duration (n=458).

	Model 1 (adjusted for age, age-squared and sex)		Model 2 (further adjusted for education and marital status)		Model 3 (further adjusted for poverty-income ratio)		Model 4 (further adjusted for health behaviors)	
	Est. (SE)	*P*	Est. (SE)	*p*	Est. (SE)	*p*	Est. (SE)	*p*
Intercept	0.809 (0.007)	<0.0001	0.809 (0.007)	<0.0001	0.809 (0.007)	<0.0001	0.809 (0.007)	<0.0001
10-year change for Foreign-born, <20 years	-0.210 (0.016)	<0.0001	-0.211 (0.016)	<0.0001	-0.211 (0.017)	<0.0001	-0.211 (0.016)	<0.0001
Difference in LTL attrition by nativity/duration								
Foreign-born, <20 years								
Foreign-born, 20-39 years	-0.018 (0.018)	0.325	-0.017 (0.019)	0.357	-0.017 (0.019)	0.366	-0.016 (0.018)	0.384
Foreign-born, ≥40 years	-0.036 (0.021)	0.090	-0.036 (0.021)	0.094	-0.035 (0.021)	0.100	-0.037 (0.021)	0.078
US born	-0.040 (0.020)	0.045	-0.040 (0.021)	0.052	-0.040 (0.021)	0.065	-0.037 (0.021)	0.085
Baseline LTL	-0.703 (0.031)	<0.0001	-0.702 (0.032)	<0.0001	-0.702 (0.032)	<0.0001	-0.702 (0.032)	<0.0001

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CHAPTER 4. **Aim 3: Increase in low birth weight among infants born to Latina mothers after a major immigration raid**

Introduction

Investigators theorize that unintended consequences of social policies affecting disadvantaged groups contribute to entrenched US health disparities (Geronimus et al., 2015; Keene and Padilla, 2010; Pearson, 2008; Richman and Hatzenbuehler, 2014; Viruell-Fuentes et al., 2012). A growing literature examines effects of US immigration policy on immigrants (particularly Latino immigrants) (Viruell-Fuentes et al., 2012), documenting links between immigration policy and health care utilization (Beniflah et al., 2013; Rhodes et al., 2015; Toomey et al., 2014; White et al., 2014), Medicaid participation (Vargas, 2015; Watson, 2014), or food insecurity (Potochnick et al., 2016). A smaller, but growing number of studies examine links between immigration enforcement and psychosocial well-being (Hacker et al., 2012, 2011), self-rated health (Lopez et al., 2016) and enforcement-related distress (Lopez et al., 2016; Quiroga et al., 2014; Sabo et al., 2014).

Many existing studies of immigration policy/enforcement and health focus on immigrant (or specifically undocumented-immigrant) samples (Martinez et al., 2013) or examine Latinos regardless of nativity (Beniflah et al., 2013; Lopez et al., 2016; Rhodes et al., 2015). While some studies have documented effects of immigration policy and enforcement on US-born children of immigrants (Dreby, 2015; Watson, 2014; White et al., 2014), far fewer examine implications specifically for co-ethnic US-born adults (Potochnick et al., 2016; Quiroga et al., 2014; Toomey et al., 2014). Although US-born Latinos are not subject to immigration deportation, many are embedded in communities targeted by immigration enforcement (Maldonado, 2014; Viruell-Fuentes, 2007), and may experience discrimination, “othering”(Viruell-Fuentes, 2007) or chronic identity-related vigilance (Geronimus et al., 2016) in response to racialized exclusion (Arellano-Morales et al., 2015; Cobas et al., 2015; Frank et al., 2010; Golash-Boza, 2006; Viruell-Fuentes et al., 2012).

Measuring causal relationships between immigration policy/enforcement and health outcomes has proved challenging: policy changes usually occur after an extended deliberation period that makes exposure classification difficult, and enforcement practices are often diffuse, covert, and occur on a small scale (Maldonado, 2014; Vargas, 2015). In contrast, the 2008 Immigration and Customs Enforcement (ICE) raid on a meat-processing plant in Postville, Iowa was the largest single-site raid yet seen in the US, and occurred without warning, allowing a clear before-and-after comparison.

We compare risk of low birthweight (LBW) and related poor birth outcomes among Latina and non-Latina White mothers in the state of Iowa before and after the Postville raid. LBW is well-suited as a health outcome in this study because birthweight data are publicly available, well-measured, and collected for all births regardless of the mother’s immigration status. Previous studies have documented increased LBW risk after population-level stressors such as terrorist attacks or natural disasters (Camacho, 2008; Eskenazi et al., 2007; Mansour and Rees, 2012; Simeonova, 2011; Torche, 2011) [although some studies report null or mixed findings (Currie and Rossin-Slater, 2013; El-Sayed et al., 2008)].

Economic and demographic commonalities across Latino population clusters in Iowa (many, like Postville, center around meat processing); and social and affective ties between foreign-born and US-born Latinos lead us to hypothesize effects for Latinos across the entire state. We hypothesize that among Iowa births, the association between LBW and birth after the raid will be modified by mother's ethnicity, such that foreign-born and US-born Latina mothers will have higher LBW rates after the raid, while non-Latina White mothers will have no change in LBW. We anticipate that this effect modification will be independent of potential socioeconomic confounders and traditional risk factors for LBW.

Exposure: the Postville raid

The ICE raid on a meat processing plant in Postville, IA on May 12, 2008 was implemented without advance warning to local or state officials. ICE deployed 900 agents using military tactics, including armed officers and a UH-60 Black Hawk helicopter, to arrest 389 employees, 98% of whom were Latino (Rigg, 2011). Agents used presumed race/ethnicity to identify suspected undocumented immigrants, allegedly handcuffing all employees assumed to be Latino until their immigration status was verified (Krogstad, 2008).

Male arrestees were detained at the National Cattle Congress in Waterloo, Iowa (80 miles from Postville), while women were detained in county jails. Mothers of small children were allowed to return to Postville with ankle monitors but, barred from working, survived on charitable aid (Camayd-Freixas, 2008; Rigg, 2011). Detainees were chained together and arraigned in groups of ten for felony charges of aggravated identity theft (knowingly working under a false Social Security Number). A plea bargain led nearly all to plead guilty although few were technically guilty of the crime, and 297 arrestees were deported after serving a 5-month prison sentence (Rigg, 2011).

The raid separated hundreds of families, most often from their primary breadwinner. Fear of follow-up home raids kept many Postville families from staying in their own homes, choosing instead to sleep in church pews or leave town altogether (Camayd-Freixas, 2008). News of the raid immediately spread throughout the state. *La Prensa*, a Spanish-language newspaper in western Iowa, published eyewitness testimony of arrestees detained at a cattle fairground, cuffed and chained together from the waist to the ankles (Lopez, 2008).

Methods

Data

We obtained birth-certificate data for all births in Iowa from 2006-2010 (n=209 389). We classified infants as "exposed" to the post-raid environment if they were born in the 37 weeks following the Postville raid (12 May 2008-26 January 2009), and "unexposed" if they were born in same period one year earlier (12 May 2007-26 January 2008). We chose 37 weeks because it was the minimum length of a normal gestation.

The primary outcome variable, LBW, was defined as birthweight <2500 grams. We used self-reported race and Hispanic ethnicity to categorize mothers as Latina or Non-Latina White, creating a "Latina" category by restricting to mothers in any Hispanic subgroup except Hispanic/Spaniard. We used self-reported birthplace to categorize mothers as US- or foreign-born. Immigration status is not collected in birth-certificate data. We included data on maternal age (<20, 20-25, 26-30, 31-35, 36-40, 41+ years), education (<8th grade, 9^{th}-11^{th} grade, high school diploma/equivalent, some college/Associate's degree, college diploma), marital status (married/unmarried at conception), and parity (first live birth/second or higher). We also divided maternal education into tertiles within strata of ethnicity/nativity. We included data on prenatal maternal smoking (no smoking, <10, 10-19, 20+ cigarettes/day) and prenatal care utilization (Kessner index for adequate, intermediate, and inadequate prenatal care (Kessner et al., n.d.)).

We used a data-cleaning algorithm to create a gestational age (GA) variable, which we categorized into preterm birth (PTB) and categories of GA. We took this step to address previously-reported data quality issues for GA estimation in vulnerable populations, including immigrant, Latina, or low-English-proficient mothers and mothers with late prenatal care initiation (Bengiamin et al., 2010; Dietz et al., 2007; Reichman and Schwartz-Soicher, 2007; Wingate et al., 2007). The algorithm used a LMP-based estimate of GA wherever possible, and the clinical estimate when LMP-based estimate was unavailable or implausible for the infant's birthweight; for more information see Basso and Wilcox (Basso and Wilcox, 2010). PTB was defined as GA <37 weeks. We further categorized GA as very-preterm (<32 weeks), moderate-preterm (32-36 weeks), early-term (37-38 weeks) and full-term (≥39 weeks)(Engle, 2006; Gynecologists, 2013).

We used the cleaned GA variable to estimate stage of gestation at the time of the raid (or the comparison date), classifying infants as not yet conceived, or in the first, second, or third trimester on the date of interest.

We restricted our analysis to singletons born in the 37 weeks following the raid or the same period one year earlier (n=57 850), although we include data from the same period two years earlier (n=26 531) for description. We excluded 4659 infants born to mothers who were not Latina or non-Latina White, and those missing data on birthweight (n=20), GA (n=115), maternal nativity (Latina mothers only, n=11), age (n=2), education (n=332), marital status (n=6), parity (n=256), and prenatal smoking (n=105). Excluded infants (n=847) were more likely to be LBW, both among Latina and non-Latina White mothers. The final sample included 52 344 infants, 25 979 born in the 37 weeks following the Postville raid, and 26 365 born during the same 37-week period one year earlier.

Statistical methods

We used modified Poisson regression (Cummings, 2009) to estimate risk ratios (RRs) comparing risk of LBW among infants born after Postville to those in the comparison period, and used Knol and VanderWeele's recommended methods for presenting analyses of effect modification (Knol and VanderWeele, 2012). This involved presenting: a) RRs for each stratum of maternal ethnicity and birth timing with a single reference category, b) RRs for being born after the raid, stratified on maternal ethnicity, and c) measures of effect modification on the additive scale (relative excess risk due to interaction: RERI), and multiplicative scale (ratio of risk ratios) (Altman and Bland, 2003; Richardson and Kaufman, 2009). We estimated a second set of models with Latina mothers further stratified on nativity.

To confirm that findings were not confounded by changes in the population of mothers, we re-estimated all models, first with adjustments for maternal risk factors for LBW (age, education, marital status and parity). We further adjusted for measured health behaviors that could have mediated changes in LBW after Postville: maternal smoking and prenatal care utilization.

We conducted additional analyses to better understand observed changes in LBW. We stratified our initial models on PTB to evaluate whether shifts in LBW were operating primarily on term or preterm births. We used conditional quantile regression (Abrevaya and Dahl, 2008; Chernozhukov and Fernández-Val, 2011) to analyze the distribution of birthweight among Latinas by exposure period. Quantile regression models the association of the exposure with the full range of the birthweight distribution, not merely above or below the set cutoff of 2500g for LBW (Abrevaya and Dahl, 2008; Liu et al., 2012). Quantiles were specified to evaluate changes in birthweights lower than the 2500g cutoff as well as changes throughout the full distribution of birthweight: the 2^{nd}, 5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th} and 98^{th} percentiles were considered. We estimated the association of birth post-raid with the distribution of birthweight, bootstrapping results 1000 times to estimate standard errors and confidence intervals.

We also examined changes in categories of GA (very-preterm, moderate-preterm, early-term, full-term) before and after the raid, among Latina mothers, using multinomial logistic regression with robust standard errors.

To examine differences in LBW risk according to stage of pregnancy at the time of the raid, we repeated initial analyses with the sample further stratified by stage of gestation at the time of the raid (Carlson, 2015; Class et al., 2011; Torche, 2011). We estimated RRs for LBW after the raid compared to before the raid, by ethnicity and gestational category. To determine whether changes in risk of LBW varied by social position within strata of ethnicity/nativity, we also estimated LBW models stratified on within-group tertiles of education. Analyses were conducted with STATA 13.

Results

Traditional risk factors for LBW varied by maternal ethnicity and nativity; however, within ethnicity/nativity groups the distribution of maternal sociodemographic characteristics remained consistent before and after the raid, as did mean birthweight (Table 4-1). Prior to the raid, Latina and White mothers had similar prevalence of LBW (4.7% for both), which is consistent with other reports of ethnicity-specific LBW risk in Iowa in this period (France et al., 2006; *Natality public-use data 2003-2006, on CDC Wonder Online Database, March 2009.*, n.d.).

Table 4-1. Descriptive statistics by mother's ethnicity/nativity, during the 37 weeks following the Postville raid (12 May '08-26 Jan '09) and during the same time period one year earlier (12 May '07- 26 Jan '08) (n=52,344).

	White		**Foreign-born Latina**		**US-born Latina**	
Time period	*Before raid (n=23 878)*	*After raid (n=23 379)*	*Before raid (n=1689)*	*After raid (n=1746)*	*Before raid (n=798)*	*After raid (n=854)*
Infant sex						
Male	51.3	51.5	50.4	50.2	50.4	48.7
Female	48.7	48.5	49.6	49.7	49.6	51.3
Mother's age						
<20	7.7	7.8	9.9	9.3	27.3	27.3
20-25	32.5	31.1	33.3	33.1	38.5	39.0
26-30	33.2	34.1	27.5	27.7	22.1	20.3
31-35	18.6	18.9	19.7	21.0	8.9	9.4
36-40	6.9	6.9	8.1	7.9	2.9	3.2
41+	1.1	1.1	1.5	1.0	0.4	0.9
Education						
8th grade or less	1.3	1.2	34.2	33.7	2.6	2.9
Some HS education	8.2	8.2	35.5	36.2	33.6	32.4
HS diploma/GED	21.4	20.4	18.1	18.4	31.1	30.8
Some college	38.5	38.8	8.2	7.8	26.2	26.2
College degree+	30.7	31.4	4.1	3.9	6.5	7.6
Maternal marital status						
Mother unmarried	31.3	31.7	44.9	47.0	64.5	56.8
Mother married	68.7	68.3	55.1	53.0	35.5	43.2
Parity						
0 previous	40.0	39.8	28.4	27.8	41.1	40.4
1 or more previous	60.0	60.2	71.5	72.2	59.9	59.6

Prenatal care (Kessner Index)						
Inadequate	2.2	2.2	5.0	4.9	4.8	3.9
Intermediate	7.7	7.7	19.2	17.5	13.4	15.2
Adequate	90.1	90.1	75.7	77.6	81.8	80.9
Smoking in pregnancy						
No smoking	80.0	80.7	98.7	99.1	82.0	87.2
<10 cigarettes/day	10.3	10.2	1.1	0.9	12.7	9.1
10-19 cigarettes/day	7.4	6.9	0.2	0.1	3.6	3.0
20+ cigarettes/day	2.4	2.2	0.1	--	1.8	0.6
Low birthweight	4.7	4.4	4.5	5.6	5.3	6.4
Mean birthweight (g)	3401	3407	3349	3339	3336	3315
Preterm birth	7.5	7.5	7.8	8.0	7.5	8.9

Figure 4-1 displays temporal trends in LBW, by ethnicity and nativity, including the two time periods in the study sample and also extending an additional year earlier (12 May 2006-26 January 2007). Among White mothers, rates of LBW declined slightly (as has been the trend nationwide since 2006) (Martin et al., 2015). Among Latina mothers, rates of LBW were stable in 2006-2007, but rose among US- and foreign-born Latina mothers after the raid.

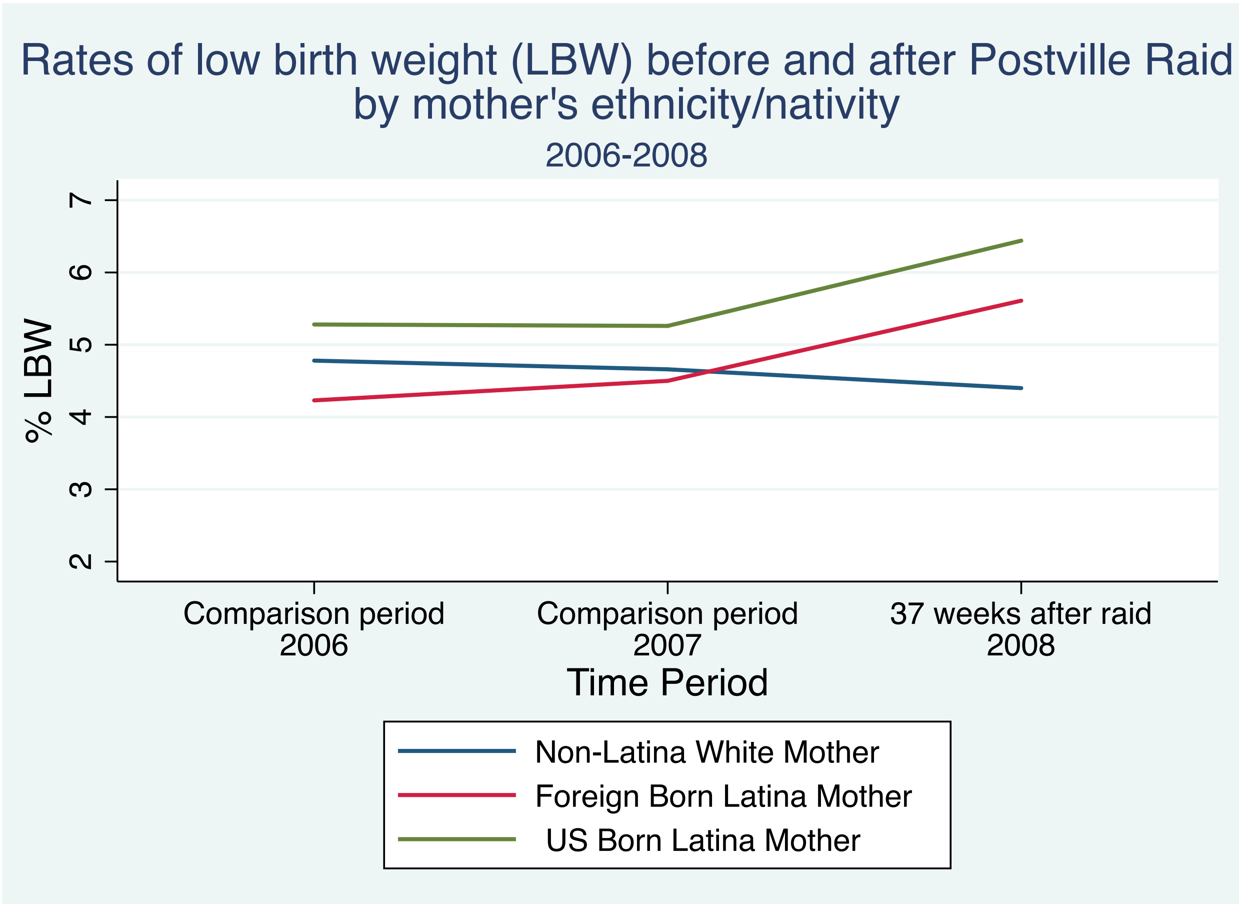

Figure 4-1 Descriptive graph: rates of low birthweight (LBW) in the 37 weeks following the Postville raid compared to the same time period one and two years earlier.

As displayed in Table 4-2, the RRs (95% CIs) comparing risk of LBW after the raid to before the raid were 1.24 (0.98-1.57) among Latina mothers and 0.95 (0.87-1.03) among White mothers. The measure of effect modification on the additive scale, the RERI, was 0.30 (95% CI 0.03-0.57), and the measure of effect modification on the multiplicative scale, the ratio of risk ratios, was 1.31 (1.02-1.68). RRs and effect modification measures were robust to adjustment for potential confounders and mediators (Table 4-7, Table 4-8).

Table 4-2 Modified Poisson regression results for risk of LBW by time period of birth (before/after Postville raid) and mother's ethnicity (White/Latina) (n=52 344).

	Before raid		After raid		RR (95% CI); *P* for after raid vs. before within strata of ethnicity
	***N* LBW/non**	**RR (95% CI); *P***	***N* LBW/non**	**RR (95% CI); *P***	
White mother	1112/22 766	1.0 (Reference)	1029/22 350	0.95 (0.87, 1.03) *P*=0.18	0.95 (0.87, 1.03) *P*=0.18
Latina mother	118/2369	1.02 (0.84, 1.23) *P*=0.84	153/2447	1.31 (1.02, 1.68) *P*= 0.03	1.24 (0.98, 1.57) *P*=0.07

Measure of effect modification on additive scale: RERI (95% CI) = 0.30 (0.03, 0.57); *P*=0.03)
Measure of effect modification on multiplicative scale: ratio of RRs (95% CI): 1.31 (1.02, 1.68); *P*= 0.03
RRs and measures of effect modification are unadjusted

Table 4-3. Modified Poisson regression results for risk of LBW by time period of birth (before/after Postville raid) and mother's ethnicity/nativity (White/Foreign-Born Latina/US-Born Latina) (n=52 344).

	Before raid		After raid		RR (95% CI); *P* for after raid vs. before within strata of ethnicity
	***N* LBW/non**	**RR (95% CI); *P***	***N* LBW/non**	**RR (95% CI); *P***	
White mother	1112/22 766	1.0 (Reference)	1029/22 350	0.95 (0.87, 1.03) *P*=0.18	0.95 (0.87, 1.03) *P*=0.18
Foreign-born Latina mother	76/1613	0.97 (0.77, 1.21) *P*=0.77	98/1648	1.32 (0.97, 1.79) P=0.07	1.25 (0.93, 1.67) P=0.14
US-born Latina mother	42/756	1.13 (0.84, 1.53) *P*=0.42	55/799	1.29 (0.87, 1.93) P=0.20	1.22 (0.83, 1.81) P=0.31

Measure of effect modification on additive scale: RERI (95% CI) =
Foreign-born Latina: 0.29 (-0.03, 0.62); P=0.07
US-born Latina: 0.31 (-0.18, 0.80); P=0.22
Measure of effect modification on multiplicative scale: ratio of RRs (95% CI):
Foreign-born Latina: 1.32 (0.97, 1.79); *P*=0.07
US-born Latina: 1.29 (0.87, 1.93); *P*=0.20

RRs and measures of effect modification are unadjusted.

Table 4-3 displays the same models with Latina mothers further stratified by nativity. Although confidence intervals widen because of the smaller sample in each group, the RRs (95% CIs) for LBW after the raid among foreign-born (1.25, 0.93-1.67) and US-born Latina mothers (1.22, 0.83-1.81) were similar in magnitude to the RR from the pooled model, as are the effect modification measures. Adjustment for potential confounders or mediators did not affect these findings (Table 4-9, Table 4-10).

In models stratified by term/preterm births, LBW was more strongly associated with birth post-raid among term infants born to Latina mothers (RR, 95% CI=1.49, 0.95-2.33) than among preterm infants (1.08, 0.88-1.33) (results not shown).

Multinomial logistic regression comparing categories of GA, by ethnicity, before and after Postville, reveals an elevation in risk of moderate-PTB after the raid among Latina mothers (Relative risk ratio, 95% CI=1.11, 0.89-1.38), but no change in risk of very-PTB (0.81, 0.46-1.41) (Table 4-4).

Table 4-4. Multinomial logistic regression results, categories of gestational age at birth in 37 weeks following Postville raid compared to same period one year earlier, by maternal ethnicity (n=52 344).

Gestational age at birth	**White (n=47907)** **RR (95% CI);** ***P***	**Latina (n=5149)** **RR (95% CI);** ***P***
Full-term (reference) (39+ weeks)	1.00	1.00
Early-term (37-38 weeks)	0.91 (0.87, 0.95) *P*<0.01	0.92 (0.81, 1.04) *P*=0.20
Moderate-preterm (32-36 weeks)	0.97 (0.90, 1.04 *P*=0.39	1.11 (0.89, 1.38) *P*=0.34
Very-preterm (<32 weeks)	0.96 (0.79, 1.17) *P*=0.70	0.81 (0.46, 1.41) *P*=0.45

Quantile regression on the distribution of birthweight indicated that, among Latina mothers, birth post-raid was associated with reduced birthweight only at the left tail of the birthweight distribution, where infants below the 5th percentile of birthweight (corresponding to 2518g before the raid) were 88g lighter after the raid (95% CI -168- -8). Birth post-raid was not associated with differences in birthweight among infants below the 2nd percentile of birthweight, which corresponded to 2084g before the raid (6g heavier, 95% CI -224-236), or at any other point in the birthweight distribution.

Table 4-5. Modified Poisson regression results for risk of LBW by time period of birth (before/after Postville raid) and mother's ethnicity (White/Latina), stratified by stage of gestation at time of Postville raid (n=52 344).

	White mothers	**Latina mothers**	**Measures of effect modification**	
Stage of gestation at time of Postville Raid	**RR (95% CI); *P***	**RR (95% CI); *P***	**Ratio of RRs (95% CI); *P***	**RERI (95% CI); *P***
Not yet conceived n=359	1.12, (0.93, 1.35) *P*=0.24	1.03, (0.65, 1.63) *P*=0.89	0.92, (0.56, 1.52) *P*=0.75	-0.08 (-0.70, 0.54) *P*=0.81
First trimester n=14302	0.89, (0.78, 1.02) *P*=0.10	1.39, (0.97, 1.98) *P*=0.07	1.55, (1.06, 2.27) *P*=0.02	0.49 (0.07, 0.92) *P*=0.02
Second trimester n=23355	0.98, (0.87, 1.11) *P*=0.75	1.12, (0.79, 1.59) *P*=0.54	1.14, (0.79, 1.65) *P*=0.49	0.14 (-0.26, 0.55) *P*=049
Third trimester n=14687	1.00, (0.81, 1.23) *P*=0.98	1.12, (0.58, 2.13) *P*=0.74	1.12, (0.58, 2.16) *P*=0.74	0.12 (-0.58, 0.81) *P*=0.74

In models examining risk of LBW among Latina mothers stratified by stage of gestation at the time of the raid, we found the strongest association between LBW and birth post-raid among mothers in the first trimester at the time of the raid (RR, 95% CI=1.39, 0.97-1.98) (Table 4-5). In LBW models stratified by within-group tertiles of education we observed the strongest association between LBW and birth post-raid in the lower two tertiles of education for both immigrant and US-born Latina mothers (Table 4-6).

Table 4-6. Modified Poisson regression results for risk of LBW by time period of birth (before/after Postville raid) and mother's ethnicity and nativity, stratified by approximate within-group tertiles of education (n=52 344).

Non-Latina White mothers (n=47257)		**Foreign-born Latina mothers (n=3435)**		**US-born Latina mothers (n=1652)**	
Within-group tertiles of education (n)	**RR for birth after Postville Raid**	**Within-group tertiles of education (n)**	**RR for birth after Postville Raid**	**Within-group tertiles of education (n)**	**RR for birth after Postville Raid**
High school diploma n=14334	0.95 (0.83, 1.08)	(Less than 8th grade) n=1165	1.42 (0.90, 2.25)	(Less than high school) n=591	1.18 (0.68, 2.06)
Associate's Degree or some college n=18261	0.98 (0.86, 1.12)	(Some High School) n=1232	1.40 (0.84, 2.35)	(High school diploma) n=511	1.48 (0.78, 2.83)
College diploma or higher n=14662	0.91 (0.76, 1.09)	High school or greater n=1038	0.89 (0.51, 1.57)	Some college or greater) n=550	0.90 (0.32, 2.54)

Discussion

We used the Postville raid, a large-scale immigration raid implemented without warning, as a quasi-experiment to investigate the health effects of immigration enforcement among Latina mothers in a Midwestern state. We found that rates of LBW were steady among White and Latina mothers in the two years preceding the raid, but that rates of LBW rose only among Latina mothers after the raid. The association between birth post-raid and LBW was modified by maternal ethnicity on both the additive (RERI > 0) and multiplicative scales (ratio of RRs > 1). This association was evident among both foreign-born and US-born Latina mothers and persisted after adjustment for maternal risk factors, maternal smoking and prenatal care utilization.

Comparing births after Postville to births in the same period one year earlier accounted for seasonality in birth outcomes and avoided the "mechanical correlation" between pregnancy duration and risk of exposure to stressful events, a methodological pitfall in studies using the time period immediately preceding an event as the comparison period (Currie and Rossin-Slater, 2013).

Our examination of births in the entire state of Iowa makes this a conservative analysis. Previous studies have examined dose-response relationships based on geographic distance from a natural disaster or attack (Currie and Rossin-Slater, 2013; Eskenazi et al., 2007), but we do not have reason to believe that stressors resulting from Postville raid would emanate in this way. Many Latino communities in Iowa are economically similar to Postville, and communication networks between communities make it plausible that Latinos across the state would feel connected to an enforcement event targeted at a single workplace. Lauderdale's finding of increased LBW among Arabic-named mothers in California after the attacks of September 11, 2001 (in NYC) lends plausibility to the view that social identity threats can affect co-ethnics at remote distances.

LBW risk increased most among Latina mothers with lower educational attainment (less than high school for the foreign-born, and less than college for the US-born). This could be because low-educated mothers were more vulnerable to the economic and psychosocial fallout of the raid or had fewer coping resources. Reports from throughout Iowa after the Postville raid include evidence of individuals and families preparing for the possibility of further immigration enforcement (Christensen, 2008; Jacobs and Perkins, 2008; Lopez, 2008; Toopes, 2008), avoiding public space ("90 miles away, Postville raid's impact is still being felt," 2008; Jacobs and Perkins, 2008), restricting spending ("90 miles away, Postville raid's impact is still being felt," 2008; Burns, 2008), losing income or economic security due to changing employment practices (Jackson, 2008; Jones, 2012; Larsen, 2008; Saul, 2008; Toopes, 2008), and experiencing increased discrimination, stereotype threat, or racialized exclusion as public discourse frequently conflated Latino/Hispanic phenotype with undocumented status (Krogstad, 2008; Saul, 2008). These reports align with findings from a recent quasi-experimental study in Michigan: after a local immigration raid led to several arrests and deportations, Latinos were more likely to report that they feared the consequences of deportation, and that their immigration status impeded social relationships (Lopez et al., 2016). In the wake of the Postville raid, similar restrictions in social support and increases in day-to-day fear may have coalesced to increase psychosocial stress and reduce coping resources.

Quantile regression indicated that the higher risk of LBW among Latina mothers after Postville resulted from decreased birthweight at the left tail of the distribution, not a shift in mean birthweight. This is similar to Lauderdale's findings for ethnicity-specific change in birthweight after 9/11 (Lauderdale, 2006). Lower birthweights at the left tail of the birthweight distribution are more likely to be associated with infant mortality than a leftward shift of the entire distribution (Lauderdale, 2006; Wilcox, 2001).

We found that the increases in LBW were greatest among term births, but that there was also a higher prevalence of moderate-preterm (not very-preterm) infants after the raid. Previous studies of psychosocial stressors and birth outcomes have found that LBW increased both through increased PTB (Carlson, 2015; Torche, 2011) and through intrauterine growth restriction (Eiríksdóttir et al., 2013; Margerison-Zilko et al., 2011); it appears that both mechanisms operated in Iowa, which is plausible given the diversity of pathways (economic, psychosocial) by which the raid may have affected Latina mothers.

Post-raid increases in LBW risk were greatest for Latina mothers in the first trimester of gestation at the time of the raid. Several other studies have also found stronger effects among first-trimester exposures (Camacho, 2008; Mansour and Rees, 2012; Torche, 2011; Zhu et al., 2010), but others have not (Carlson, 2015; Class et al., 2011; Currie and Rossin-Slater, 2013; Simeonova, 2011). Our finding in Iowa could suggest that early-gestation infants were more vulnerable, or it may be that those infants were simply exposed to the post-raid environment for a larger proportion of gestation.

Several complex immune, inflammatory and endocrine pathways are proposed to link psychosocial stressors and birthweight. One hypothesis is that maternal psychosocial stress disrupts the balance between maternal glucocorticoid levels and 11 beta-hydroxysteroid dehydrogenase type 2 (HSD2), an enzyme that metabolizes cortisol into inactive cortisone (O'Donnell et al., 2012; Reynolds, 2013). Placental HSD2 typically upregulates in tandem with serum glucocorticoid levels during gestation, protecting the fetus from 80-90% of circulating maternal glucocorticoids (Benediktsson et al., 1997). However, psychosocial stress and disruption of maternal emotional support have been linked to both higher prenatal glucocorticoid concentrations and lower placental HSD2 (Graignic-Philippe et al., 2014; La Marca-Ghaemmaghami et al., 2013; O'Donnell et al., 2012; Reynolds et al., 2015), both of which are linked to LBW (Baibazarova et al., 2013; Benediktsson et al., 1997; Bolten et al., 2011; Cottrell and Seckl, 2009; Guardino et al., 2016; McTernan et al., 2001). The psychosocial, economic, communal and identity-based stressors activated by the Postville raid may have interfered with Latina mothers' neuroendocrine balance and coping resources, leaving infants vulnerable to a dysregulated endocrine environment.

Limitations

If healthy pregnant Latinas left Iowa after Postville, increased LBW among Latinas might reflect selection effects. However, analyzing Census data (Ruggles et al., 2015), we found no evidence that the raid was associated with a change in the size of Iowa's Latino population, overall or among women of reproductive age. And, as noted, we found no difference in demographic characteristics among Latinas mothers before or after the raid.

There is random year-to-year variation in LBW prevalence, especially in small populations, which raises concerns that the observed increase in LBW among Latina mothers was a chance finding. We do not have access to birth microdata pre-2006, but we used publicly-available data (*Natality public-use data 2003-2006, on CDC Wonder Online Database, March 2009.*, n.d.) to calculate crude LBW prevalences among singleton births to non-Hispanic White and Hispanic mothers during May-January for the 5 years preceding and following the raid. LBW prevalence among infants born to Hispanic mothers is higher from May 2008-January 2009 than in any other May-January period from 2003-2013 (Figure 4-2).

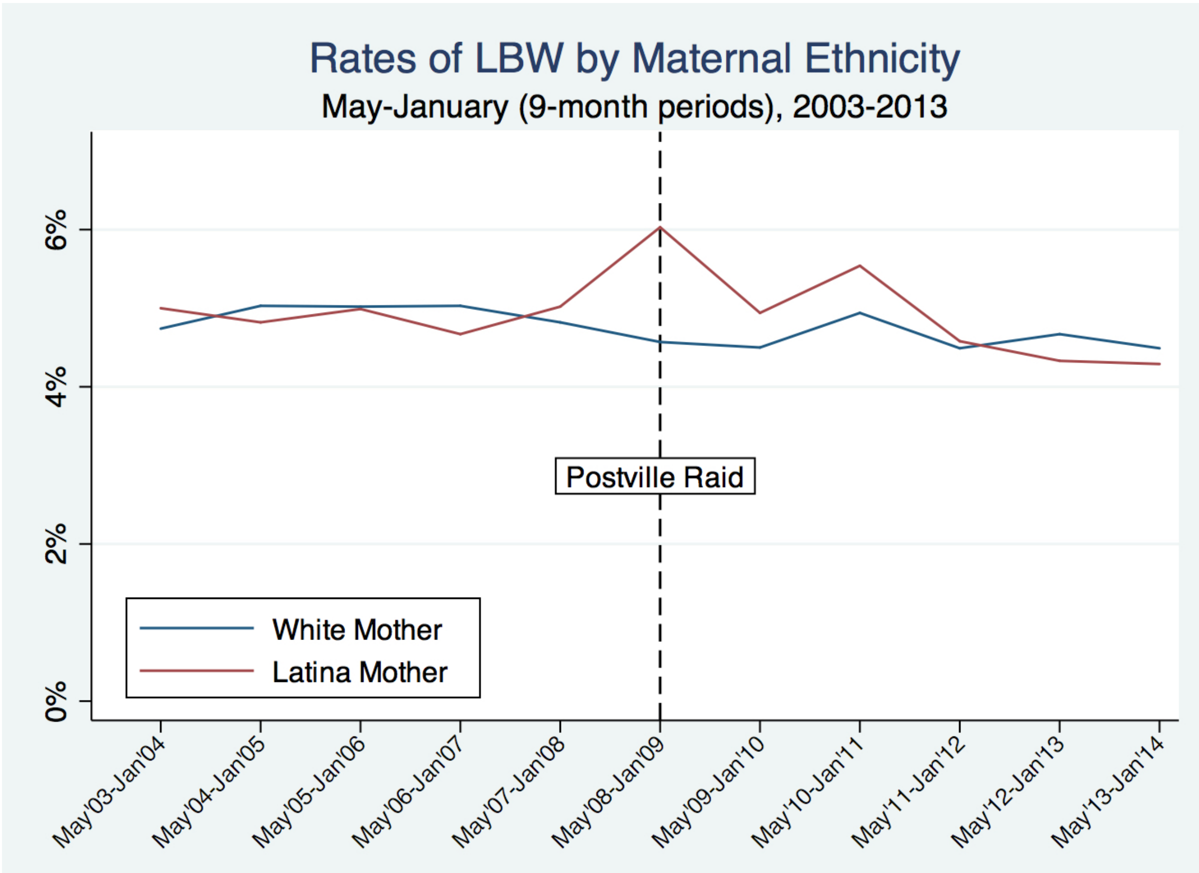

Figure 4-2. Descriptive graph: rates of low birthweight (LBW) among singleton births in the 9 months following the Postville raid (May 2008-January 2009) compared to the same 9-month periods in the 5 years preceding and the 5 years following.

Birth-certificate data for birthweight, maternal ethnicity and maternal birthplace have high validity relative to medical records (Baumeister et al., 2000; Buescher et al., 1993; DiGiuseppe et al., 2002; Northam and Knapp, 2006). However, data on GA are of lower quality (DiGiuseppe et al., 2002), particularly for Latina and non-English-proficient mothers (Dietz et al., 2007; Wingate et al., 2007), which affects our classification of PTB and stage of gestation at the time of the raid. We used a data-cleaning algorithm to mitigate data-quality issues, but this entails several assumptions (Parker and Schoendorf, 2002), and while it is unlikely that remaining misclassification of GA differs by raid timing, even non-differential misclassification may have biased findings for PTB and stage of gestation towards the null. Birth-certificate data for our hypothesized mediators, prenatal smoking and prenatal care, are also of lower quality (Buescher et al., 1993; DiGiuseppe et al., 2002; Northam and Knapp, 2006), which reduces our ability to observe mediation by changed health behaviors.

Conclusions

Our findings are consistent with studies observing changes in LBW risk after a major population-level stressor (Carlson, 2015; Eskenazi et al., 2007; Lauderdale, 2006; Torche, 2011), and contribute to literature on racialized stressors and ethnicity-specific birth outcomes (El-Sayed et al., 2008; Lauderdale, 2006). We extend the literature on immigration policy/enforcement and health by specifically examining a physical outcome and by examining both immigrant and US-born Latinos.

The Postville raid was an extreme example of diffuse and pervasive racialized economic and psychosocial stressors that Latinos face throughout the US. The scale and temporality of this event created conditions that lend insight into the pervasive effects of these stressors, which are often difficult to measure. Exclusive immigration policies and their militarized enforcement exacerbate the racialized exclusion of Latinos in the US, which may contribute to a cumulative health burden for immigrant and US-born Latinos alike.

Table 4-7. Modified Poisson regression results for risk of LBW by time period of birth (before/after Postville raid) and mother's ethnicity (White/Latina) (n=52 344)

	Before raid		**After raid**		**RR (95% CI); *P* for after raid vs. before within strata of ethnicity**
	***N* LBW/non**	**RR (95% CI); *P***	***N* LBW/non**	**RR (95% CI); *P***	
White mother	1112/22 766	1.0 (Reference)	1029/22 350	0.95 (0.87, 1.03) *P*=0.19	0.95 (0.87, 1.03) *P*=0.19
Latina mother	118/2369	0.80 (0.66, 0.97) *P*=0.02	153/2447	1.32 (1.03, 1.69) *P*= 0.03	1.25 (0.99, 1.58) *P*=0.06

Measure of effect modification on additive scale: RERI (95% CI) = 0.25 (0.03, 0.47); *P*=0.03)
Measure of effect modification on multiplicative scale: ratio of RRs (95% CI): 1.32 (1.03, 1.69); *P*= 0.03
RRs are adjusted for maternal age, education, marital status and parity

Table 4-8. Modified Poisson regression results for risk of LBW by time period of birth (before/after Postville raid) and mother's ethnicity/nativity (White/Foreign-Born Latina/US-Born Latina) (n=52 344)

	Before raid		**After raid**		**RR (95% CI); *P* for after raid vs. before within strata of ethnicity**
	***N* LBW/non**	**RR (95% CI); *P***	***N* LBW/non**	**RR (95% CI); *P***	
White mother	1112/22 766	1.0 (Reference)	1029/22 350	0.95 (0.87, 1.03) *P*=0.19	0.95 (0.87, 1.03) *P*=0.19
Foreign-born Latina mother	76/1613	0.74 (0.58, 0.94) *P*=0.01	98/1648	1.32 (0.97, 1.78) P=0.08	1.26 (0.94, 1.68) P=0.12
US-born Latina mother	42/756	0.90 (0.66, 1.21) *P*=0.48	55/799	1.32 (0.89, 1.96) P=0.19	1.24 (0.84, 1.82) P=0.28

Measure of effect modification on additive scale: RERI (95% CI) =
Foreign-born Latina: 0.23 (-0.02, 0.48); P=0.07
US-born Latina: 0.28 (-0.12, 0.67); P=0.17
Measure of effect modification on multiplicative scale: ratio of RRs (95% CI):
Foreign-born Latina: 1.33 (0.98, 1.80); *P*=0.06
US-born Latina: 1.31 (0.88, 1.94); *P*=0.18
RRs are adjusted for maternal age, education, marital status and parity

Table 4-9. Modified Poisson regression results for risk of LBW by time period of birth (before/after Postville raid) and mother's ethnicity (White/Latina) (n=52 344)

	Before raid		**After raid**		**RR (95% CI); *P* for after raid vs. before within strata of ethnicity**
	***N* LBW/non**	**RR (95% CI); *P***	***N* LBW/non**	**RR (95% CI); *P***	
White mother	1112/22 766	1.0 (Reference)	1029/22 350	0.95 (0.87, 1.03) *P*=0.22	0.95 (0.87, 1.03) *P*=0.22
Latina mother	118/2369	0.99 (0.82, 1.20) *P*=0.92	153/2447	1.34 (1.05, 1.71) *P*= 0.02	1.27 (1.01, 1.61) *P*=0.04

Measure of effect modification on additive scale: RERI (95% CI) = 0.32 (0.05, 0.59); *P*=0.02)
Measure of effect modification on multiplicative scale: ratio of RRs (95% CI): 1.34 (1.05, 1.72); *P*= 0.02
RRs are adjusted for maternal age, education, marital status, parity, maternal smoking and prenatal care utilization.

Table 4-10. Modified Poisson regression results for risk of LBW by time period of birth (before/after Postville raid) and mother's ethnicity/nativity (White/Foreign-Born Latina/US-Born Latina) (n=52 344)

	Before raid		**After raid**		**RR (95% CI); *P* for after raid vs. before within strata of ethnicity**
	***N* LBW/non**	**RR (95% CI); *P***	***N* LBW/non**	**RR (95% CI); *P***	
White mother	1112/22 766	1.0 (Reference)	1029/22 350	0.95 (0.87, 1.03) *P*=0.22	0.95 (0.87, 1.03) *P*=0.22
Foreign-born Latina mother	76/1613	0.98 (0.77, 1.25) *P*=0.87	98/1648	1.32 (0.98, 1.79) P=0.07	1.27 (0.95, 1.69) P=0.11
US-born Latina mother	42/756	1.00 (0.74, 1.35) *P*=0.87	55/799	1.37 (0.92, 2.02) P=0.12	1.29 (0.88, 1.90) P=0.20

Measure of effect modification on additive scale: RERI (95% CI) =
Foreign-born Latina: 0.30 (-0.02, 0.63); P=0.07
US-born Latina: 0.35 (-0.10, 0.79); P=0.13
Measure of effect modification on multiplicative scale: ratio of RRs (95% CI):
Foreign-born Latina: 1.33 (0.99, 1.80); *P*=0.06
US-born Latina: 1.36 (0.91, 2.01); *P*=0.13
RRs are adjusted for maternal age, education, marital status, parity, maternal smoking and prenatal care utilization.

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CHAPTER 5. **Conclusions**

In this dissertation I sought to fill a gap in the public health literature about biological mechanisms that link stressful life circumstances and risk of poor health among US Latinos.

Review of findings

Nativity/duration and diurnal cortisol (Chapter 2)

In Chapter 2, I examined cross-sectional and longitudinal associations between nativity and duration of US residence and diurnal cortisol curves. Diurnal cortisol is a marker of the function of the hypothalamic-pituitary-adrenocortical (HPA) axis, a component of the body's response to psychosocial stress. We saw limited evidence that Latinos with the greatest "exposure to the US" (US-born Latinos) had a more dysregulated diurnal cortisol curve than Latinos with the least exposure to the US (immigrants with fewer than 30 years of US residence): US-born Latinos had higher waking cortisol (a marker of a more "aged" diurnal cortisol curve) than recently-arrived immigrants, but did not have different declines in cortisol over the course of the day. However, when we examined longitudinal change in diurnal cortisol over a 5-year period, the group with the most quickly accelerating dysregulation of diurnal cortisol was the group with the least exposure to the US (recently-arrived immigrants), which was the opposite of what we had hypothesized.

It is somewhat surprising that we did not observe stronger cross-sectional associations between exposure to the US and diurnal cortisol because several conditions that disproportionately affect Latinos with longer US residence (obesity, depression) are consistently associated with diurnal cortisol. The fact that our longitudinal results were in the opposite direction as hypothesized is more interpretable; longitudinal studies of diurnal cortisol are very new and it is possible that in the age group we observe here (individuals age 45-84), the individuals with the greatest change in diurnal cortisol are those who have the healthiest curves at baseline.

Nativity/duration and leukocyte telomere length (Chapter 3)

In Chapter 3, I examined cross-sectional and longitudinal associations between nativity and duration of US residence and leukocyte telomere length (LTL), a marker of cellular aging. We did not observe cross-sectional differences in LTL according to "exposure to the US", but we saw strong evidence that Latinos with the greatest exposure to the US (US-born Latinos) had faster shortening of LTL over a 10-year period relative to immigrants with fewer than 20 years of US residence.

It is plausible that we would not observe cross-sectional differences in LTL according to nativity/duration of US residence; much of LTL is determined by early-life exposures, which may vary widely within and between categories of nativity/duration of residence in our sample. However, longitudinal change in LTL may better capture differences in experiences of stress (and its physiological sequelae) in the study population at hand.

Low birthweight after the Postville raid (Chapter 4)

In Chapter 4, I continue to examine a stress-related health outcome (low birthweight, LBW), but use a study design that turns further upstream to consider structural influences on stress. After a major immigration raid that exaggerated structural vulnerability for Latinos throughout a region, we observed an increase in the risk of LBW for infants born not only to immigrant Latinas but also to US-born Latinas.

Limitations

It is important that I comment briefly on other factors that may shape patterns in nativity and duration of residence, which may affect the interpretation of my results. I have framed nativity and duration of residence as a measure of "exposure to the US", but among immigrants duration of residence could also reflect effects of age of arrival (i.e., those with the longest residence are also those who arrived earlier in life) The poor health observed among individuals with longer duration of residence could be due to their length of exposure to the US, but it could also be attributed to the timing of their migration in the life course (Angel et al., 2010; Colon-Lopez et al., 2009).

Nativity and duration of residence may also reflect arrival cohort effects, which vary widely by country of origin. Latino immigrants are very heterogeneous, and flows of migration from different countries at different times may vary by social class, reason for migration, means of migration, and context for reception (Hamilton et al., 2015; Miranda et al., 2011; Sabo et al., 2014; Torres and Wallace, 2013). Similarly, differences in nativity may also reflect generational cohorts of different social classes or family histories. For example, Cuban immigrants (or refugees) in the mid-twentieth century were relatively wealthy elites, whereas Cuban immigrants arriving in the 1980's after the Mariel boatlift were of a different social class and encountered a dramatically different context for reception in the United States. As a more recent example, immigrants (or refugees) from Central America may have migrated for economic reasons in the 1990's, but more recently many are coming to flee violence. Differences in arrival cohorts may modify the "healthy migrant" selection effects, which may lead to differences in nativity effects and their interpretation.

Lastly, in these papers I generally frame nativity and duration of residence as a single continuum, i.e. recently-arrived immigrants have the lowest risk of poor health, risk of poor health increases with increasing duration of US residence, and the group at the highest risk of poor health is the US-born. However, it is also possible that nativity and duration are two separate issues—nativity effects could be largely due to selection (the "healthy migrant" effect), for example, while duration effects are due to accumulation of stress with increasing residence in the United States—as a separate process. It is also important to note that certain features of the US environment may be more or less salient for immigrant Latinos vs. US-born Latinos; for example, some evidence suggests that US-born Latinos are more attuned to experiences of discrimination and marginalization than recently arrived immigrants (Cook et al., 2009; Viruell-Fuentes, 2007). Some exposures may even have opposite effects for US-born Latinos versus immigrant Latinos; for example, in immigrant women of Mexican origin low educational status is *protective* against low birth weight, while the SES gradient in risk of low birth weight is reversed in US-born Latina mothers (Acevedo-Garcia et al., 2007). Similarly, residence in highly ethnically segregated areas is protective against low birth weight among immigrant mothers, but is associated with a higher risk of low birth weight for US-born Latina mothers (Osypuk et al., 2010).

Implications and future research

The findings of this dissertation are generally consistent with the idea that psychosocial stress mediates health disparities within Latino populations, which suggests that interventions on psychosocial stressors or psychosocial stress itself may mitigate some of the observed disparities. The psychophysiological literature I read for chapters 2 and 3 tends to come from ethnically homogenous and highly educated participant pools (e.g. Puterman et al., 2015), and many of the interventions emerging from these studies focus on the individual. For example, a number of studies evaluate meditation, mindfulness or yoga to manage and mitigate stress responses and their harmful physiological sequelae (Corey et al., 2014; Daubenmier et al., 2014; Epel et al., 2009; Lavretsky et al., 2013). As valuable as these approaches may be at the individual-level, or maybe even a community-level, evaluating disparities in stress responses according to social position leads me to look further upstream.

Much of the theory that informs these papers highlights the broad structural origins of stressors for Latinos (racialized nativism, economic marginalization, exclusive immigration policy and its militarized enforcement), and there is certainly potential for intervention on this level. There is growing conversation about "immigration policy as health policy" (LeBrón, 2015; Lopez et al., 2016; Viruell-Fuentes et al., 2012), and I am interested in raising public health scholars' awareness of the salience of immigration policy and enforcement for the health and well-being of many individuals in the US, including people who are not themselves immigrants. Many entrenched disparities within Latino populations and between Latino populations and other groups are not likely to be mitigated by intervention approaches that ignore the immense and existential threats that pervade daily life for many Latinos in the United States.

“Interventions” on immigration policies and their effects can occur at many levels, including the city and county level, where city and county law enforcement have the discretion not to cooperate with federal immigration enforcement (Potochnick et al., 2016), or cities can even establish “sanctuary” policies that offer further protection from exclusive state or federal policies. Enhancing labor and housing protections and reinstating driving privileges for undocumented immigrants and their families are other policy measures that have the potential to mitigate the harmful and stigmatizing effects of restrictive immigration policies on Latino health (Hall and Greenman, 2013; LeBron, 2014; Minkler et al., 2014).

Another promising intervention on identity-related stigma includes the Community ID programs popping up throughout the country (Mathema, 2015). These local government-issued IDs are accessible regardless of immigration status and are a creative, community-driven policy intended to increase access to resources such as banking, safe engagement with law enforcement, and social services, while sending a powerful message of inclusion and reducing the day-to-day stress of life without ID.

To conclude, the approach I have taken in this dissertation evaluates biological mechanisms that many scholars have theorized mediate Latino health disparities in the United States. More research on these pathways is needed—especially research throughout the life course—and future work can also take advantage of changes in the racialized social environment to further explore the broader exposures that shape the health of Latinos in the US.

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