UNIVERSITY OF CALIFORNIA SAN DIEGO

Epigenetic embodiment in the context of shifting sociopolitical environments for Latinx immigrant families: implications for mental and cardiometabolic health.

A Dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Anthropology

by

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The Dissertation of Elizabeth Sarah Clausing is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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DEDICATION

I dedicate this dissertation to my parents, Flint and Sandra Collier, for their unfailing support and love. I appreciate their sacrifices and I would not have been able to get to this stage without them.

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Chapter 3, in full, is adapted from a manuscript currently under review and submitted as an invited paper to the journal *Frontiers in Systems Neuroscience* for a special edition on developmental embodiment: Clausing, ES and Non, AL. "Epigenetics as a mechanism of developmental embodiment of stress and resilience across generations of Latino immigrant families." *Manuscript Under Review, Frontiers in Systems Neuroscience*. The dissertation author was the primary investigator and author.

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Corona, J., **Clausing, E.S.**, and Non, A.L. (2018). Methods of study of hair cortisol in healthy children: A systematic review and case study in children of Mexican immigrants. Poster session at the Chancellor's Research Excellence Scholarships (CRES) Symposium; October 25th; San Diego, CA.

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Non, A.L., **Clausing, E.S.**, Redwine, L.S., and Rodney, N.C. (2017). Can acupuncture decrease stress and increase telomerase activity to promote healthy cellular aging among older adults with depression or anxiety? Presented for a special symposium on "Collaborations across Anthropology and Genetics: Examples of Transdisciplinary Work" at the 86th Annual Meeting of the American Association of Physical Anthropologists; April 19-22; New Orleans, LA.

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ABSTRACT OF THE DISSERTATION

Epigenetic embodiment in the context of shifting sociopolitical environments for Latinx immigrant families: implications for mental and cardiometabolic health

by

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Doctor of Philosophy in Anthropology

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Psychosocial stressors can become embodied to alter biology throughout the life course in ways that may have lasting health consequences. Immigrants are particularly vulnerable to high burdens of stress, which have heightened in the current sociopolitical climate. This study is an investigation of how immigration-related stress may impact the mental health, cardiometabolic health, and epigenetic markers of Latinx immigrant mothers and children in

Nashville, TN, across a timeframe of increasing anti-immigrant political policies. The overall aim was to investigate how stress experiences of both mothers and children may become biologically embedded through epigenetic pathways to increase risk of cardiometabolic disease later in life.

We compared stress and resilience factors reported by Latina immigrant mothers and their children (aged 5-13) from two time points spanning the 2016 presidential election with cardiometabolic health markers (BMI, waist circumference, and blood pressure), mental health outcomes (e.g., anxiety and depressive symptoms), DNA methylation of stress-related genes, and epigenome-wide/epigenetic aging. Three manuscripts comprise the bulk of this dissertation, and all use data from a study entitled, "Children of Immigrants Collaborating to Overcome Stress" (CHICOS). CHICOS is a longitudinal study of primarily low-income Mexican immigrant families living in Nashville, TN between 2015-2018. The first project examined responses to open-ended questions along with quantitative scales of mental health, psychosocial stressors, and resilience factors. The second project investigated associations between psychosocial stress and resilience with cardiometabolic health biomarkers and DNA methylation of two select stress-related genes. The final project conducted a comprehensive epigenomic assessment, with an analysis of epigenetic aging and an epigenome-wide association study. Taken together, our results indicate that psychosocial stressors have been consistently high among Latinx families over time, which has had profound impacts on cardiometabolic and mental health across two generations. While epigenetic effects are modest, they may be part of important pathways of embodiment. More research is needed to determine the role of these epigenetic differences for documenting embodiment of stress across generations.

Chapter 1

INTRODUCTION

One of the most striking characteristics that make us human is our ability to successfully adapt to a constantly changing environment as well as respond to an increasingly complex suite of stressors. Our daily lives are comprised of emotionally driven experiences that range from mild annoyances (e.g., traffic or work deadlines) to major transformative life events like the loss of a family member. The degree to which the event affects us is hypervariable and highly individualistic. Collectively, these events can potentially disrupt our bodily homeostasis, as what is referred to as stress (Levine 2005). Stressors, or stressful events, can be of a physical or psychological nature, and can have long-term and short-term effects. Stress, the physiological and neurological activation of the body when individuals face environmental challenges or threats, frequently results in strain or disequilibrium of the body and the mind (Le Fevre et al. 2003). It is the body's automatic response to any physical or mental demand placed upon it. Perhaps uniquely to humans, physiological stress responses can even result from anticipation of future stressful events (Aschbacher et al. 2013; Sapolsky 2004). For humans, particularly those in historically disadvantaged groups, stress is often chronic. There is a biological response; however, stress is heavily influenced by sociocultural and/or psychosocial factors (stressors). For the purposes of this dissertation, stress is broadly defined as the appraisal of a challenge or biological demand that exceeds one's resources (Lazarus 1990).

Stress activates two highly conserved biological systems among vertebrates: the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis (Joels et al. 2006). Both ANS and HPA regulators are connected and regulated by the hypothalamus with varied acting speed – fast and slow, respectively. The ANS is a segment of the peripheral

nervous system that influences the function of internal organs that is largely responsible for the unconscious-acting bodily functions, such as heart rate, respiratory rate, urination, digestion, sexual arousal, and pupillary response (de Kloet et al. 1999). The ANS is the primary mechanism in control of the fight-or-flight and the freeze-and-dissociate responses. Most autonomous functions are involuntary, like sneezing, swallowing, vomiting, and coughing, but they can also work with the somatic nervous system, which provides voluntary control.

The second biological system, the HPA axis, involves hormones released from the brain's hypothalamic stress center and can cause illness, including loss of appetite, weakness, cardiac arrhythmias, and vascular collapse (Lupien et al. 2007). The HPA axis releases cortisol (in humans) and corticosterone (in most rodents) hormones through intermediate steps (Joels et al. 2006). Cortisol, a glucocorticoid hormone synthesized from cholesterol by enzymes, is the primary hormone responsible for stress response. Its main function is to restore homeostasis following exposure to stress, and the effects of cortisol are felt throughout the entire body and impact several homeostatic mechanisms. Although its primary targets are metabolic processes, cortisol also affects immune response, ion transport, and memory. Corticosteroid hormones enter the brain, binding discretely to localized intracellular receptors, which are comprised of high-affinity mineralocorticoid receptors (Joels et al. 2006). They coordinate together with other components of the stress system to divert the energy supply to challenged tissues that are in distress (Figure 1.1).

Pathways of embodiment

Embodied stress is an important area of anthropological research. As first emphasized by Franz Boas more than a century ago through his demonstration of descendants of immigrants embodied the new American environment (Boas 1912), the research area of embodied stress

remains an important area of anthropological research (Kuzawa and Thayer 2011; Non and Thayer 2015). To understand the impact of our stressors on our health I draw upon the ecosocial theory. A central focus of ecosocial theory is how we biologically embody various exposures from societal and ecological contexts to address health disparities (Krieger 2012). Societal exposures that become embodied can induce pathogenic outcomes that are mediated by physiology, behavior, and gene expression. This in turn affects development, growth, regulation, and death of our body's biological systems, organs, and cells, which ultimately culminates in disease, disability, and/or death (Krieger 2012).

Extensive research has found that individuals exposed to a relatively large number of stressors tend to report worse mental health compared to those with very few stress events throughout their life (Boardman and Alexander 2011; Kessler et al. 1994; Turner and Lloyd 1999). The accumulation of stress over time can contribute to biological embodiment across the life course. Stressors in the early life environment may influence susceptibility to later life disease. Chronic stress in particular increases the risk of developing mental health disorders in both children (Cicchetti 2016; Green et al. 2010; McLaughlin 2016) and adults (Bovier et al. 2004; Clarke et al. 2008); however, the precise mechanisms of how stress is linked to mental health illness are unclear.

Cardiometabolic health (cardiovascular and metabolic diseases) may be inversely related to risk for obesity, insulin resistance, type 2 diabetes mellitus, high blood pressure, and cardiovascular diseases (Lotta et al. 2015; Haffner 2007). Cardiometabolic health biomarkers (e.g., body mass index, blood pressure, and waist circumference) may also be paths of embodiment that are either influenced by epigenetics or behavioral processes. One study's findings suggested childhood social disadvantage may contribute to adult cardiometabolic

disease by predisposing them to adopt certain unhealthy behaviors (Non et al. 2016b). In a follow-up study, they found higher levels of optimism and social support were both associated with higher probabilities of engaging in healthy behaviors, which is consistent with the possibility of positive psychosocial factors contributing to maintaining a healthy lifestyle and buffering the negative effects of childhood social disadvantage (Non et al. 2020). Childhood adversity has also been related to poor health in adulthood via increased coronary heart disease, hypertension, arthritis, diabetes, and migraines (Cuijpers et al. 2011). While behaviors may be modified by child adversity, there are other potential pathways, such as direct effects of stress on epigenomes.

Types of epigenetic mechanisms – adapted from (Clausing and Non 2018)

While there are many different processes that can be considered "epigenetic," most scientists describe three main types of epigenetic mechanisms: DNA methylation, histone modification, and non-coding RNAs. DNA methylation, the most studied epigenetic mechanism, is a process used by mammalian cells in which a methyl group (CH3) is added to the 5' carbon of a cytosine in DNA. A cytosine gets methylated through the action of a methyltransferase enzyme, attaching a methyl group through covalent bonds at a cytosine-phosphate-guanine dinucleotide, or CpG site. Most CpG sites in the genome are methylated (70-80%), except for those found in CpG islands, or regions of DNA rich in CpG sites. The effect of DNA methylation on gene expression is highly context-dependent; DNA methylation in the promoter region of a gene typically reduces gene expression, while methylation in the gene body can increase gene expression.

Chemical modification of histones and non-coding RNA are two other important epigenetic processes. Histones are proteins that form spools around which DNA is wound.

Histones have amino-terminal tails of 25 to 40 amino acids, and histone modifications are a set of heritable post-translational changes in which molecules bind to the various amino acids in these tails or on the globular core region. Modifications such as methylation, acetylation, and sumoylation, among many others comprise the histone code, which can either enhance or repress transcription. Non-coding RNAs (ncRNAs) are a third class of epigenetic mechanism, which can regulate gene expression by binding to complementary regions of DNA, blocking translation into proteins or triggering their degradation. Among these, DNA methylation is the most stable epigenetic process, and has thus been a primary focus of genetic anthropology research. For this reason, this dissertation focuses primarily on the epigenetic mechanism of DNA methylation.

Early/Notable Experiments

In the foundational study of behavioral epigenetics, researchers discovered that DNA methylation was affected by maternal behavior towards rat pups in the first week of life (Weaver et al. 2004). A rat pup that is raised by a relaxed high-nurturing mother that licks her pups often becomes a relaxed adult rat that in turn is a high-nurturing mother. On the other hand, a rat pup that is raised by an anxious, low-nurturing mother becomes an anxious adult rat and a low-nurturing mother itself. When low-nurtured rat pups are fostered by high-nurturing parents, they take on the behavior of their rearing parent, rather than their birth parent. Nurturing mothers transmit their relaxed phenotype through a decrease in methylation at the promoter region of the glucocorticoid receptor gene in the hippocampus region of the brain. The glucocorticoid receptor is a key component of the hypothalamic pituitary adrenal (HPA) axis, the primary stress response system in the body. When the hormone cortisol is produced in response to stress, it binds to the glucocorticoid receptor, triggering a feedback loop that down-regulates the HPA axis response to

stress. In individuals with fewer glucocorticoid receptors, this feedback regulation is disrupted, which can lead to higher anxiety and other mental disorders later in life.

The most notable study to replicate this effect in humans found the same increased pattern of methylation in the glucocorticoid receptor in the brains of suicide victims who had suffered child abuse (McGowan et al. 2009). Since brain tissue is so difficult to acquire, many studies have since examined the effects of early life adversity on methylation in peripheral tissues, such as cord blood and saliva. There are also methodological considerations when attempting to replicate findings from non-human studies in humans as you cannot use the same tight experimental controls as you can with animals/rats. Thus far, anthropological studies have found epigenetic changes at stress related genes and throughout the genome in response to exposure to war trauma in utero (Mulligan et al. 2012), and orphanage rearing in early childhood (Non et al. 2016b), among other adverse exposures.

An example of epigenetics influencing health in non-human primates investigated social status and immune gene expression via RNA sequencing in wild baboons, where kinship determines status in females and fighting ability determines status in males (Lea et al. 2018). They found a much stronger relationship between status and gene expression in males than in females, and inflammation-related genes were more active in high-status males than in low-status males. This work suggests that males who compete successfully for high status may already be immunologically distinct, and, therefore, how social hierarchies are formed shapes their relationship to immune function and health (Lea et al. 2018).

Despite being the most stable of the epigenetic markers (Cedar and Bergman 2009), in certain gene regions, DNA methylation can vary in response to environmental influences (Mitchell et al. 2016) or aging (Horvath 2013). Santos et al. investigated the relationship between

the complex biological pathways between perceived discrimination and epigenetic modification in pregnant Latinx women in the US for the first time (2018). They discovered that discrimination in pregnant mothers was associated with methylation at key stress-related genes in maternal blood. A recent study also found Latinx adults to have an accelerated "epigenetic age" relative to white populations (when accounting for age-related changes in blood cell populations) (Horvath et al. 2016). Our publication (Chapter 4) is the first to investigate the epigenetic consequences of stress and resilience in Latinx children.

Stress among Latinx youth: a case study for embodiment

Since the 1980s, immigrants and children of immigrant parents represent the fastest growing segment of America's population. Today there are double the number of Latinx children living in the US compared to 20 years ago, and 92% of them are US citizens (Foxen 2010). According to the 2017 Current Population Survey, immigrants and their US-born children now number 86.4 million, or 27 percent of the overall US population (Zong et al. 2018). Almost 45 percent of immigrants (~19.6 million) reported having Latinx origins, with Mexicans comprising a third of the immigrant population in the US (Gonzalez-Barrera et al. 2013; Zong et al. 2018).

Children of Latinx immigrants are disadvantaged on numerous fronts, including access to good education and healthcare as well as job security for their parents, while being confronted at the same time with implicit or explicit discrimination, resentment, racism, and often violence. Additionally, these children and their parents must negotiate heightened stereotypes (including bullying) and fears projected onto them in the course of highly publicized ongoing debates about immigration policy and the US-Mexico border (Huang and Cornell 2019; Perreira et al. 2019; Santos et al. 2018). Over 33% of Latinx children lived below the poverty level in 2009, relative

to only 12% of white children (Foxen 2010). In combination, these adverse exposures may contribute to worse health outcomes, through numerous interrelated pathways.

In recent years and especially during the previous presidential administration, discrimination towards Latinx immigrants has changed for the worse, even leading to devastating policies that separate children of all ages from their parents. This could cause adverse health outcomes to these families for generations. Social determinants such as unstable employment, caustic living environments, and trauma are persistent social stressors that can affect immigrant families' lifestyles, health status, and mortality, and all have been shown to have biological consequences, e.g., by affecting immunologic activity (Cabassa 2003). Even though the majority (66%) of US Latinx are native-born, identifying as Latinx in the US at this particular political moment can have devastating biological and health consequences. Children of Latinx immigrants may be living in a state of chronic stress, constantly on edge with concerns about the deportation of their family members, or their ability to remain in the country in which most of them were born.

The overarching research question of this dissertation is how the life circumstances and experiences of Latinx immigrant mothers and their children may alter stress response systems, potentially setting them up for higher risk for stress-related diseases in adulthood and later life. The schematic of my dissertation is present in Figure 1.2. My goal was to determine if there have been changes in the stress physiology of Latinx immigrant mothers or children over time. This study focuses specifically on stress experiences of Latinx immigrant mother-child dyads living in Nashville, Tennessee, and how these experiences affected their health. This is a pressing and timely question given the rapidly changing pace of current national policies toward immigrants which could significantly alter the lives of immigrant mothers and their children in the US,

creating an environment of uncertainty for current immigrant families, regardless of documentation status.

Nashville is a city with a growing Latinx population (currently 10.5%, U.S. Census Bureau 2019). Nashville is also a city with rapidly changing policies towards immigrants leading to much uncertainty and anxiety about their status and safety. As many other southern cities, it has been a location with early adoption of policies, such as 287(g), that permit local law enforcement to take control of immigration enforcement, resulting in over 10,000 deportations, a ten-fold increase relative to the years prior to the program, and most of these were Mexican or other Latinx men arrested for minor driving violations (Armenta 2017; Kee 2012). These policy changes and the dynamics of the growing immigrant presence in Nashville create a unique and important site for research on immigrant stress.

This dissertation (Figure 1.2) draws on theory and methods across biological and cultural anthropology, social epidemiology, physiology, and molecular biology to inform how stress experiences among Latinx youth may become biologically embedded to affect lifetime risk of stress-related diseases. Here I investigate how immigration-related stress may impact the biology and health of Latinx immigrants and their children, in light of recent divisive policy debates surrounding Latinx immigrants in the US. Despite the extensive work on racial/ethnic inequalities in health, less is known about the specific social determinants that may be risk factors for disease. One example is discrimination, as a growing literature has found a strong inverse association between discrimination and health and well-being (Almeida et al. 2016; Huang and Cornell 2019; Perreira et al. 2019). Exploring the biological embedding of stressors among children of Latinx immigrants is especially pressing in the current social and political climate of the US.

Immigrant stress.

When adapting to a new environment, immigrants experience significant stressors including dealing with language barriers, discrimination, low socio-economic status (SES), marginalization (Cabassa 2003), loss of social support from family and friends, and for some, stress related to their undocumented status (Smart and Smart 1995). Children of immigrants face additional stressors such as acculturation strains, psychological adjustment, parents' difficulties acculturating, parents' undocumented status, in some cases, and being pulled between cultures (Crockett et al. 2007). These stressors are not solely experienced by children, it also influences adults, though children may be more vulnerable, and time periods of vulnerability or sensitive windows for various embodiment pathways is an open question.

Discrimination.

A high prevalence of discrimination has been reported by immigrants in the US, and it only increased during the previous presidential administration of Donald Trump (Almeida et al. 2016). The increase of anti-immigrant policies contributes to experiences of discrimination and health behavior, healthcare, and psychological distress (Alvarez and Butterfield 2000; Ayón and García 2019; Hacker et al. 2011; Martinez et al. 2015; Monogan 2013; Sabo et al. 2014; Salas et al. 2013; Szkupinski Quiroga et al. 2014). There are multiple ways of measuring discrimination, and none of them are ideal because some individuals or groups do not want to discuss it, others are in denial, and some do not recognize it, which is why a mix of subjective measures and biomarkers are important (Diener et al. 2018). In this dissertation, I measure discrimination in multiple ways, including the widely used everyday discrimination scale (Williams and Mohammed 2008) and a newly created measure of discrimination stress developed specifically for these mothers and their children.

Resilience.

Resilience is a complex construct but can be broadly defined as the process of adapting positively to harness resources and sustain well-being in the face of adversity (Panter-Brick and Leckman 2013; Southwick et al. 2014). Resilience has been measured in various ways. One is via scales that capture self-efficacy by prompting interviewees/respondents to rate how well they identify with statements such as, "I am able to depend on myself more than anyone else" (Wagnild and Young 1993). Anthropologists have critiqued this individualized conceptualization of resilience as one designed for a Western cultural context that should not be applied elsewhere (Panter-Brick et al. 2015). However, a resilience measure has been found to associate with a molecular measure of resilience in a Nepali population, suggesting it is more generalizable than anticipated (Kohrt et al. 2016). Other anthropologists have emphasized socio-ecological components of resilience, such as access to community and family resources, and have focused on resilience as a process for harnessing those resources (Panter-Brick et al. 2015; Panter-Brick and Leckman 2013). Different approaches to measuring resilience across studies yield inconsistent results and many items may not be culturally sensitive for this study. Therefore, in this dissertation, resilience is operationalized in two ways, as positive and protective psychosocial factors including optimism and social support, in mothers and children.

Understanding the range of perspectives on terminology is important, especially when discussing pan-ethnic terms and/or references to national origin/descent. Racial categories reflect the historical and contemporary consequences of social, political, and economic opportunities as well as exclusions (Almaguer 2009; Omi and Winant 2015). The pan-ethnic terms "Hispanic" and "Latino/Latins" are often used to refer to persons from or with familial ties to Latin American countries/territories. The term "Hispanic" is often favored by US government entities

and was first used officially by the US government in the 1970 Census to refer to "a person of Mexican, Puerto Rican, Cuban, South, or Central American, or other Spanish culture or origin, regardless of race" (U.S. Census Bureau, 2014). Although they are often used interchangeably, the terms "Hispanic" and "Latino" are not identical in meaning. According to the US Census Bureau, the terms "Hispanic" and "Latino" refer collectively to the inhabitants of the US who are of Latin American or Spanish origin; however, "Hispanic" is not used to classify persons of Portuguese or Brazilian descent. "Hispanic" has broader references than "Latino," potentially encompassing all Spanish-speaking peoples throughout the world and emphasizes the commonality of language, even if that is all that is similar. "Latino" refers exclusively to Spanish-speaking persons of Latin American origin. Although "Hispanic" is most frequently found in the literature, it is descriptive through a Westernized lens through the elevation of the identity of the colonizing country of Spain and will not be used (Alcoff 2005; Hayes-Bautista and Chapa 1987). The participant families in this study are from Mexico, Peru, Honduras, Guatemala, El Salvador, and Colombia. Though it would be preferable to separately analyze each of these participant countries, sample sizes are too small from all countries other than Mexico to allow for a more nuanced analysis. Also, since Spanish is a gendered language, I will refrain from using the traditional terms of "Latino/a," unless discussed with participants. In recent years, the term "Latinx" has been used more frequently in effort to be more inclusive and move away from rigid conceptions of gender and sexuality (Rodríguez 2017). For these reasons, I will use the academically favored term "Latinx" when discussing the children, according to most of the literature (Hunley et al. 2017), throughout the remainder of this dissertation. I will be using the term "Latina" when referring to the mothers as that was their preference term.

OUTLINE OF THE DISSERTATION

This dissertation examines how objective and subjective measures of stress may differ in Latina immigrant mothers and their children to investigate how life circumstances and experiences may become embodied. Three manuscripts comprise the bulk of this dissertation, and are meant to serve as stand-alone publications. All three chapters make use of data from a study of immigrant stress entitled, "Children of Immigrants Collaborating to Overcome Stress" (CHICOS). CHICOS is a longitudinal study of primarily low-income Mexican immigrant families living in Nashville, TN between 2015-2018. The overall dissertation was organized with a progressively narrowing approach, starting with broad lived experiences and moving towards the more specific molecular pathways. I started by examining self-reported, open-ended and validated scales of mental health, psychosocial stressors, and resilience factors. I then investigated the possibility of DNA methylation of a select stress-related genes and possible influence on cardiometabolic health biomarkers. My final project is the most comprehensive assessment with an analysis of epigenetic aging and an epigenome-wide association study.

Chapter 2 examines changes in immigrant-related stressors and resilience factors experienced by Latinx immigrant children and their mothers in Nashville, TN before and after the 2016 presidential election. We also examine how these psychosocial stressors and resilience factors associate with mental health outcomes following Trump's election to the US presidency. This chapter was originally published in two parts: one as a paper prepared for submission to the Journal of Immigrant and Minority Health focusing on effects on children's mental health (where I serve as first author), and the other as part of a submission to the journal Cultural Diversity & Ethnic Minority Psychology (currently in review), which focused on effects on maternal mental

health (I served as second author along with coauthors Drs. Amy L. Non and Kimberly L. D'Anna-Hernandez).

Chapter 3 examines associations between psychosocial stressors and resilience factors with targeted bisulfite pyrosequencing in the FKBP5 and SLC6A4 genes in saliva of children of Latinx immigrant mothers and their children. It is currently in preparation for submission to a special issue on embodiment in Frontiers in Systems Neuroscience, co-authored with Dr. Amy L. Non. I am the first author of this publication.

Chapter 4 examines associations of psychosocial stressors and resilience factors with epigenetic age estimates and epigenome-wide patterns of DNA methylation in the saliva of children of Latinx immigrants at two time points spanning the 2016 US Presidential election. We examined all psychosocial factors in relation to four different measures of epigenetic age – at each time point, as well as change in epigenetic age estimates over time. Chapter 4 was originally published in part as an invited submission for a special issue on racial disparities in epigenetics research in the journal Epigenomics, and I served as first author, with Drs. Alexandra Binder and Amy L. Non as co-authors.

Chapter 5 provides a general discussion and conclusion for the dissertation, and includes future directions for measuring the biological embedding of stress from the social environment.

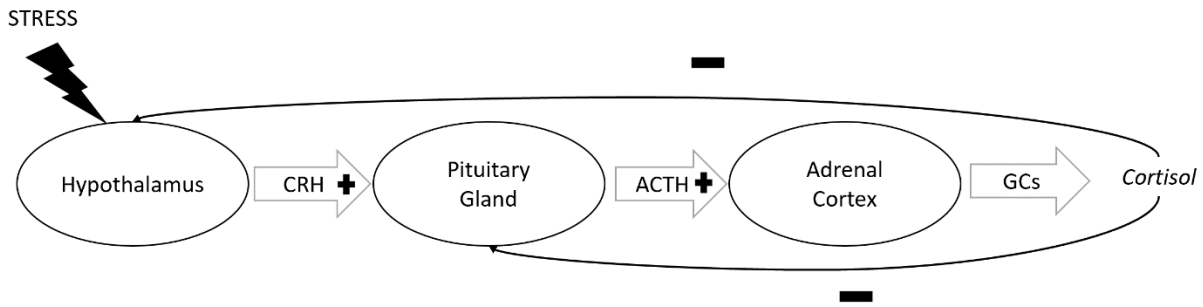

Figure 1.1: Simplified schematic representation of the hypothalamic-pituitary-adrenal (HPA) axis (adapted from (Smith and Vale 2006)). The negative arrows represent a negative feedback loop where an accumulation of cortisol feeds back into the hormonal pathway. Key: CRH – Corticotropin Releasing Hormone; ACTH – Adrenocorticotropic Hormone; GCs – Glucocorticoids.

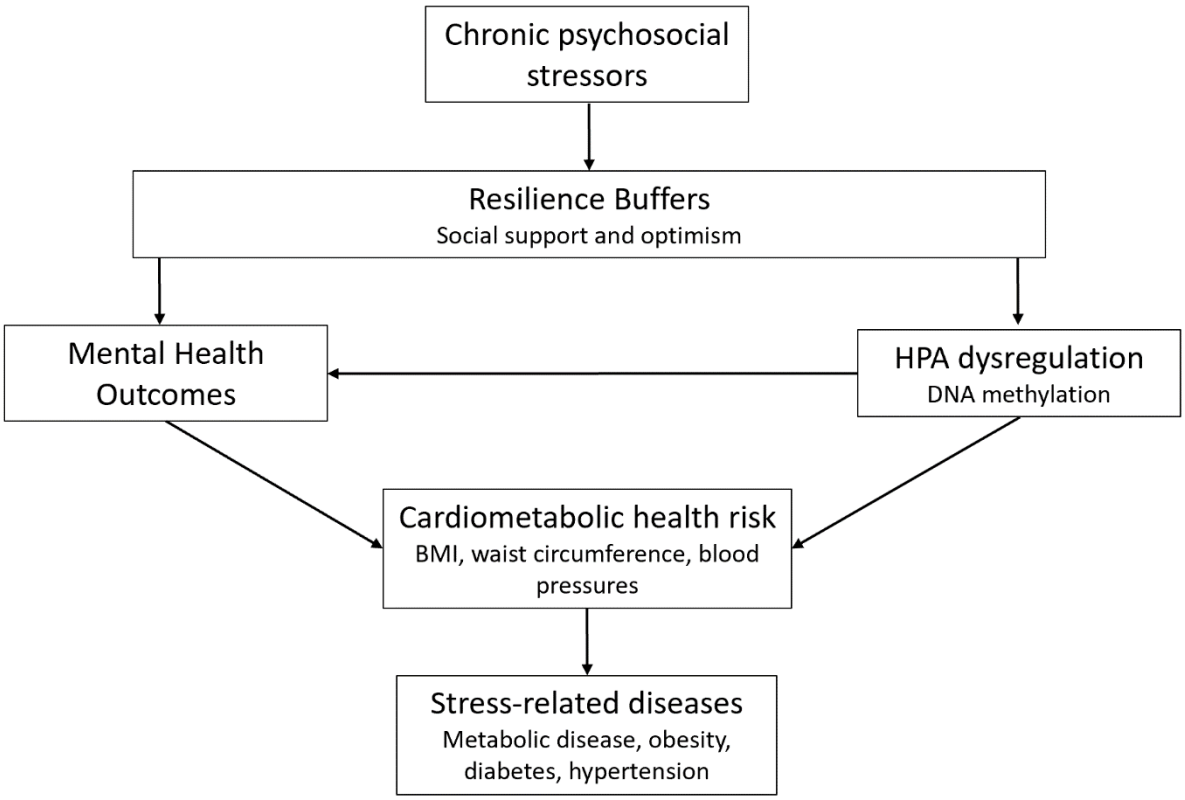

Figure 1.2: Conceptual framework of the dissertation.

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Chapter 2

Do immigrant-related stressors associate with Latinx maternal and child mental health?

ABSTRACT

This study is an investigation of how immigration-related stress may impact the mental health of Latinx immigrant mothers and children, considering increases in divisive rhetoric and policies towards U.S. immigrants surrounding the recent 2016 election. This project involves comparison of survey data about stressors and mental health in Nashville, TN from two time points spanning the recent presidential election. Surveys including a mix of closed response and open-ended questions were administered in person with 82 immigrant mothers and one child from each family (aged 5-13) between 2015 and 2016 and again in 2018. Using mixed-methods, we analyze perceived stressors and buffering factors from mothers and children in relation to mental health at the post-election time point. The children reported increased levels of immigrant-related stress ($p<0.007$) and social support from their parents ($p=0.001$) over time. The mothers reported small but significant decreases in levels of total stress, immigrant-related stress, and overall discrimination stress ($p=0.04$). Over time, mothers also reported significantly decreased optimism ($p<0.0001$) and decreased social connection/support ($p=0.04$). In the children at post-election, only immigration-related stress and separation anxiety maintained significance after the Bonferroni correction. In the mothers, only total stress and depression maintained significance following a Bonferroni correction. Dramatic changes in stress over time can have significant mental health consequences, especially for these already vulnerable families.

INTRODUCTION

The sociopolitical climate since President Trump's election may be particularly harmful for the mental health of Latinx families. Historically, Latinx immigrant families in the US have been disadvantaged on numerous fronts, including access to quality education, job security, and healthcare (Tienda and Mitchell 2006), while simultaneously being confronted with racism and often violence (Feagin and Cobas 2014). In recent years, Latinx individuals face heightened stereotypes, bigotry, and fears resulting from increasingly racist language and anti-immigrant sentiments in politics and the media (Morey 2018). Policies such as separating children from their parents at the border, the removal of DACA, increased deportations and ICE raids, and antagonistic media attention against Latinx individuals all contribute to a toxic climate; however, little is known as to the changes in mental health outcomes during the time of this particular administration.

This sociopolitical climate may be particularly toxic for the mental health of Latina mothers who struggle with discrimination and/or fears about deportation for themselves or their family members. In fact, Latina mothers have experienced increases in preterm birth rates since the 2016 election nationwide (Gemmill et al. 2019), likely resulting from increased sociopolitical stress and anxiety. These mothers are also likely facing heightened racial discrimination, which has been significantly associated with worse mental health across studies of racial/ethnic minorities (Carter et al. 2017). Even before the current policy changes, perinatal Latina mothers reported 2-3 times the rates of depression and anxiety compared to women in the general U.S. population (Luis Sanchez et al. 2020). Although much is known about maternal mental health and its significant effects on both maternal health and early child development, little is known,

about the extent to which mental health in Latinx mothers is related to their children's socioemotional development.

Exposure to childhood adversity, including abuse or poverty, is one of the strongest risk factors for decreased health across the lifespan, with estimates linking such exposures to at least a two-fold increase in subsequent risk for mental disorders (Dunn et al. 2012; McLaughlin et al. 2010). Though these associations are well-established, less research has investigated the additional burden of immigrant-related stressors, such as fears of deportation and discrimination that may exacerbate the stressors of low socioeconomic Latinx families, especially during this particular sociopolitical moment.

Children of immigrants are understudied, but may be particularly vulnerable because they are exposed to the stressors of their parents as well as their peers, and some may shoulder the burden of their family's anxieties about deportation. However, it is not clear if children experience or report stressors in the same way as their parents. According to the 2017 Youth Risk Behavior Survey, Latinx youth have high rates of sadness/hopelessness (33.7%) (Kann et al. 2018; Perreira et al. 2019). Early research on Latinx adolescent mental health found that foreign-born youth and adults often had better mental health than their US-born peers despite the stressors of migration and often poorer socioeconomic circumstances (Alegría et al. 2008; Perreira and Ornelas 2011). One study by Perreira et al. examined associations of immigrant generation, acculturation, and sources of stress (e.g., discrimination, economic stress, neighborhood disorder) and resilience (e.g., ethnic identity, parental closeness, family functioning, and social support) with anxiety and depressive symptoms (Perreira et al. 2019). They found that greater acculturative stress among children was associated with depression and anxiety symptoms, and well-functioning family support systems may protect against negative

behavioral and health-related consequences of stress. Questions remain about how early in life these effects are detectable, and which types of exposures are most harmful for what aspects of mental health.

Resilience is a complex construct but can be broadly defined as the process of adapting positively to harness resources and sustain well-being in the face of adversity (Panter-Brick and Leckman 2013; Southwick et al. 2014). Anthropologists have emphasized socio-ecological components of resilience, such as access to community and family resources, and have focused on resilience as a process for harnessing those resources (Panter-Brick et al. 2015; Panter-Brick and Leckman 2013). Three important aspects of resilience are high levels of social support, optimism, and subjective social status. An extensive literature has supported the relationship between community level social connection and health (Lochner et al. 2003; Umberson and Montez 2011). Social support factors have been cited as mediating variables for both better physical health (Finch and Vega 2003) and mental health (Galea et al. 2004) for low-income, Latinx immigrants but has not been studied extensively in children. Optimism has also been found to influence mental and physical well-being through promoting a healthy lifestyle (Carver et al. 2010; Carver et al. 2006; Conversano et al. 2010; Härtl et al. 2010). Subjective social status represents a person's sense of social position, and has been found to be positively associated with self-rated health (Joffer et al. 2019) and negatively associated with several poor health outcomes and risk factors for disease (Euteneuer 2014). In this study, resilience will be operationalized in three ways, as positive and protective psychosocial factors (e.g., optimism), social support, and subjective social status, in mothers and children, which may both serve as protective benefits for the children (Applebaum et al. 2014).

The current study examines changes in immigrant-related stressors and resilience factors experienced by Latina immigrant children and their mothers in Nashville, TN before and after the 2016 Presidential election. We also examine how these psychosocial stressors and resilience factors associate with mental health outcomes following Trump's election to the US presidency. In a prior study, we reported on changes in Latina mother's immigrant related stress and mental health before and after Trump's candidacy. This study extends upon those analyses by additionally examining changes in children's stressors over time, as well as a deeper investigation into a wider range of stress measures in the mothers, including some qualitative data to contextualize these findings. Further, we examined associations between immigrant-related stressors and mental health outcomes across both generations during a time of heightened sociopolitical stress for Latinx people in the first few years of Trump's presidency.

MATERIALS/METHODS

Study population

The original study sample included 81 families (mother-child dyads), recruited between 2015 and 2016 and assessed on a number of different stress and resilience measures. The ages of the children range from 5 and 13 years old. Two years later, on average, children were prospectively assessed for a range of biological, physical, and psychosocial measures. The initial time point is hereafter referred to as pre-election, and the second time point as post-election, to emphasize the timing in relation to the 2016 US Presidential election. The study protocol was approved by the University Institutional Review Boards (IRBs) of Vanderbilt University and the University of California, San Diego.

Study Setting:

The CHICOS study context is located in Nashville, TN (Davidson County), a city with a growing Latinx population (10.5%, U.S. Census Bureau 2019). Nashville is also a quickly expanding destination for immigrants. Tennessee experienced a 92% growth in its immigrant population between 2000 and 2013, and was the state with the largest percent growth (145%) of children living with immigrant parents (Zong and Batalova 2015). Nashville is also a city with rapidly changing policies towards immigrants leading to much uncertainty and anxiety about their status and safety (Figure 2.1 Timeline). As have many other southern cities, it has been a location with early adoption of policies that permit local law enforcement to take control of immigration enforcement, resulting in over 10,000 deportations, a ten-fold increase relative to the years prior to the program, and most of these were Mexican or other Latinx men arrested for minor driving violations (Armenta 2017; Kee 2012). In April of 2018, just a week after our post-election study collection began, the largest ICE raid of the state took place, arresting 97 workers at a meat processing plant in Morristown, TN, a city just 3 hours from Nashville and well known to many of our study participants. These dynamics created an especially perilous environment for immigrant families in Nashville, and subsequently posed challenges for recruiting participants into the study.

Changes to federal anti-immigrant policies:

In addition to shifts in local policy, a number of federal policies directed specifically against immigrants were issued during the post-election time period (Figure 2.1). Three executive Orders (13767, 13768, and 13769) were issued by the President within the last week of January 2017. These orders collectively included demands for a border wall, expanded use of detention of immigrants, limited access to asylum, enhanced enforcement along the border and

increases in the number of ICE agents, prohibition of sanctuary jurisdictions from receiving federal funding, and limiting travel from Muslim majority countries. Additionally, a policy specifically aimed at separating families at the border was enacted in spring of 2018. All together these policies sent a collective message that immigrants were not welcome, and increased anti-immigrant media attention.

Demographics:

At both time points, mothers were asked to self-report their years of education, number of years in the US, marital status (i.e., married vs. unmarried), and legal status (i.e., documented vs. undocumented). We also measured economic hardship using a variable called "trouble paying bills." In this variable, mothers were asked, "I frequently had problems paying basic bills," and responses were classified into yes/no.

Maternal acculturation was measured using the Short Acculturation Scale for Hispanics (SASH) subscale to assess participants' language use (e.g., language they speak, think (Marin et al. 1987). The survey has 5-items with subscales assessing participants' language use, media preference, and ethnic social relations. Participants rated their acculturation level from "Only Spanish: to "Only English," with higher scores indicating preference for English. The SASH has been validated in low-income immigrant Latinx individuals (Ellison et al. 2011).

Exposures:

All exposure data were collected in person with mothers in Spanish (1.5-2 hours) and children primarily in English (45 minutes). Surveys were a combination of validated scales and new interview questions developed following a set of ten initial individual interviews with children and focus groups with 32 Latina immigrant mothers in Nashville, TN, USA (Non et al. 2019).

Psychosocial stressors:

We measured several different domains of stress in the children during the pre-election time point, including school stress, immigrant-related stress (IRS), biggest daily worry, fear of parent's deportation, discrimination stress, and total stress, which was a summation of all listed stress domain scores. We measured the same domains of stress in the post-election time period, and additionally measured everyday discrimination (Williams et al. 1997).

For the mothers in both pre- and post-election time points, we measured immigrant-related stress, discrimination stress, household stress, health stress, family economic stress, and a summation of these stress domains as a measure of total stress. We additionally measured everyday discrimination in the post-election time point.

Resilience factors:

Subjective social status (SSS) was used as a measure of resilience, as it has been linked with better self-reported health among immigrant Latinas, and has been hypothesized to capture immigrant experiences that may alter perceived self-worth (Garza et al. 2017). Maternal SSS was measured at pre- and post-election time points with the MacArthur SSS scale, which asks mothers to report where they felt they fit on a social ladder (range 1-10) in relation to others in the US (Adler et al. 2000). For children we used a modified SSS scale, which asked them to report how their family fit on a social ladder in relation to other families in the US (poorer, same, or richer for children). Higher scores indicated better perceived social standing.

Social support was measured differently in the children and their mothers. We measured parental social support in the children as further described in Table 3.1 in Chapter 3 (in brief, other forms of peer support were invariable in our dataset). Social support and social connection in the mothers were measured with a combined index from the Berkman Syme Social Network

Index (Berkman and Syme 1979) in addition to questions stemming from our focus groups (Non et al. 2019).

Optimism was measured in the mothers using the revised version of the Life Orientation Test (LOT-R), a 10-item version of the original LOT (Carver et al. 2010). Optimism was measured in children only at the post-election time point using the youth LOT (Y-LOT). Y-LOT has been validated in a racially diverse set of 3rd to 6th grade children (Ey et al. 2005).

Outcomes:

In both time points, we asked mothers to report on their self-rated health; children were asked only at the post-election time point. Self-rated health was measured with the question: "In general, I would say my health has been: Excellent, Very Good, Good, Fair, Poor." This intentionally vague question is widely used in nationally representative surveys, and found to be a powerful predictor of morbidity and mortality, regardless of other physical and psychosocial health factors (Idler and Angel 1990; Idler and Benyamini 1997; Kaplan and Camacho 1983). While the type of health is left unspecified (e.g., mental or physical), the question is designed to capture individuals' personal assessment according to their own definition of health (Snead 2007).

Mental Health:

To detect anxiety and depression symptoms in the children, we used the Revised Child Anxiety and Depression Scale (RCADS) (Chorpita et al. 2000). RCADS is a 47-item self-report questionnaire for youth that has subscales of separation anxiety disorder, social phobia, generalized anxiety disorder, panic disorder, obsessive compulsive disorder, and major depressive disorder. A total anxiety scale was also calculated from the sum of the 5 anxiety subscales, and a total internalizing scale was calculated from all of the subscales. Internalizing

symptoms here are those that are experienced by the individual, such as sadness, anxiety, and loneliness, rather than externalizing problems, such as aggression and hyperactivity (Levesque 2011). Additionally, we also used a parent's version (RCADS-P) to similarly assess the mother's perception of her child's anxiety and depression symptoms (Ebesutani et al. 2010; Ebesutani et al. 2011). The scores were transformed based on child's grade and gender. Transformed scores by subscale were classified as meeting the normal threshold, borderline clinical threshold, and clinical threshold.

We also measured the perception of stress through the Perceived Stress Scale (PSS) in both children and their mothers (Cohen et al. 1983). It is a measure of the perceptions of how situations in one's life are stressful. It is one of the most frequent tools to measure stress in chronic conditions and situations often not listed in other life-event scales (Leung et al. 2010). We used a shortened 10-item scale as it has shown high reliability (Ruisoto et al. 2020). Scores were divided into low, moderate, and high stress.

To measure anxiety and depression in the mothers, we used the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983). The HADS is a 14-item self-reported questionnaire that is reliable tool for detecting states of anxiety and depression. It has seven items each for depression and anxiety subscales with scoring ranking participants in Normal, Borderline Abnormal (borderline case), and Abnormal (case).

Covariates

We present unadjusted correlations, minimally adjusted models (adjusted for child's age, child's gender, mother's age, and mother's smoking status), and fully adjusted models (adjusted for those in minimally adjusted models plus marital status, number of years lived in the US, and

legal status). We did not include trouble paying basic bills as a covariate as it correlated strongly with most of our stress measures.

Statistical analyses

We first tested correlations between each psychosocial stressor and resilience factor, key demographic factors, and mental health outcomes to assess basic relationships among all our variables of interest.

Pre/post analyses.

Paired sample t-tests investigated differences in means of continuous measures in the same mothers pre- and post-election. McNemar tests for paired samples were conducted on all categorical variables.

Linear Regressions.

We next used multivariate linear models to analyze these same associations after adjusting for a minimal set of key covariates. In fully adjusted models, we additionally included socioeconomic and immigrant-related demographic factors. Although these variables could also contribute to stress, we included them as covariates as we were interested in the effects of the stress scales independent of these factors. Though they were treated as covariates, we report the effects of each of these factors given their role in contributing to the IRS context. We used Bonferroni correction to adjust for multiple testing within each group (8 exposures in children and 10 exposures in mothers multiplied by seven mental health outcomes in the children and four in the mothers). The Bonferroni threshold for significance is 0.00089 in children and 0.00125 in mothers. All analyses were conducted in R (http://www.R-project.org).

Qualitative data analysis

Some of the survey responses were in the form of open-ended answers, which were translated into English by native Spanish speakers. These transcripts were investigated in a qualitative assessment to identify common themes (e.g., immigrant-related) across mother and child surveys. Two independent investigators reviewed translated responses and developed a simple, rapid coding analysis which identified key stress-related themes that were common across many interviews. This paper focuses on key topics that emerged relating to stress, deportation, and family separation stemming from the 2016 Presidential Election and Presidential policies.

RESULTS

Demographics

Characteristics of our analytical sample of 81 pre-election and 38 post-election CHICOS participant children are displayed in Table 2.1. At the pre-election time point, the children ranged in age from 5-14 years, with a mean of 8.7 years. Slightly more than half were female (56.3%), and the majority of the children were born in the US (72.8%). Most of the mothers were born in Mexico (86.4%), were undocumented (83.8%), were married (85.2%), and were not smokers (97.5%). Mothers on average were in the US for 12.7 years, though with a wide range (4-27). Mothers were generally of low SES, with an average of 9.4 years of education, and on average reported low mean subjective social status of 4.07 (out of 10). At the post-election time point, children were on average 2.0 years older than at pre-election, with a mean age of 10.7 years. All other demographics were largely similar over time.

Children's stressors, resilience, and mental health post-election

Children's report of immigrant-related stress increased significantly, and social support from parents also increased significantly. School stress and fear of parent deportation also increased over time, though these changes were minimal.

Mothers and children reported significantly different levels of mental health for the children across all of the RCADS mental health outcomes, with mothers reporting lower levels of anxiety and depressive symptoms for their children relative to children's self-reports (Table 2.2). The mothers reported high levels of separation anxiety among their children while the children reported even higher levels for this outcome, and the trends were similar across all of the other mental health subscales.

Maternal stressors, resilience, and mental health over time

There were small but significant decreases post-election in levels of immigrant-related stress and overall discrimination stress ($p=0.04$). However, reported frequency of women being arrested or harassed by police, though low to start, both increased over time (Table 2.1). Post-election, mothers reported significantly decreased optimism ($p<0.01$) and marginally decreased social connection/support ($p=0.08$) that did not reach statistical significance (Table 2.1).

At post-election, mothers reported significantly higher levels of tiredness relative to pre-election (64% vs 87%, McNemar $x^2=4.27$, $p=0.04$), but no difference in other symptoms of stress. When mental health measures were classified into diagnostic groups, a high proportion reported borderline or clinically diagnostic levels of depressive symptoms (29%), anxiety symptoms (39.5%), and moderate levels of perceived stress (86.8%) post-election. No women reported high stress.

Correlations

At both time points, all stressors correlated positively with each other, and resilience factors negatively correlated with stressors (Tables 2.3 – 2.6). Self-rated quality of health correlated negatively with stressors and positively with resilience factors.

Linear regressions

Though few of our associations passed Bonferroni correction, we note that in an exploratory study, Bonferroni can be overly conservative given that the methylation levels at the sites are correlated with each other, as are the stressors, so they should not all be considered independent tests. Below we present both uncorrected and corrected associations.

Association with children's mental health at post-election:

School stress was positively associated with total anxiety, total internalizing, social phobia, and major depressive disorder (all p<=0.031). Immigrant-related stress was positively associated with total anxiety, total internalizing, generalized anxiety, separation anxiety, self-reported quality of health, and perceived stress (all p<=0.033). Only the association between immigration-related stress and separation anxiety maintained significance after the Bonferroni correction (p<0.0001). All minimally adjusted models are reported in Table 2.7.

The results of the fully adjusted models (Table 2.8) were similar. The only additional findings revealed with fully adjusted models included positive associations between total stress and panic disorder (B: 16.786(6.698), p-value=0.019), and between Immigrant-related stress with major depression disorder (B:6.719(3.230), p-value=0.047). No associations passed the Bonferroni correction.

Associations with Mothers' mental health at post-election:

Total maternal stress was positively associated with anxiety, depression, and perceived stress (all p-value<=0.016). Household stress was positively associated with depression (B:

6.221(2.523), p-value=0.019). Family economic stress was positively associated with anxiety, depression, and perceived stress (all p-value<=0.014). Subjective social status was inversely associated with perceived stress (B: -0.986(0.474), p-value=0.046). Optimism was inversely associated with depression (B: -0.578(0.235), p-value=0.020). Only the association between total maternal stress and depression maintained significance following a Bonferroni correction (p<0.0003). All minimally adjusted models are reported in Table 2.9.

The fully adjusted models (Table 2.10) in the mothers showed similar findings, with the exception of two new significant associations. Discrimination stress was associated with PSS (p-value=0.043). Health stress was associated with depression and self-reported quality of health (p-value=0.040). SSS was negatively associated with self-reported quality of health (p-values=0.025). Only the association between maternal total stress and depression maintained significance after Bonferroni correction.

Contextualizing with brief qualitative analyses

Children were asked several questions about their feelings regarding President Trump. Common words that described many of the children's responses include the feelings of "frustrated," "unsafe," "mad/angry," "scared," "nervous," "shocked," and "worried." Several children described the President as "racist against all non-whites." Some children described him as uncaring, wanting to separate their families. When asked about their feelings regarding the election, common responses related to feelings of frustration, worry, anger, fear, sadness, and uncertainty. One 11-year-old child stated, "I felt like there will be a lot of changes in the future" when asked if things have changed for you or your family since Trump became President. Another 15-year-old child mentioned that "the future is very uncertain" with regards to immigration status. Most (73.7%) of the children reported that they do not discuss politics at

home/try to avoid the topic at home. Several children whose parents did talk to them about Trump, were told not to worry by their parents, including phrases such as "…to calm down and everything will be fine" and "he's racist and wants [to be] the Latinos [to] leave – but he won't do anything."

In an open-ended question about the most commonly reported worry among children at the pre-election time point, most children responded with worries related to school, sports activities, pets, and friends with none describing worries about their own safety and/or their parents' safety. An 11-year-old said that "some people won't let us go into certain restaurants." Only 17% reported worries related to family separation at this time point. In contrast, at the post-election time point, 37% of responses were related in some way to family separation. Some characteristic responses included "my parents having to leave," "my parents getting arrested," "that we need to come back to Mexico," "[my] family being reported and sent back to home country because of the president," "…what if ICE agents come to my house and take me to a detention center in the middle of the night away from my parents," and "…never seeing my family again."

When asked if their parents' behaviors have changed at all since Trump was elected many children mentioned more cautious behavior changes, saying that they "go out less than before," "they are more protective," "they are trying to learn more English," "[they] are worried," "more stressed," and "less relaxed" than before he was elected.

Several children reported instances of racism/discrimination. Some reported "more dirty looks" when they went out over the last two years. One 15-year-old said, "I feel afraid, I remember that once we went to the supermarket and there was an American and he started

saying racist things to us. Trump told him he was going to get us out of the US that it was us for them to return to Mexico."

Mothers were also asked about how often they spoke with their children about Trump and/or his policies, and the majority seemed to be going out of their way to not talk to their children about Trump/politics in their homes. Similar to what the children described, there were overwhelming sentiments observed in the mothers' responses that they felt sad, unsafe, or threatened. Similarly, their described behavior changes were fear-based; being more cautious when going out, limiting their outings, etc. For example, one mother said, "Going out is no longer the same. I go out of necessity. Otherwise, I'd be home." Other responses of behaviors being affected include fear/avoidance of large crowded events, being out too late (fear of being seen by the police), follow traffic laws (respecting speed limits), and generally avoiding anything that could jeopardize their residence in the US. This is especially poignant as the majority of arrests for deportation in Nashville began from minor traffic violations.

Many mothers felt that their children were adversely affected by the election results. One mother stated, "They were shocked at first. After the election, they're very worried that we would be deported." Another said, "[The children] have been affected, especially the ones who go to school. [They] aren't capable of understandings the threats that they'll be deported from the USA." One interesting response from the mother captured the fear and sadness of separating families by stating, "I feel very sad because they're doing the same as East Germany and West Germany, dividing families."

Many of the women found support and solace in God to help them through this particular time, with various mothers stating that they have "strength in God," "God protects me," and "We as Christians leave everything in God's hands."

DISCUSSION

We identified pre/post changes in sociocultural stressors, protective factors, and mental health among Latinx children and mothers since the election of President Trump. As hypothesized, our data support heightened levels of sociocultural stressors over time, though changes were not always consistent among family members. For example, the children reported an *increase* in immigrant-related stress, while mothers reported a surprising *decrease* in immigrant-related stress and discrimination stress post-election, though the latter is modest. The mothers also reported higher rates of police harassment or arrests, as there were few to none at the pre-election time point. Mothers consistently reported significant *decreases* in protective factors (e.g., lower optimism and social support/social connection), while the children reported an *increase* in parental social support.

The reduction in protective factors in the mothers is particularly concerning, since factors like familism and social support are important for maintaining mental health, particularly in high stress environments (Corona et al. 2016; Valdivieso-Mora et al. 2016) and especially in Latinx communities (Campos et al. 2014). Interestingly, most of these decreasing factors were related to the value of family, which is an important source of social support in Latinx families (Campos et al. 2014). While part of this loss may be simply due to time away from extended families, the observed decrease in protective factors, regardless of years in the US, may relate to Trump's policies towards immigrants. The decrease in social support may be due to loss of community integration as family and friends get deported (Society for Community Research and Action 2018). Reduced social support could also result from fear-related behavior changes, as several of the children and mothers in our study reported going out less, staying inside unless absolutely necessary, a reduction in driving/stricter adherence to speed limits, and worried about attending

larger events, etc. The reduction in optimism we identified is consistent with findings that during the first 18 months of the Trump presidency, there was an increased number of Latinx individuals who saw a worsening situation for themselves and Latinx individuals overall (Lopez et al. 2018). There has also been an erosion of optimism about the future, and the well-being of their children, particularly for non-citizen immigrants (Lopez et al. 2018).

Interestingly, the decreased discrimination reported in mothers is consistent with findings from a nationally representative study of White Americans, who self-reported a decline in prejudice towards Latinx people after Trump's political emergence (Hopkins and Washington 2019), potentially in rejection of rising racist presidential rhetoric (Hopkins and Washington 2019). Alternatively, mothers may simply have been more hesitant to report discrimination under the current political climate.

The decrease in immigrant-related stress and discrimination could also be related to our post-election sample attrition rate of 53.1%. With several mothers within our study reporting behavioral changes, those that are experiencing higher extremes of negative experiences likely did not participate in the post-election study.

Mental health

The children reported high levels of anxiety and depression symptoms at the post-election time point– including elevated levels of internalizing, anxiety, major depression disorder, panic disorder, and separation anxiety. Approximately a quarter of the children exhibited clinical levels of separation anxiety, which aligns with qualitative responses about being worried of being separated from their families. The children reported elevated anxiety and depression symptoms, especially in separation anxiety, major depression disorder, and panic disorder in comparison to earlier reports from low-income black and white children (Latzman et al. 2011). The mothers

reported high levels of only separation anxiety among their children while the children reported even higher levels for this outcome, and across all of the subscales, indicating that their mothers may have underestimated the level of mental health problems in their children. This is consistent with other findings that caregivers reported lower levels of anxiety and depressive symptoms compared with the children's self-reports (Martin et al. 2020).

We found children's stressors, such as immigrant-related stress, everyday discrimination, and school stress, positively associated with multiple anxiety and depression scales. Anxiety and depressive symptoms often co-occur in adolescence (Essau et al. 2018) with anxiety disorders being the most frequent in childhood, adolescence, and adulthood globally. If left untreated, anxiety disorders beginning in early childhood can become chronic (Essau et al. 2014; Gregory et al. 2007; Woodward and Fergusson 2001). Youth who suffer from anxiety and depression have been found to be more likely to suffer from disrupted peer relationships and impaired school performance (Kochel et al. 2012; Patalay et al. 2015). Internalizing symptoms are the most prevalent of mental health problems in childhood and adolescence, and have been linked to school performance (Patalay et al. 2015).

These data speak to the importance of increasing screening and treating Latinx children for mental health disorders, even as young as early childhood. Unfortunately, treatment of mental health disorders in Latinx children may be compromised by limited healthcare access and quality of healthcare, and lack of routine mental health screenings by primary care doctors (Caballero et al. 2016). Interventions in a school setting might benefit Latinx children of immigrants because some barriers of traditional mental health treatment (e.g., stigma, cost, and time) may be reduced, relative to within the clinic setting (Barrett and Pahl 2012; Masia Warner and Fox 2012).

In mothers, we found discrimination stress, family economic stress, and household stress were positively associated with anxiety, depression, and perceived stress. Subjective social status and optimism were both negatively associated with perceived stress and with depression. Given decreasing protective factors over time in the mothers, targeted interventions to increase these factors and increase screenings could offset declines in mental health. Extensive research exists on maternal depression and childhood financial well-being and their effects on both maternal health and early childhood development (Harris and Santos 2020). Depression and anxiety are important indicators of increasing disability and, if unaddressed, represent a social and economic health burden on society.

Strengths and limitations:

Our study contains a number of important strengths. We uniquely included perspectives of mothers and children, and found that mothers and children reported differently on many measures, such as bullying and school stress. We also were able to contextualize some of the quantitative findings by integrating some qualitative data. However, interpretation of our findings is limited by small samples sizes, especially at the post-election time point, and self-reported measures, highlighting the need for follow-up studies in larger cohorts. The majority of our mothers were born in Mexico, and were surveyed just before and up to 2 years after the 2016 Presidential election, and therefore may not generalize to all Latinx mothers in other geographic locations or time periods. Larger studies could examine Latinx mothers who immigrated from different countries, across different generations of immigrants, as well as interactions between immigrant status and sociocultural stressors on mental health outcomes.

CONCLUSION

This study explored how a shift in political leadership might be associated with the mental health of a vulnerable population in the US. We found that immigrant-related stress, everyday discrimination, and school stress in children were all positively associated with anxiety and depressive symptoms, including separation anxiety. In mothers, we found discrimination stress, family economic stress, and household stress were positively associated with anxiety, depression, and perceived stress, respectively. Subjective social status and optimism were negatively associated with perceived stress and depression, respectively. Given decreasing protective factors over time in the mothers, targeted interventions to increase these factors and increase screenings for children and mothers could offset declines in mental health. Access to mental (or any medical) health care has historically been limited for immigrant communities, and further inhibited by stressful events such as the COVID-19 pandemic, and changes to the "public charge" rule, which penalizes immigrants for using Medicaid (Duncan and Horton 2020). Continued research on increasing access to healthcare, particularly for children, and best practices for enhancing protective factors for Latinx health is warranted.

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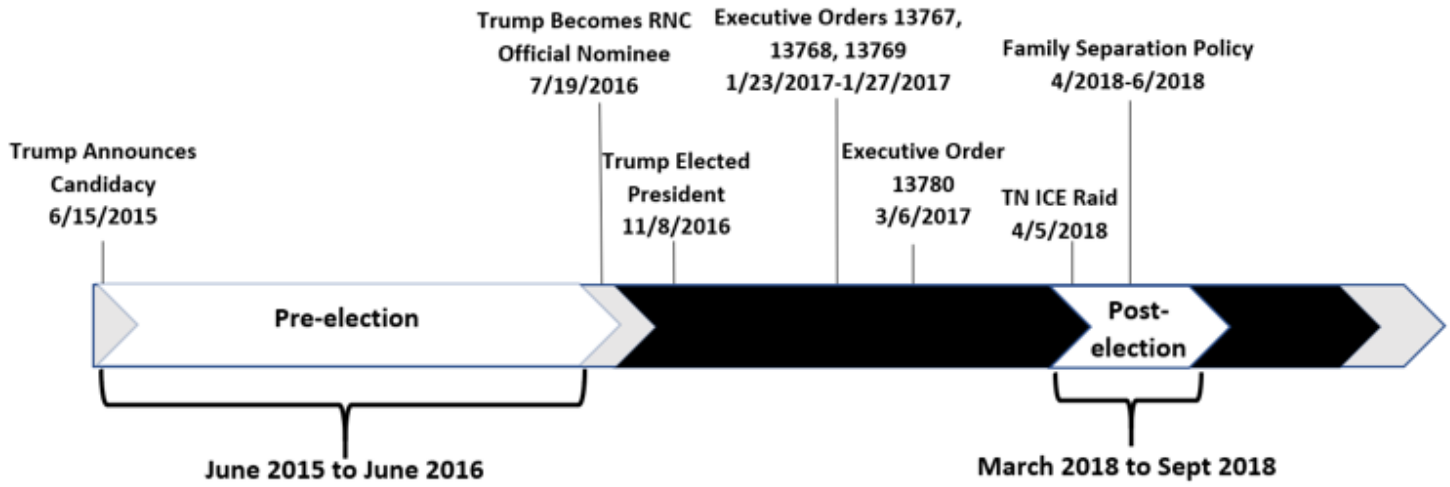
Citation: Clausing, E.S. & Non, A.L. Do immigrant-related stressors associate with Latinx child mental health? (in preparation)

Citation: Non, A.L., Clausing, E.S., D'Anna-Hernandez, K.L. Shifts in sociocultural stressors, protective factors, and mental health for US Latina mothers associated with the 2016 Republican presidential nomination. Submitted to *Cultural Diversity & Ethnic Minority Psychology*.



1. Executive Order 13767 "Border Security and Immigration Enforcement Improvements" demands that a wall be built along the US-Mexico border; expanded use of detention; limits on access to asylum; enhanced enforcement along US-Mexico border.
2. Executive Order 13768 "Enhancing Public Safety in the Interior of the United States" prohibits "sanctuary jurisdictions" from receiving federal funding; enforces local-federal immigration cooperation; expands priority list of noncitizens subject to deportation; and 10,000 additional ICE agents authorized.
3. Executive Order 13769 "Protecting the Nation from Foreign Terrorist Entry into the United States" limits travel from Libya, Syria, Yemen, Somalia, Iran, North Korea, and Venezuela and all refugees who do not possess visas or travel documents for 90 days; bans Syrian refugee resettlement indefinitely.
4. Executive Order 13780 "Protecting the Nation from Foreign Terrorist Entry into the United States"

Figure 2.1: Timeline of policies enacted during data collection. Descriptions of each policy are in the textbox below.

Table 2.1. Demographics, social stressors, and resilience factors pre- and post-election complete case data.

	Pre-election (n=81) n, % or mean (sd, range)	**Post-election (n=38)** n, % or mean (sd, range)	**Missing data pre-/post-**	**p-value‡**
Child Demographics				
Age in years	8.67 (2.19, 5-14)	10.68 (1.94, 8-15)	--/--	**<2.2e-16**
Gender (female)	46 (56.8%)	19 (50%)	--/--	
Country of birth				
United States	59 (72.8%)	27 (71.1%)	--/--	0.568
Other	22 (27.2%)	11 (28.9%)		
Mother Demographics				
Age in years	34.80 (5.93, 23-52)	37.44 (4.78, 29-47)	--/--	**<2.2e-16**
Country of birth			--/--	**0.000696**
Mexico	70 (86.4%)	35 (92.1%)		
Other Latinx country	11 (13.6%)	3 (7.9%)		
Years in US	12.69 (4.10, 4-27)	15.03 (3.42, 6.67-22.42)	--/--	**<2.2e-16**
Years in Nashville	11.75 (4.06, 2-22)	14.48 (3.77, 4.75-22.42)	--/--	**0.0005238**
Legal status			1/1	4.161e-06
Undocumented	67 (83.8%)	33 (89.2%)		
Documented	13 (16.2%)	4 (10.8%)		
Marital status			--/--	**0.04123**
Married	69 (85.2%)	30 (76.9%)		
Single	12 (14.8%)	9 (23.1%)		
Years of Education	9.37 (3.30, 2-18)	9.64 (3.22, 2-16)		--
Trouble paying basic bills (yes)	31 (38.3%)	10 (26.3%)	--/--	0.2278
Smoking frequency	2 (2.5%)	3 (7.7%)	--/--	0.6171
Child Psychosocial Stressors				
Total Child Stress	0.55 (0.26, 0.06-1.31)	0.43 (0.15, 0.12-0.75)	4/2	0.3171
Immigrant stress score	0.83 (0.39, 0-1.75)	0.98 (0.38, 0.2-1.8)	2/--	**0.006908**
Discrimination stress	0.26 (0.36, 0-2)	0.22 (0.33, 0-1.4)	2/--	0.8798
School-related stress	0.52 (0.32, 0-1.43)	0.55 (0.30, 0-1.43)	3/1	*0.06655*
Fear of parent deportation			2/--	0.1541
Never	30 (38.0%)	9 (23.7%)		
Sometimes	30 (38.0%)	19 (50.0%)		
Always	19 (24.0%)	10 (26.3%)		
Child Resilience Factors				
Subjective SES			16/2	0.4036
Richer	15 (23.1%)	17 (47.2%)		
Same	42 (64.6%)	14 (38.9%)		
Poorer	8 (12.3%)	5 (13.9%)		
Social support parents	1.40 (0.43, 0.5-2.0)	1.54 (0.34, 0.6-2.0)	2/--	**0.001021**
Optimism	--	33.16 (7.04, 20-46)	81/--	--

‡ p-value based on paired t-tests for continuous variables, and McNemar (paired Chi Square) test for categorical variables. Comparisons were calculated only on the 38 individuals in both time points (significant associations shown in bold).

Table 2.1. Demographics, social stressors, and resilience factors pre- and post-election complete case data, continued.

	Pre-election (n=81) n, % or mean (sd, range)	**Post-election (n=38)** n, % or mean (sd, range)	**Missing data pre-/post-**	**p-value‡**
Child Mental Health				
RCADS Clinical Levels No. (%)				
Anxiety Elevation		5 (13.2%)		
Total Internalizing		6 (15.8%)		
Generalized Anxiety		1 (2.6%)		
Major Depression		6 (15.8%)		
Panic Disorder		6 (15.8%)		
Social Phobia		2 (5.3%)		
Separation Anxiety		9 (23.7%)		
OCD		5 (13.2%)		
Mother report of Psychosocial Stressors				
Total maternal stress	0.29 (0.17, 0.02-0.78)	0.25 (0.12, 0.02-0.53)	5/3	**0.02051**
Immigrant stress score	0.46 (0.23, 0-0.9)	0.42 (0.21, 0-0.8)	--/--	**0.003249**
Discrimination score	0.43 (0.24, 0-1)	0.36 (0.24, 0-0.86)	3/--	*0.05956*
Child's school-related stress score	0.25 (0.22, 0-1)	0.20 (0.17, 0-0.57)	--/--	0.1147
Household stress	0.21 (0.21, 0-0.8)	0.23 (0.20, 0-0.8)	--/--	0.6672
Family economic stress	0.23 (0.23, 0-1)	0.17 (0.17, 0-0.63)	3/2	*0.06724*
Health stress	0.31 (0.26, 0-1)	0.26 (0.22, 0-1)	--/--	0.2057
Domestic violence in the family	9 (11.3%)	4 (10.3%)	1/--	0.3711
Mother Resilience variables				
Subjective SES	4.07 (1.90, 1-9)	4.41 (1.60, 1-8)	--/--	*0.06374*
Social support and connection	2.48 (0.57, 0.25-3.40)	2.20 (0.55, 1-3.4)	--/--	**0.04383**
Optimism	17.70 (3.00, 12-24)	13.64 (2.28, 8-18)	2/--	**9.252e-08**
Maternal Mental Health				
HADS – Anxiety				
Abnormal		5 (13.2%)		
Borderline		10 (26.3%)		
Normal		23 (60.5%)		
HADS – Depression				
Abnormal		5 (13.2%)		
Borderline		6 (15.8%)		
Normal		27 (71.1%)		
RCADS Clinical Levels No. (%)				
Anxiety Elevation		2 (5.6%)		
Total Internalizing		6 (15.8%)		
Generalized Anxiety		2 (5.6%)		
Major Depression		2 (5.6%)		
Panic Disorder		2 (5.6%)		
Social Phobia		3 (8.3%)		
Separation Anxiety		6 (16.7%)		
OCD		2 (5.6%)		

‡ p-value based on paired t-tests for continuous variables, and McNemar (paired Chi Square) test for categorical variables. Comparisons were calculated only on the 38 individuals in both time points (significant associations shown in bold).

Table 2.2: RCADS comparison between parent and child's perspective at post-election.

	Mother's Perspective (n's=36-37)	Child's Perspective (n=38)	p-value‡
Total Anxiety	22.47 (12.45, 6-73)	37.61 (17.67, 5-81)	**2.35E-05**
Total Internalizing	26.53 (14.57, 8-80)	45.95 (22.45, 7-97)	**1.87E-05**
Generalized Anxiety	4.49 (2.83, 1-13)	6.82 (3.70, 0-15)	**0.00268**
Major Depression	4.35 (3.34, 0-13)	8.34 (5.83, 1-24)	**0.00036**
Panic Disorder	2.35 (3.07, 0-14)	6.76 (5.55, 0-25)	**5.16E-05**
Social Phobia	8.41 (5.08, 0-20)	11 (5.76, 0-26)	**2.05E-02**
Separation Anxiety	4.57 (4.32, 0-13)	6.63 (3.82, 1-14)	**9.04E-03**
OCD	2.92 (3.14, 0-17)	6.39 (4.26, 0-15)	**1.45E-04**

‡ p-value based on paired t-tests. Comparisons were calculated only on the 36-37 paired dyads (significant associations shown in bold).

Table 2.3: Psychosocial and resilience factors correlations in the child variables at pre-election. Values in **bold** represent having p-values less than 0.05. *Italicized* values represent having p-values that are marginal.

	Total Stress	IRS	Discrimination Stress	School Stress	Fear of Parent Deportation	Biggest Worry	SSS	Social Support	Child's age
Total Stress	1.000								
IRS	**0.665**	1.000							
Discrimination Stress	**0.703**	**0.223**	1.000						
School Stress	**0.833**	**0.275**	**0.478**	1.000					
Fear of Parent Deportation	**0.564**	**0.693**	0.193	**0.373**	1.000				
Biggest Worry	**0.224**	0.146	**0.245**	0.123	**0.257**	1.000			
SSS	0.178	0.139	0.073	0.160	0.101	0.142	1.000		
Social Support	**0.296**	**0.302**	0.121	**0.264**	*0.190*	0.038	*-0.207*	1.000	
Child's age	*0.199*	**0.300**	-0.153	*0.198*	**0.253**	-0.051	-0.043	**0.225**	1.000

Table 2.4: Psychosocial and resilience factors correlations in the child variables at pre-election.

Values in **bold** represent having p-values less than 0.05. *Italicized* values represent having p-values that are marginal.

	Total Stress	IRS	Discrimination Stress	Fear of Parent Deportation	Biggest Worry	EDS	PSS	Total Anxiety	Total Internalizing	Major Depression	Generalized Anxiety	Panic Disorder	Social Phobia	Separation Anxiety	SSS	Social Support	YLOT	Self-rated health	Child's age
Total Stress	1.000																		
IRS	**0.647**	1.000																	
Discrimination Stress	**0.510**	-0.193	1.000																
Fear of Parent Deportation	**0.384**	**0.646**	-0.164	1.000															
Biggest Worry	0.218	**0.430**	-0.206	**0.388**	1.000														
EDS	**0.480**	0.354	0.242	0.106	-0.182	1.000													
PSS	0.262	**0.393**	0.016	0.189	0.036	0.270	1.000												
Total Anxiety	0.256	0.240	0.245	0.033	-0.277	**0.385**	**0.453**	1.000											
Total Internalizing	0.270	0.231	0.285	0.003	-0.309	**0.421**	**0.488**	**0.986**	1.000										
Major Depression	0.261	0.161	**0.355**	-0.086	**-0.348**	**0.463**	**0.507**	**0.766**	**0.863**	1.000									
Generalized Anxiety	0.205	**0.332**	0.079	0.145	-0.190	0.362	**0.387**	**0.869**	**0.826**	**0.550**	1.000								
Panic Disorder	0.306	0.123	**0.362**	-0.100	**-0.342**	0.279	0.319	**0.782**	**0.808**	**0.742**	**0.545**	1.000							
Social Phobia	0.134	0.187	-0.019	0.072	-0.081	0.299	**0.360**	**0.725**	**0.682**	**0.429**	**0.599**	**0.348**	1.000						
Separation Anxiety	0.283	**0.355**	0.256	0.171	-0.052	0.181	**0.380**	**0.615**	**0.620**	**0.525**	**0.515**	**0.508**	0.114	1.000					
SSS	-0.229	*-0.304*	0.050	**-0.333**	**-0.370**	-0.249	-0.075	-0.202	-0.194	-0.133	-0.127	-0.157	-0.267	-0.140	1.000				
Social Support	*0.308*	-0.060	-0.131	-0.192	0.141	**0.463**	*0.304*	-0.175	-0.197	-0.229	-0.154	-0.124	-0.253	-0.009	0.126	1.000			
YLOT	-0.118	-0.110	0.103	-0.135	-0.075	**0.371**	**0.321**	0.050	-0.010	-0.190	0.065	0.003	-0.109	0.195	-0.024	**0.383**	1.000		
Self-rated health	-0.235	-0.175	*-0.315*	0.052	0.088	-0.301	-0.155	**-0.479**	**-0.513**	**-0.524**	**-0.414**	**-0.404**	-0.224	*-0.287*	0.199	0.056	-0.131	1.000	
Child's age	0.068	**0.329**	**-0.435**	*0.319*	0.231	0.096	0.073	-0.081	-0.102	-0.149	0.007	-0.153	0.164	*-0.285*	-0.034	0.092	-0.231	**0.369**	1.000

Table 2.5: Psychosocial and resilience factors correlations in the maternal variables at pre-election.

Values in **bold** represent having p-values less than 0.05. *Italicized* values represent having p-values that are marginal.

	Total Stress	IRS	Discrimination Stress	Household Stress	Health Stress	Family Economic Stress	SASH	SSS	SSSC	LOPT	Trouble Paying Bills	Marital Status	Years in US	Self-Related Quality of Health	Legal status	Education	Maternal age
Total Stress	1.000																
IRS	**0.737**	1.000															
Discrimination Stress	**0.633**	**0.452**	1.000														
Household Stress	**0.719**	**0.355**	**0.312**	1.000													
Health Stress	**0.846**	**0.546**	**0.433**	**0.489**	1.000												
Family Economic Stress	**0.870**	**0.498**	**0.501**	**0.685**	**0.594**	1.000											
SASH	0.128	-0.027	-0.062	0.059	0.138	0.015	1.000										
SSS	**-0.310**	**-0.393**	-0.190	-0.131	**-0.301**	-0.151	-0.065	1.000									
SSSC	-0.130	-0.108	0.033	-0.100	-0.181	-0.023	-0.130	**0.287**	1.000								
LOPT	-0.133	-0.215	0.161	**-0.237**	-0.127	-0.129	0.105	0.061	**0.271**	1.000							
Trouble Paying Bills	**0.655**	**0.346**	**0.332**	**0.520**	**0.459**	**0.573**	0.049	**-0.232**	-0.194	-0.179	1.000						
Marital Status	*-0.206*	-0.161	-0.171	*-0.185*	-0.166	-0.159	-0.028	**0.296**	0.036	-0.069	-0.114	1.000					
Years in US	-0.125	-0.125	-0.009	-0.058	-0.179	-0.060	**0.350**	-0.012	0.038	**0.245**	0.013	-0.003	1.000				
Self-Related Quality of Health	**-0.414**	**-0.241**	*-0.197*	**-0.225**	**-0.386**	**-0.378**	-0.049	0.166	0.154	**0.236**	**-0.285**	0.030	0.163	1.000			
Legal status	0.055	0.180	-0.057	-0.036	0.132	-0.002	**0.232**	**-0.319**	**-0.288**	**-0.247**	0.061	0.090	*0.209*	-0.174	1.000		
Education	0.068	0.052	-0.134	0.126	0.126	0.036	**0.309**	0.029	-0.147	-0.008	-0.058	0.091	0.141	0.070	0.066	1.000	
Maternal age	0.009	0.013	0.168	-0.004	0.025	0.050	-0.002	-0.080	-0.005	0.172	-0.103	0.049	**0.534**	0.084	0.082	0.122	1.000

Table 2.6: Psychosocial and resilience factors correlations in the maternal variables at post-election.

Values in **bold** represent having p-values less than 0.05. *Italicized* values represent having p-values that are marginal.

	Total Stress	IRS	Discrimination Stress	Household Stress	Health Stress	Family Economic Stress	PSS	HADS Anx	HADS Dep	EDS	SASH	SSS	SSSC	LOPT	Trouble Paying Bills	Marital Status	Years in US	Self-Related Quality of Health	Legal status	Maternal age
Total Stress	1.000																			
IRS	0.413	1.000																		
Discrimination Stress	**0.774**	0.094	1.000																	
Household Stress	0.429	0.027	0.073	1.000																
Health Stress	0.385	0.144	-0.119	**0.633**	1.000															
Family Economic Stress	**0.903**	0.238	**0.828**	0.264	0.039	1.000														
PSS	**0.697**	0.322	0.457	0.424	0.332	**0.660**	1.000													
HADS Anx	**0.627**	0.037	**0.521**	0.346	0.215	**0.667**	**0.779**	1.000												
HADS Dep	**0.648**	0.015	0.383	**0.623**	0.465	**0.626**	**0.728**	**0.854**	1.000											
EDS	**0.678**	0.136	**0.925**	-0.034	-0.315	**0.820**	0.414	0.419	0.253	1.000										
SASH	-0.220	0.122	-0.019	-0.371	-0.339	-0.221	-0.065	-0.340	-0.351	0.097	1.000									
SSS	-0.509	-0.263	**-0.517**	-0.064	0.036	**-0.503**	**-0.669**	**-0.519**	-0.360	-0.481	-0.310	1.000								
SSSC	**-0.593**	-0.048	**-0.639**	-0.319	-0.011	**-0.642**	**-0.702**	**-0.516**	-0.418	**-0.645**	-0.086	**0.645**	1.000							
LOPT	-0.003	-0.159	0.326	-0.435	**-0.535**	0.137	-0.350	-0.327	**-0.538**	0.478	0.290	-0.127	-0.201	1.000						
Trouble Paying Bills	**0.613**	**0.380**	0.274	**0.453**	0.290	**0.678**	**0.381**	**0.426**	**0.520**	**0.342**	-0.157	-0.110	0.008	0.083	1.000					
Marital Status	-0.085	-0.259	-0.034	0.111	-0.207	0.142	**0.351**	0.233	0.214	-0.037	0.061	**-0.335**	**-0.423**	-0.075	-0.052	1.000				
Years in US	-0.101	-0.189	-0.082	-0.108	-0.074	-0.216	-0.125	-0.137	-0.141	-0.216	0.165	0.116	0.259	*-0.305*	-0.198	0.011	1.000			
Self-Related Quality of Health	-0.263	0.064	-0.067	**-0.344**	**-0.359**	0.055	-0.205	*-0.167*	-0.299	0.122	-0.202	0.161	0.055	0.037	-0.110	0.029	0.025	1.000		
Legal status	0.001	0.043	0.048	0.231	-0.080	0.049	0.057	0.071	0.211	-0.009	*-0.303*	-0.204	-0.133	-0.036	0.259	0.065	-0.217	-0.023	1.000	
Maternal age	-0.135	-0.167	-0.029	-0.080	-0.001	**-0.347**	-0.153	0.056	-0.171	-0.263	0.014	0.017	-0.022	-0.140	-0.206	0.233	**0.551**	-0.119	-0.156	1.000

Table 2.7: Children's psychosocial stressors and resilience factors and mental health outcomes.

	Mental Health								
	Total Anxiety	**Total Internalizing**	**Generalized Anxiety**	**Panic Disorder**	**Social Phobia**	**Major Depression**	**Separation Anxiety**	**Self-Reported Health Status**	**PSS**
Child variables									
Stress factors:									
Total stress score	34.720 (20.656)	43.954 (26.177)	7.107 (4.360)	*12.128 (6.506)*	5.600 (7.216)	9.234 (6.803)	7.335 (4.162)	-2.363 (1.415)	8.046 (6.910
School stress	**25.305 (10.757)**	**33.146 (13.525)**	2.970 (2.406)	*6.232 (3.465)*	**8.348 (3.604)**	**7.841 (3.461)**	1.347 (2.358)	-0.876 (0.743)	-0.479 (4.045)
Immigrant-related stress	**18.326 (8.128)**	**23.173 (10.269)**	**4.757 (1.653)**	4.046 (2.626)	2.437 (2.887)	*4.847 (2.657)*	**5.981 (1.450)**	**-1.266 (0.520)**	**6.362 (2.860)**
Fear of parent's deportation	2.166 (4.398)	1.875 (5.568)	1.020 (0.918)	-0.336 (1.372)	0.152 (1.472)	-0.291 (1.408)	*1.627 (0.859)*	-0.146 (0.284)	1.291 (1.534)
Everyday Discrimination	*6.325 (3.258)*	**9.124 (4.221)**	*1.144 (0.665)*	1.554 (1.169)	1.554 (1.087)	**2.800 (1.106)**	0.717 (0.724)	*-0.442 (0.232)*	1.565 (1.215)
Discrimination stress	11.101 (11.153)	14.938 (14.063)	1.084 (2.393)	4.697 (3.424)	1.051 (3.773)	3.836 (3.549)	0.456 (2.321)	-0.501 (0.739)	0.115 (3.977)
Resilience factors:									
SSS	-4.188 (4.455)	-5.526 (5.551)	-0.074 (0.103)	-1.376 (1.397)	-1.840 (1.507)	-1.339 (1.335)	-0.534 (0.890)	0.341 (0.294)	-1.224 (1.526)
Parental social support	-10.842 (8.877)	-14.458 (11.187)	-2.122 (1.888)	-1.801 (2.807)	*-5.643 (2.860)*	-3.616 (2.826)	-0.208 (1.862)	0.188 (0.654)	*-5.613 (3.031)*
Optimism	-0.171 (0.472)	-0.402 (0.593)	-0.017 (0.100)	-0.054 (0.147)	-0.152 (0.155)	-0.231 (0.145)	0.030 (0.097)	0.002 (0.032)	-0.243 (0.160)

Values are represented as betas (standard deviation). Values in **bold** represent having p-values less than 0.05. *Italicized* values represent having p-values that are marginal.

Table 2.8: Children's psychosocial stressors and resilience factors and mental health outcomes (fully adjusted models).

	Mental Health Outcomes								
	Total Anxiety	**Total Internalizing**	**Generalized Anxiety**	**Panic Disorder**	**Social Phobia**	**Major Depression**	**Separation Anxiety**	**Self-Reported Quality of Health**	**PSS**
Child variables									
Stress factors:									
Total stress score	39.584 (23.741)	50.842 (30.057)	6.544 (5.009)	**16.786 (6.698)**	6.686 (8.382)	11.258 (7.918)	6.197 (4.712)	-0.890 (0.620)	6.553 (7.473)
School stress	*24.300 (12.453)*	*21.180 (15.722)*	3.753 (2.665)	3.495 (3.831)	*8.204 (4.189)*	6.880 (4.085)	1.548 (2.599)	-0.482 (0.316)	-0.417 (4.441)
Immigrant-related stress	*20.214 (10.060)*	**26.933 (12.613)**	*4.163 (2.102)*	**7.241 (2.828)**	2.030 (3.605)	**6.719 (3.230)**	**5.475 (1.849)**	*-0.495 (0.249)*	3.919 (3.542)
Fear of parent's deportation	-2.678 (5.585)	-4.184 (7.046)	0.127 (1.169)	-1.391 (1.618)	-1.403 (1.867)	-1.506 (1.786)	0.777 (1.096)	0.002 (0.137)	-0.899 (1.875)
Everyday Discrimination	6.098 (3.665)	*8.975 (4.744)*	1.093 (0.752)	1.766 (1.148)	1.537 (1.204)	**2.876 (1.257)**	0.168 (0.774)	-0.157 (0.101)	0.875 (1.366)
Discrimination stress	15.301 (13.458)	19.424 (17.012)	2.251 (2.840)	4.667 (3.926)	1.915 (4.618)	4.123 (4.373)	1.314 (2.706)	-0.375 (0.334	2.262 (4.605)
Resilience factors:									
SSS	-1.772 (5.609)	-3.268 (7.061)	0.489 (1.184)	-1.117 (1.663)	-1.730 (1.896)	-1.496 (1.718)	0.250 (1.036)	0.113 (0.140)	-0.495 (1.856)
Parental social support	-6.307 (10.529)	-9.355 (13.279)	-1.382 (2.194)	-0.709 (3.095)	-4.826 (3.441)	-3.048 (3.368)	1.685 (2.066)	-0.020 (0.289)	-3.863 (3.480)
Optimism	0.109 (0.524)	-0.082 (0.663)	0.025 (0.109)	0.037 (0.153)	-0.084 (0.176)	-0.191 (0.165)	0.084 (0.102)	0.006 (0.014)	-0.186 (0.172)

Values are represented as betas (standard deviation). Values in **bold** represent having p-values less than 0.05. *Italicized* values represent having p-values that are marginal.

Table 2.9: Maternal psychosocial stressors and resilience factors and mental health outcomes.

	Mental Health Outcomes			
	HADS Anxiety	**HADS Depression**	**Self-Reported Quality of Health**	**PSS**
Maternal variables				
Stress factors:				
Total stress score	**14.651 (5.741)**	**19.371 (4.564)**	-1.692 (1.142)	**18.235 (6.971)**
Immigrant-related stress	1.877 (4.068)	3.838 (3.608)	0.250 (0.753)	6.024 (4.794)
Household stress	4.561 (2.955)	**6.221 (2.523)**	*-1.027 (0.533)*	3.480 (3.706)
Health stress	3.827 (2.849)	*4.740 (2.489)*	*-1.014 (0.499)*	3.174 (3.477)
Family economic stress	**10.104 (3.855)**	**10.483 (3.142)**	0.255 (0.822)	**12.464 (4.750)**
Everyday Discrimination	*2.126 (1.054)*	0.936 (0.994)	0.048 (0.208)	*2.243 (1.313)*
Discrimination stress	**5.842 (2.420)**	3.636 (2.282)	-0.345 (0.495)	*5.388 (3.164)*
Resilience factors:				
Subjective social status	-0.231 (0.423)	-0.324 (0.378)	0.094 (0.075)	**-0.986 (0.474)**
Social support/social connection	-0.946 (1.110)	-0.424 (1.008)	0.025 (0.205)	*-2.424 (1.289)*
Optimism	-0.382 (0.277)	**-0.578 (0.235)**	0.029 (0.051)	-0.527 (0.332)
Demographics/Immigrant-Related				
SASH	-1.104 (0.863)	-0.255 (0.795)	-0.137 (0.169)	0.382 (1.06)

Values are represented as betas (standard deviation). Values in **bold** represent having p-values less than 0.05. *Italicized* values represent having p-values that are marginal.

Table 2.10: Maternal psychosocial stressors and resilience factors and mental health outcomes (fully adjusted models).

	Mental Health Outcomes			
	HADS Anxiety	**HADS Depression**	**Self-Reported Quality of Health**	**PSS**
Maternal variables				
Stress factors:				
Total stress score	**13.719 (6.017)**	**18.500 (4.960)**	-1.859 (1.144)	**17.689 (6.630)**
Immigrant-related stress	0.528 (4.404)	3.129 (4.018)	0.312 (0.808)	6.846 (4.757)
Household stress	3.854 (3.164)	**6.205 (2.744)**	-0.864 (0.568)	3.839 (3.653)
Health stress	5.061 (3.021)	**5.833 (2.711)**	**-1.120 (0.523)**	*6.054 (3.364)*
Family economic stress	**9.957 (4.423)**	**10.460 (3.750)**	0.038 (0.940)	*10.153 (5.041)*
Everyday Discrimination	*2.058 (1.090)*	0.944 (1.057)	0.035 (0.211)	1.881 (1.279)
Discrimination stress	**5.863 (2.447)**	3.666 (2.389)	-0.423 (0.493)	**6.224 (2.930)**
Resilience factors:				
Subjective social status	0.329 (0.534)	-0.018 (0.496)	**0.205 (0.086)**	-0.568 (0.585)
Social support/social connection	0.162 (1.341)	0.104 (1.237)	0.078 (0.240)	-1.375 (1.469)
Optimism	-0.463 (0.283)	**-0.607 (0.247)**	0.037 (0.053)	-0.524 (0.320)
Demographics/Immigrant-Related				
SASH	-1.157 (0.995)	-0.173 (0.941)	-0.320 (0.195)	-0.211 (1.150)

Values are represented as betas (standard deviation). Values in **bold** represent having p-values less than 0.05. *Italicized* values represent having p-values that are marginal.

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Chapter 3

Epigenetics as a mechanism of developmental embodiment of stress and resilience across generations of Latinx immigrant families

ABSTRACT

Psychosocial stressors can become embodied to alter biology throughout the life course in ways that may have lasting health consequences. Immigrants are particularly vulnerable to high burdens of stress, which have heightened in the current sociopolitical climate. This study is an investigation of how immigration-related stress (IRS) may impact the cardiometabolic health and epigenetic markers of Latinx immigrant mothers and children in Nashville, TN, considering recent increases in divisive rhetoric and anti-immigrant policies in the U.S. We compared stress and resilience factors reported by Latina immigrant mothers and their children (aged 5-13) from two time points spanning the 2016 presidential election with cardiometabolic health markers (BMI, waist circumference, and blood pressure). We also analyzed these factors in relation to DNA methylation in saliva of stress-related candidate genes (*SLC6A4* and *FKBP5*), generated via bisulfite pyrosequencing (n's range from 80 baseline to 36 follow-up). In mothers at baseline, higher social support was associated with lower BMI. At follow-up, discrimination and school stress associated with greater waist circumferences in children, and in mothers, acculturation was associated with lower BMI, while greater subjective social status was associated with lower SBP. After Bonferroni corrections, children's everyday discrimination at follow-up associated with 1 CpG site in *FKBP5,* and immigrant related stress associated with one site in *SLC6A4.* In mothers at baseline, total mother stress, IRS, health stress, and discrimination stress associated with various sites of *SLC6A4*. At both time points, mothers had significantly higher mean methylation at *SLC6A4* than children ($p<0.001$). More research is needed to determine the role of these epigenetic differences for documenting embodiment of stress across generations.

INTRODUCTION

The accumulation of stress over time can contribute to biological embodiment across the life course. Stressors in the early life environment may influence susceptibility to later life disease. Latinx Americans experience high rates of chronic stress, and are at risk for high rates of cardiometabolic disease later in life, including obesity and hypertension. For example, Latinx adults have nearly twice the rate of diabetes (CDC 2012), 34% higher rate of stroke (Morgenstern et al. 2013), and 10% higher rate of obesity (Flegal et al. 2012; Ogden et al. 2013), relative to non-Latinx whites. These health disparities often emerge early in life: Latinx children aged 2-5 have nearly quadruple the rates of obesity as white children in the US (Ogden et al. 2016; Skinner and Skelton 2014). According to the 2017 Current Population Survey, immigrants and their US-born children represent 27 percent of the overall US population (Zong et al. 2018), and thus represent an important demographic for the health of the future of the US population.

Latinx *immigrant families may be particularly at risk* for stress-related diseases, such as cardiometabolic diseases like hypertension and diabetes, as they experience high rates of stressors related to immigrant experiences, including legal status, uncertain immigrant policies, and acculturative stress (Hovey and King 1996; Negy et al. 2009; Pérez et al. 2008). Children of recent immigrants may be at even higher risk than their 1st generation immigrant parents, as health outcomes tend to worsen with longer duration in the US, and risk increases across generations, suggesting that racism, xenophobia, or living conditions in the US are the cause rather than immigration itself (Creighton et al. 2012; Gordon-Larsen et al. 2003; Liu et al. 2009). Regardless of immigrant status, children of Latinx immigrants are disadvantaged on numerous fronts, including access to good education, health facilities, and job security for their parents, while being confronted at the same time with resentment, racism, and often violence.

Additionally, these children and their parents face heightened stereotypes and fears resulting from recent and highly publicized ongoing debates on immigration policy for immigrants across the Mexican border in the US. These social determinants can affect immigrant families' lifestyles, health status, and mortality, and all have been shown to have biological consequences, e.g., by affecting immunologic activity (Cabassa 2003). However, the mechanisms through which these stressors may become embodied to influence cardiometabolic disease are yet unknown.

Embodiment, in this paper, refers to the process by which one's life experiences are literally incorporated biologically, at a molecular level, to influence later life health and disease (Krieger 2005). This process of embodiment is in contrast to the notion of genetic determinism, in which one's phenotype is permanently set by the genes one inherits, epigenetic mechanisms allow for an individual's phenotype to change over their lifetime in response to the environment. The epigenome may be particularly sensitive to embodiment in early life environments, or critical periods, when biological systems are actively being developed (Kuzawa and Sweet 2009).

While most epigenetic differences between groups or over time discovered thus far have been very small in magnitude, the long-term consequences of these differences are yet to be determined. It is possible that even small epigenetic changes in early life, including pregnancy and early childhood, may alter lifetime risk of disease. While early life may be the most sensitive period for epigenetic processes, the accumulation of experience over a life course can also alter the epigenome, as evidenced by identical twins reared apart (Czyz et al. 2012; Segal et al. 2017) and aging studies (Braga et al. 2020; Topart et al. 2020; Wang et al. 2018). In this sense, epigenetic changes may be a mechanism for the process of weathering, an epidemiological

concept in which the cumulative effect of social disadvantage, such as poverty or discrimination, disproportionately affects the health of disadvantaged populations (Goosby and Heidbrink 2013).

Regardless of the time period of exposure, it is clear that the epigenome is sensitive to environmental forces. Thus, epigenetic mechanisms may help explain the persistence of racial and social health disparities, such as the increased burden of cardiovascular disease among Black relative to white Americans (Kuzawa and Sweet 2009). If epigenetic marks are demonstrated to transmit across generations in humans, then epigenetic processes may contribute to the intergenerational transmission of health disparities. However, this topic is sorely understudied as parents and their children are both usually exposed to the same environments. Additionally, most prior research only examines one time point for methylation, usually early in childhood, so we do not yet know how the epigenome responds to environmental exposures across different time periods of exposure.

Most epigenome wide studies rely on preselected sites on a microarray, which tend to miss important gene regions, while targeted approaches can be more useful when specific hypotheses exist for certain genes. For example, there are two genes well established to be involved in the regulation of stress response, including the glucocorticoid receptor chaperone protein gene FK506 Binding protein 5 (FKBP5), which is an important regulator of glucocorticoid receptor sensitivity (Zannas et al. 2015; Zannas et al. 2019) and serotonin transporter gene (SLC6A4), which has been implicated in stress response and increased risk for psychiatric disorders (Bennett et al. 2002).

FKBP5 is a gene known to regulate the glucocorticoid receptor, an important part of the HPA axis that binds cortisol, a stress hormone. Several studies and reviews have examined the impact of adverse childhood experiences, socioeconomic adversity, and other environmental

stressors on DNA methylation of *FKBP5* (Binder et al. 2008; Harms et al. 2017; Klengel et al. 2013; McEwen and Sapolsky 1995). Demethylation in the *FKBP5* gene has been shown to disrupt the HPA axis and contribute to glucocorticoid resistance, higher cortisol levels, and prolonged recovery following exposure to stress (Zannas and Binder 2014). A dysfunctional HPA stress axis has been implicated in increased vulnerability to early life stress – like post-traumatic stress disorder (PTSD) and chronic fatigue syndrome as well as disruptions in cognitive processing (Kempke et al. 2015). Thus, *FKBP5* is a good candidate to mediate an epigenetic response to psychosocial stress. One study of maternal-neonatal pairs in the Democratic Republic of Congo found significant methylation increases and decreases at different transcription factor binding sites in *FKBP5*, along with other HPA axis related genes, in association with chronic stress and war trauma in maternal blood, placenta, and newborn cord blood (Kertes et al. 2016). Decreased methylation at *FKBP5* has also been identified in adults who had experienced childhood trauma (in blood), as well as among Holocaust survivors with PTSD and their offspring (blood), and in the buccal epithelial cells of adolescents who experienced early-life institutionalization in Romania (Klengel et al. 2013; Needham et al. 2015; Non et al. 2016a; Yehuda et al. 2016). Low socioeconomic status (SES) trajectories across the life course were associated with increased methylation across several shore/shelf type sites of *FKBP5* in adult blood (Needham et al. 2015). Miller et al. found that methylation in one site of *FKBP5* was a predictor of both PTSD symptom severity and resilience in opposite directions in saliva (Miller et al. 2020).

A second gene with established associations with maternal care, early life adversity, and long-term child development is *SLC6A4*. This gene is involved in serotonin and dopamine releases and has been implicated in stress response and in increased risk for psychiatric disorder

(Jans et al. 2007). *SLC6A4* serves a major role in modulating the bioavailability of serotonin and in modulating mood, anxiety, and energy homeostasis. The majority of studies investigating this gene have focused on early life adversities. Childhood adversities were significantly associated with higher methylation in people with major depression disorder (Devlin et al. 2010). Altered methylation at *SLC6A4* may moderate an individual's response to adversity and contribute to altered cortisol stress responses (Bogdan et al. 2014; Karg et al. 2011). Polymorphisms within *SLC6A4* have been associated with obesity in children (Sookoian et al. 2007) and adults (Sookoian et al. 2008). *SLC6A4* promoter hypermethylation is significantly associated with an increased prevalence of obesity (Zhao et al. 2013). Altered methylation of CpG5 was found in cord blood to be associated with greater concurrent measures of adiposity including BMI and waist circumference (Lillycrop et al. 2019).

Latinx immigrant families may be living in a state of chronic stress, constantly on edge with concerns about deportation of their family members, or their ability to remain in the country in which most of them have lived for the majority of their lives. The epigenetic effects of increasing stress and anxiety associated with this particular sociopolitical moment for Latinx families are understudied. To our knowledge, only one other study to date has investigated associations between discrimination of Latina mothers and DNA methylation (Santos et al. 2018). This study assayed DNA methylation via bisulfite pyrosequencing at *NR3C1*, *FKBP5*, and *BDNF* in blood of 147 pregnant Latina women. They identified small but significant differences (mostly decreased methylation in *FKBP5*) with increased discrimination over time. In some cases, these associations went in the opposite direction than expected. Few studies have investigated the effects of multiple stress forms on HPA axis functioning. Only our prior study has investigated epigenetics of children of immigrants in relation to multiple psychosocial stress

and resilience factors (Clausing et al. 2021). We generally found that increased stress and decreased resilience associated with decreased epigenetic age, suggesting stress may slow child development. This study examined epigenetic age and epigenome-wide patterns of methylation, but did not fully cover the regions of these stress-related genes known to associate with early life adversity.

An increasing body of research has focused on the identification of resilience factors that may counteract the deleterious impact of life stressors, thus possibly also serving to compensate for biological risk. For instance, availability of social support has consistently been linked to beneficial mental health outcomes by buffering anxiety (Howell and Miller-Graff 2014; Reinelt et al. 2014). Few studies, however, have published on epigenetics of social support or any other positive social factor.

Study purpose and hypotheses

The current study examined associations between psychosocial stressors and resilience factors with cardiometabolic risk factors, along with targeted DNA methylation in the *FKBP5* and *SLC6A4* genes in saliva of children of Latinx immigrant mothers and their children. Based on prior studies of embodiment of childhood adversity, we hypothesized that stressors measured both in childhood and adulthood would be associated with higher BMI, waist circumference and blood pressure. We further predicted that stressors would associate with decreased DNA methylation at key CpG sites within *FKBP5,* and with increased methylation of *SLC6A4*. Finally, we predicted that methylation at these genes may associate with the cardiometabolic markers. Overall, this study may be the first to examine epigenetic mechanisms related to embodiment of stress and resilience within a community and longitudinal sample of Latina mothers and their children.

MATERIALS/METHODS

Study population

The study sample draws from a longitudinal analysis of stress in Latina immigrant mothers and their children located in Nashville, TN. The study, entitled "Children of Hispanic Immigrants Collaborating to Overcome Stress" (CHICOS), recruited 81 families (mother-child dyads), between 2015 and 2016. This initial time point is called "baseline" throughout the rest of the study. Participants were recruited from local immigrant-serving community centers with subsequent snowball sampling. Inclusion criteria were self-described Latina, foreign-born immigrant mothers above age 18, with a child between the ages of 5-13. The mother and focal child were assessed on a number of different biological, psychosocial, and health-related measures. Following baseline assessment of the dyads, we then revisited the same families 2-3 years later, collecting the same data and new interviews focused on changes since the 2016 presidential election, from all available mothers and children who participated in the baseline sample (n=39). This time point is referred to as "follow-up" throughout the study. Informed oral consent was provided by all participants, and Vanderbilt University and University of California San Diego Institutional Review Boards approved all protocols.

Exposures: Psychosocial stressors and resilience factors

All exposure data were collected using surveys administered in person with mothers in Spanish (1.5-2 hours) and children primarily in English (45 min). Surveys were a combination of validated scales and new interview questions developed following a set of preliminary individual interviews in 2014 with children, and focus groups with Latina immigrant mothers in Nashville, TN (Non et al. 2019). Questions included in each scale are described in brief below, and detailed further in Clausing et al. 2021, but can also be found in Table 3.1.

Psychosocial Stressors

We tested the wide range of stress domain measures developed specifically for this population (Non et al. 2019). We coupled these stress domains with validated questionnaires including maternal and child assessment of each domain. Multiple measures of psychosocial stress were assessed, covering a range of domains, and including maternal and child assessment of each domain. Measures reported at both time points separately by children and mothers included *immigrant-related stress (IRS), discrimination stress,* and a *total stress score*. Measures additionally reported by only mothers included *family economic stress, family health stress,* and *household stress*. Additional measures reported only by the children included *school stress*. The questions included in each stress scale and Cronbach's alpha score for internal reliability are listed in Table 3.1. The previously validated e*veryday discrimination* scale was also reported separately for mothers and children at the follow-up time point (Williams et al. 1997). Thus, we included two different measures of discrimination at the follow-up time point. All indices were calculated by taking the mean of responses for those not missing more than two questions, and higher scores indicate more stress across all measures. Outside of the scales, we also examined a few individual questions of interest, including *child fear of parent deportation.*

Resilience Measures

Measures of resilience included *social support* and *optimism* reported separately by mothers and children. We developed child-focused social support questions developmentally appropriate to our sample population based on social support reported by children from their friends and parents. Since there was very little variation in children's reports of social support from friends (e.g., >90% reported having close friends who ask them to join activities), we focused primarily on *parental social support*. Social support and social connection were

measured with a combined index from the Berkman Syme Social Network Index (Berkman and Syme 1979) in addition to questions stemming from our focus groups (Non et al. 2019). Generalized dispositional optimism was measured in the mothers using the revised 10-item version of the Life Orientation Test (Carver et al. 2010). To measure optimism in the children, we used the Y-LOT, the youth version of the LOT-R, which has been validated in a racially diverse set of 3rd to 6th grade children (Ey et al. 2005). Y-LOT was only collected at follow-up.

Measures of *subjective social status* (SSS) were also considered a resilience factor, as higher scores indicate better social standing. SSS has been linked with self-reported health among immigrant Latinas, and has been hypothesized to capture immigrant experiences that may alter perceived self- worth (Garza et al. 2017). Maternal SSS was measured at baseline and follow-up time points with the MacArthur SSS scale, which asks mothers to report where they felt they fit on a social ladder (range 1-10) in relation to others in the US (Adler et al. 2000).

Outcomes: Cardiometabolic biomarkers and DNA methylation

Cardiometabolic biomarkers

Multiple measures of cardiometabolic health were assessed in both the children and the mothers. In the children, we used Body Mass Index (BMI) percentile (adjusted for child age and gender) and waist circumference. Blood pressure was also assessed but excluded as we were unable to collect this data point on all children due to their ages. In the mothers, we used BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP).

DNA methylation

Genomic DNA was extracted from 79 Oragene Saliva samples from children in 2015-2016 and again in 2018 (38 samples) using standard protocols (DNA Genotek, Ottawa, Ontario, Canada). DNA was extracted from 80 mothers at baseline and 40 mothers in follow-up. Saliva

was stored at room temperature, per manufacturer's recommendation until DNA extraction. DNA was isolated from 500 µl of children's saliva using prepIT-L2P (Zymo Research, CA, USA) and stored at -20ºC until time of analysis. DNA was excluded from four child samples at baseline and one child and two mother samples collected follow-up due to low quality/concentration of DNA, as measured by Nanodrop and Qubit. The level of DNA methylation was assessed via bisulfite pyrosequencing at 2 CpG sites within intron 7 of the *FKBP5* gene and within the promoter region of the *SLC6A4* gene. In the end, we generated quality methylation results of 78 child and mother samples at baseline and 36 child and 38 mother samples at follow-up at *FKBP5*. At *SLC6A4*, we ended with 78 child and 80 mother results at baseline and 37 samples for both groups at follow-up. These gene regions were chosen based on prior studies highlighting their importance in early life adversity in humans, other primates, and rodents (Binder et al. 2008; Non et al. 2016a; Provençal et al. 2012). Specific primer information of these gene regions can be found in Table 3.2.

In brief, 500 ng of DNA from each sample was bisulfite converted in duplicate using the EZ DNA Methylation Gold Kit (Zymo Research, CA), according to manufacturer's protocol. Bisulfite-converted DNA was mixed with 0.2 µM of each primer and amplified using the HotstarTaq plus Master Mix (Qiagen, CA). Primers for *FKBP5* were designed by EpigenDx to cover the regions found to be most associated with early life adversity in prior studies (Binder etc.). For each sample, PCRs were performed on each of the duplicate bisulfite treatments using the following protocol for *SLC6A4* gene: one cycle of 95ºC for 5 min, 45 cycles of 94ºC for 1 min, 58ºC for 1 min, 72ºC for 1 min, and 72º for 10 min. For *FKBP5* gene: one cycle of 95ºC for 5 min, 45 cycles of 95ºC for 30 sec, 56ºC for 30 sec, 72ºC for 30 sec, and 68º for 10 min. Primer information for each gene is provided in Table 3.2.

DNA methylation levels for all CpG sites were assessed using the Pyromark Q24 pyrosequencer, following standard protocols (Qiagen, CA). A bisulfite conversion check was included in each assay to verify full conversion of the DNA. If the difference between two bisulfite replicates exceeded two standard deviations (SDs) of the variation in the entire study population, a third bisulfite treatment was tested and the average of the two closest results was used. Of the 80 samples assayed for methylation, and not missing exposure data, the baseline analytical sample for children ranged from 67-68, and for mothers n=72, and follow-up children's sample n=29-31, and mother's sample n=30-31.

Covariates

Mothers self-reported at each time point their own age, marital status, number of years lived in the US, legal status, and maternal smoking status. Children reported their own age and gender at each time point. We present unadjusted correlations, minimally adjusted models (adjusted for child's age, child's gender, mother's age, and mother's smoking status), and fully adjusted models (adjusted for those in minimally adjusted models plus marital status, number of years lived in the US, and legal status).

Data analyses

We first tested correlations between each psychosocial stressor and resilience factor, key demographic factors, and all measures of cardiometabolic health, and DNA methylation across all studied sites of *SLC6A4* and *FKBP5*, separately at each time point.

We next modeled these associations using multivariate models after adjusting for a minimal set of key covariates, including child's age, mother's age, child's gender, and maternal smoking, which are known confounders in epigenetic studies (Kaur et al. 2019). In fully adjusted models, we additionally included socioeconomic and immigrant-related demographic factors,

including mother's years in the US, mother's legal status, mother's marital status, and maternal education level. Although these variables could also contribute to stress, we included them as covariates as we were interested in the effects of the stress scales independent of these factors. Though they were treated as covariates, we report the effects of each of these factors given their role in contributing to the IRS context. We used Bonferroni correction to adjust for multiple testing within each gene (5-7 exposures in children and 8-10 exposures in mothers multiplied by two sites in *FKBP5* and six sites in *SLC6A4*). For baseline, the *FKBP5* Bonferroni threshold for significance is 0.005 in children and 0.003 in mothers. The *SLC6A4* Bonferroni threshold is 0.002 in children and 0.001 in mothers. For follow-up, the *FKBP5* cutoff is 0.00036 in children and 0.003 in mothers. The *SLC6A4* cutoff is 0.0012 in children and 0.0008 in mothers. All analyses were conducted in R (http://www.R-project.org). Though few of our associations passed Bonferroni correction, we note that in an exploratory study, Bonferroni can be overly conservative given that the methylation levels at the sites are correlated with each other, as are the stressors, so they should not all be considered independent tests.

In a secondary set of analyses, we tested a few additional associations. Because children's methylation may be influenced by their mother's exposures, in addition to their own reported stressors, we tested the associations of the child's methylation relative to the mother's stress and resilience variables. In order to examine if stress or resilience influences longitudinal trends, we also examined associations between all psychosocial stressors and resilience factors in relation to changes in methylation over time in both mothers and children.

Finally, we examined general trends of changes in raw methylation levels over time in both mothers and children, as well as relationship between mothers and children's methylation at each time point using paired t-tests.

RESULTS

Demographics

Population characteristics

Demographic characteristics of our analytical sample of 79 baseline and 39 follow-up CHICOS participant mothers and children are displayed in Table 3.3. In brief, at baseline, mean age of children was 8.7 at baseline, 56% female, majority born in the US (72%). Mothers were mean age 34.6, primarily non-smokers (97.4%), mostly born in Mexico (86.8%), lived in the US on average 12.6 years, majority undocumented (85.3%). Mothers were mostly married (85.5%) and with few years of education (mean 9 years), and over a third had trouble paying basic bills (39.5%) (Table 3.3).

Stress and resilience levels

Several stress and resilience levels changed over time, as first reported in Chapter 2 (Tables 2.1 and 3.3).

Correlations among all study variables

Correlations between all study variables can be found in Supplemental Tables S3.1, S3.2, S.3.3, and S3.4. Results of these correlations are described in supplemental text. These exploratory analyses guided the building of linear models, described below.

Associations between stressors and cardiometabolic markers

Baseline:

No associations were detected between stressors/resilience factors and cardiometabolic markers in the children at baseline (Table 3.4). In mothers, social support and social connection inversely associated with BMI (B: -2.153(SD=0.004), p-value=0.0335) (Table 3.5).

Follow-up:

Children's school stress (B:22.152(10.722), p-value=0.0482) and everyday discrimination (B: 9.920(3.722), p-value=0.0149) were positively associated with children's waist circumference. Other marginal associations are described in Table 3.4. In the mothers (Table 3.5), a negative association was detected between SASH and BMI (B= -2.962(1.438), p-value=0.04847). A negative association was also detected between SSS and SBP and (B: -2.706(1.268), p-value=0.04044).

Associations between stressors and epigenetics

Linear Regressions

Most of the results from the correlation analysis remained significant in the regression analyses after adjusting for a minimal set of covariates, including age of the mother and child, sex of the child, and smoking status. Below we report the regression results that were significant in these minimally adjusted linear models, as well as more fully adjusted models, which additionally adjusted for maternal years in the US, maternal legal status, parental marital status, and maternal educational level. Results are in Table 3.6 for *FKBP5* and Table 3.7 for *SLC6A4*. Below we present both uncorrected and corrected associations.

Baseline *FKBP5*

Children: No significant associations were detected between children's psychosocial variables at baseline and children's level of methylation at *FKBP5,* in minimal or fully adjusted models. Results for fully adjusted models can be found in Supplemental Table S3.5.

Mothers: A negative association was found between mother's acculturation score (SASH) and mother's *FKBP5* methylation, such that those who communicated more comfortably in English had lower methylation at the first position (B: -1.19(0.44), p-value=0.008) and with the average methylation (B: -0.89(0.36), p-value=0.017) across sites of *FKBP5*.

Follow-up *FKBP5*

Children: In minimally adjusted models with children's methylation, a negative association was found between child's report of Everyday Discrimination and methylation at the second site of *FKBP5* (B: -1.03(0.38), p-value=0.0141). A positive association was also detected between child's report of parental social support and methylation at the first site (B:2.86(1.29), p-value=0.035) of *FKBP5*. Only the association with everyday discrimination remained significant in fully adjusted models (B: -1.00(0.42), p-value=0.029).

Mothers: No associations were detected between mother's variables and methylation at this gene.

Baseline *SLC6A4*

Children: In children at baseline, positive associations were detected between IRS with CpG3 (B:0.76(0.36), p-value=0.038) and CpG5 (B:0.91(0.44), p-value=0.044). CpG sites 3, 5, and 6 of *SLC6A4* were also associated with children's fear of parent deportation (all p values<0.04). Only CpG 5 remained significantly associated with fears of parent deportation in fully adjusted models Supplemental Table S3.6).

Mothers: In mothers at baseline, various sites of *SLC6A4* were positively associated with total mother stress, IRS, health stress, and discrimination stress (Table 3.7, all p<0.04). SSS was negatively associated with CpG1, CpG3, CpG6 and average methylation (all p<0.03). We also detected a negative association between SASH and CpG1 (B: -0.88(0.44), p-value=0.049). These results remained similar in fully adjusted models, except SASH and discrimination were no longer significantly associated in this gene.

Follow-up *SLC6A4*

Children: At follow-up, in minimally adjusted models, no stress variables associated with any sites in *SLC6A4*, but optimism was negatively associated with CpG2 in *SLC6A4* CpG2 (B: -0.07(0.03), p-value=0.0404).

Mothers: At follow-up, in the opposite direction as seen at baseline, both IRS and household stress *negatively* associated with CpG4 of *SLC6A4* (all p<0.02), while SASH was *positively* associated with CpG3, CpG4, CpG5, and average methylation at *SLC6A4*. These positive associations with SASH remained significant in fully adjusted models.

Methylation vs. cardiometabolic markers

In testing how methylation may be on the pathway towards cardiometabolic disease, we analyzed associations between methylation with cardiometabolic markers at both time points in children and mothers. No associations were found between *FKBP5* and cardiometabolic health measures at either time point. However, we detected inverse associations at baseline between several sites and the average methylation of *SLC6A4* and BMI percentile in the children (Table 3.8). We also detected inverse associations between several sites in *SLC6A4* and waist circumference, including sites CpG1 (B: -2.000(0.709), p-value=0.00646), CpG3 (B: -2.913(1.335), p-value=0.03299), CpG5 (B: -2.241(1.079), p-value=0.042098), and average methylation (B: -4.627(1.544), p-value=0.00395) (Table 3.8). We did not detect any associations at the follow-up time point in the children.

In the mothers, no associations were found with physical health variables at baseline. At follow-up, we detected positive associations with DBP in *SLC6A4* at CpG2, CpG3, CpG4, CpG5, and CpG6, and average (Table 3.9).

Secondary analyses: Associations between maternal psychosocial variables and children's methylation

Because children's methylation may also be influenced by their mother's experiences, we additionally analyzed how methylation of children associated with maternal variables and found several positions to be significantly associated across generations (Table 3.10-3.11). No maternal stressors associated with *FKBP5* in children at baseline, though the resilience factor of maternal social support and connection was positively associated with CpG2 and average methylation of *FKBP5*. The only stressor associated with *SLC6A4* at baseline was legal status, which associated with lower methylation in Cpg1. At this gene, we also detected positive associations between SASH at sites CpG3 and CpG6, and negative associations with maternal SSS at CpG1 (Table 3.11).

In the follow-up time point, no maternal variables were significantly associated with *FKBP5* methylation in children (Table 3.10). For *SLC6A4*, we detected a positive association between maternal total stress and site CpG3, and between household stress and sites CpG2, CpG3, CpG4, and average, and family economic stress with CpG4. Maternal social support/social connection was inversely associated with CpG5 and average methylation (Table 3.11).

Other general trends

Comparing methylation across generations: mothers vs children

At the baseline timepoint, paired t-tests revealed no significant differences between mothers and children at *FKBP5*, though mothers had a trend of lower methylation at CpG1 and the average. Mother's DNA methylation was significantly elevated relative to the child's methylation in *SLC6A4* average and sites CpG1, CpG2, and CpG4, all $p<0.005$ (Figure 3.1).

At the follow-up time point, there was no difference in *FKBP5*, but the mother's methylation was significantly higher than the child's at *SLC6A4* CpG4 (t=2.41, df=34, p=0.022; Figure 3.2).

Longitudinal Analyses:

No significant changes were found over time in children's methylation at *FKBP5*. Children showed an increase over time in methylation at CpG1 site (t=2.146, df=34, p=0.0391) in *SLC6A4* but no other sites. Mothers showed a decrease in methylation at CpG3 site (t=-2.857, df=23, p-value=0.00893) and average (t=-2.144, df=23, p-value=0.0429) in *FKBP5*, but no changes for *SLC6A4* (Figure 3.3). Only sites that were significant over time are displayed in Figure 3.3.

DISCUSSION

This study is the first, to our knowledge, to demonstrate the impact of daily stressors of immigrant families (mothers and children) on cardiometabolic health and DNA methylation of stress related genes over time. In general, stressors were associated with increased adiposity, while protective factors, such as social support and higher subjective social status were negatively associated with adiposity and BP. Associations with epigenetic factors were generally in the expected direction in both mothers and children, such that increased levels of stress were associated with higher DNA methylation in *SLC6A4*, and greater levels of resilience factors were associated with lower methylation. While fewer associations were detected with *FKBP5*, generally, greater stress was associated with lower DNA methylation, and greater resilience with higher methylation. These trends were consistent with prior studies of these genes, where greater stress was associated with higher methylation in *SLC6A4*, and lower methylation in *FKBP5* (Needham et al. 2015; Non et al. 2016a; Yehuda et al. 2016).

Below we describe the magnitude and directions of associations, the potential functional relevance of findings, and how our results relate to similar studies and contribute to theories of embodiment across the life course.

Embodiment via cardiometabolic health measures

We found children's stressors, such as everyday discrimination and school stress, positively associated with larger waist circumferences. This trend is consistent with other studies in adults that have shown stressors such as everyday discrimination to be associated with increased weight circumference (Hunte 2011) and low socioeconomic status to be related to greater abdominal fat deposit (Baltrus et al. 2010). In one study of children, racial discrimination was associated with increased BMI, waist circumference, and SBP (mean age 11 years) in Australia (Hunte 2011). Though few studies have investigated these associations in children, our data suggest that increased risk for obesity may be influenced by stress exposures in mid-childhood, even earlier in life than usually studied.

In the mothers, we found lower cardiometabolic risk factors associated with more acculturation as well as greater resilience factors (higher subjective social status, higher social support), but little evidence that stress associated with either BMI or BP. Social support has long been known to associate with BP and BMI. For example, social support has been associated with lower BP reactivity to laboratory stress in older adults (Howard et al. 2017) and was protective against intergenerational transmission of obesity in a study of Finns in mid-adulthood (Serlachius et al. 2014). A systematic review found inconsistent effects of acculturation on BMI, such that 3 studies were consistent with our finding of lower BMI with more acculturation (which were mainly among women), while 6 studies of mixed gender showed the opposite (Delavari et al. 2013). BMI can be influenced by many complex factors, including American body image, food

availability, physical activity norms, and loss of "healthy migrant effect" over time, such that it is challenging to predict how acculturation may influence this trait. Further research is needed to determine the factors that can protect against elevated rates of these cardiometabolic biomarkers, as they contribute to multiple health outcomes, including hypertension, diabetes, stroke, and overall mortality (Kumanyika et al. 2014).

HPA axis dysregulation may be a mediating factor between psychosocial stress and increased risk of cardiometabolic disease. Many studies have found chronic stress from various sources associates with BMI, waist circumference, and adiposity, potentially linked through elevated cortisol (Björntorp 1988; Björntorp 1992; Janssen et al. 2004). For this reason, we examined DNA methylation of genes related to HPA axis functioning. Both general trends and specific findings are discussed below.

Embodiment via epigenetics

In comparing overall results across all methylation analyses, generally we found more significant associations with DNA methylation among mothers than among children. Though this pattern could be due to the fact that we measured more stress and resilience factors in the mothers, many of the same stressors were significantly associated with methylation in maternal saliva but not in children. In fact, when comparing raw methylation values between mothers and children, we found mothers had lower levels of DNA methylation in *FKBP5* and higher levels in *SLC6A4* as compared to their children. Decreased methylation at *FKBP5* and increased at *SLC6A4* has been associated with increased stress in this and prior studies. These patterns may suggest that mothers are affected more by the daily stressors they are experiencing than their children, or potentially that mothers have accumulated more epigenetic changes over their life course than children. This result is counter to the hypothesis that childhood is a more sensitive

period of development, and may instead support a weathering hypothesis where effects accumulate over time (Geronimus et al. 2006). Alternatively, the mother's childhood exposures in Mexico and other Central American countries (which were not measured in this study) may have been more adverse than their US born children.

In comparing across time points, significant associations were found at similar frequencies at baseline and follow-up time points. In fact, in many cases the findings were similar across time points (with the exception of *SLC6A4* data in the mothers at follow-up, where the sample size was the smallest). The consistency of associations with methylation over time was unsurprising, giving the relative similar reports of stress exposures over time. This finding speaks to the ongoing challenges faced by immigrant families over the past few decades.

Despite measuring more stress than resilience factors, we found a surprisingly high number of associations with resilience factors in both mothers and children, justifying further study of epigenetics of resilience (Non et al. 2020). While resilience effects can sometimes be viewed as the flip side of stress (i.e., lack of stress), our findings suggest there may be unique benefits to social support and optimism. These same factors have shown to buffer the effects of adverse childhoods on adult health behaviors and health outcomes (Non et al. 2020), and thus the epigenetic effects may be mediators of this pathway.

When comparing findings across tested genes, *SLC6A4* methylation was associated with more variables than *FKBP5,* though both were associated with a range of stress and resilience factors in both mothers and children. Specific results of each gene are discussed in detail below.

We found very little significant associations with *FKBP5* in our baseline sample. Only maternal acculturation (SASH) was associated with lower methylation at this gene, which is the expected direction for a stressor in *FKBP5*. Interestingly, we found acculturation was also

associated with lower methylation in *SLC6A4*, though higher methylation is expected for stress in this gene. While acculturation can be a stressful process, it can also have health benefits. Our measure of acculturation did not capture acculturative stress specifically, but rather simply English over Spanish language preference. More detailed acculturation measures in the future could help clarify whether it is a risk or resilience factor for health, and how it relates to these epigenetic markers.

At the follow-up time point, we found children's reports of everyday discrimination associated with lower methylation at *FKBP5*, and parental social support with higher methylation. These associations were significant even after adjusting for covariates, and were in the expected direction based on prior studies where stress associates with lower methylation at this gene (Klengel et al. 2013; Needham et al. 2015). Our findings expand this literature by investigating these associations for the first time in children. The lack of significant findings at this gene in mothers relative to children may support the hypothesis that there are timing specific effects that may vary by gene, as found in previous longitudinal studies (Non et al. 2016a).

We found many different stressors associated with increased methylation (the expected direction) at *SLC6A4* in both children and mothers (e.g., immigrant related stress, fear of parent deportation) at baseline, while greater SSS was associated with decreased methylation in mothers. To our knowledge, SSS has never been evaluated with epigenetic data before, but appears to be protective against stress-related epigenetic changes in our findings. At follow-up, optimism was associated with lower methylation in children at this gene. In our prior research (Chapter 4, (Clausing et al. 2021), we found increased optimism to be associated with increased epigenetic age in this same sample of children, which was attributed to potentially faster development in children (e.g. potentially reaching developmental milestones more rapidly). In

mothers at follow-up, the few findings (mostly at one CpG site in *SLC6A4*) were inconsistent with baseline trends, and also inconsistent with prior studies. These findings should be interpreted with caution as they could be potentially spurious associations related to the much smaller sample size at this time point.

In regards to the functional relevance of these results, one striking finding was that methylation at *SLC6A4* was significantly associated with lower BMI percentile and waist circumference in the children, and both greater BMI and BP in the mothers, at the follow-up time point. Similar to our findings in the children, one prior study found greater methylation of a CpG site in the same region in *SLC6A4* in blood of adolescents was associated with lower measures of adiposity including BMI, skin fold thickness, and waist circumference (Lillycrop et al. 2019). Lillycrop et al. also found lower methylation at the same site in obese compared with lean adults in adipose tissue. Another study found no association between methylation at this gene and BMI in adults (Drabe et al. 2017). These findings also suggest directions of effect may vary with age.

Given that these same sites of *SLC6A4* also associated with stress factors in our dataset, taken together with these cardiometabolic findings, our data suggest that methylation may be a pathway through which stressful experiences like discrimination can become embodied and ultimately affect cardiometabolic health. Larger sample sizes in longitudinal studies will ultimately be needed to formally address the role of this gene in mediating cardiometabolic outcomes

Longitudinal trends

Over time, we found a decrease in mothers' average methylation levels at *FKBP5* and an increase in children's methylation at one CpG site in *SLC6A4*. These longitudinal trends, though small in magnitude, are in the direction expected for increased stress in their environments but

could also result from an aging effect. In contrast, our measures of stress did not increase over time in mothers, but they did in children, who may have become increasingly aware of sociopolitical environments as they aged. While there have been increasing policies directed against Latinx people during this two-year study period, these changes may not represent a unique moment in time for this population, who have consistently faced high levels of discrimination and anti-immigrant policies for decades. Thus, this current sociopolitical moment may be less impactful than a lifetime of exposure to these stressors experienced by the mothers, consistent with the weathering hypothesis.

Strengths and limitations

Several limitations should be noted. First, interpretation of our findings is limited by relatively small sample sizes, especially at the follow up time point. The large attrition was expected, considering how recruitment at the follow up time point was limited due to several factors regarding the socio-politically stressful time period. This is typical in studies of vulnerable populations as there are inherent difficulties in recruiting a largely undocumented immigrant population (Olukotun and Mkandawire-Valhmu 2020). A second limitation is the lack of generalizability of our findings. While Nashville, TN represents a growing site for immigration settlement, our study is only based in one location in the US South where the majority of the families were from Mexico, low SES, undocumented, and thus we cannot generalize widely. Third, any analysis of DNA methylation in saliva samples cannot be generalized to other tissues of interest, like neurons where methylation patterns are different, and often potentially larger. Because saliva samples are made up of both epithelial cells and blood cells, there are concerns of cellular heterogeneity that can be difficult to account for with bioinformatic adjustment (McGregor et al. 2016). Future studies are needed to address this issue,

ideally using samples of isolated cell types across tissues. Finally, although we only investigated a few sites within two genes, we carefully chose these sites and genes based on prior studies to represent known pathways of stress embodiment. Though few of our associations passed Bonferroni correction, we note that in an exploratory study, Bonferroni can be overly conservative given that the methylation levels at the sites are correlated with each other, as are the stressors, so they should not all be considered independent tests.

We also acknowledge that BMI is not an ideal instrument to measure health. BMI was originally created as a way of quantifying an "ordinary man's weight" based solely on the size and measurements of French and Scottish participants (Eknoyan 2007), and is thus biased by design for Western Europeans. Although it has a problematic history and is not always associated with medical conditions, we include it here as it is widely used in medicine as a measure of health and may have clinical relevance. Some research has demonstrated that waist circumference, and not BMI, explains obesity-related health risk; however, when dichotomized as normal vs. high, BMI remains a significant predictor of health risk (Janssen et al. 2004). While waist circumference may be a more informative measure, we only measured waist circumference in the children due to the already high time burden on the mothers.

Our study contains a number of unique strengths as well. First, despite a small sample size, our study was unique in the depth of collected data, which includes comprehensive measures of psychosocial stress and resilience. Our survey data were obtained through extensive 2–3-hour interviews with the mothers and an hour with the children. Another strength of this study lies in the depth of data from two perspectives – mothers and children. This is especially important as children's perspectives on stress are very underrepresented in the literature, and provides insights on different epigenomic dynamics in different life stages. Further, the

longitudinal design permits comparison of stress and methylation across different sociopolitical periods and different periods of childhood. Longitudinal methylation data are very rare, especially during a difficult sociopolitical transition and among a vulnerable population. This study is also one of the only studies of stress and methylation in Latinos, a particularly vulnerable population during the time of the study. Finally, our targeted and hypothesis driven epigenetic approach is valuable, particularly for a focused study with extensive and detailed sociocultural/environmental data that are impossible to collect on larger samples necessitated by genome wide approaches (Non 2021).

CONCLUSION

Our findings demonstrate an epigenetic pathway through which early adversity and ongoing life events associate with DNA methylation within regulatory regions of two well-characterized stress-related genes. This study explored these epigenetic associations within the context of a shifting sociopolitical environment. Many different stressors were associated with methylation in both children and mothers at both genes and across time points. Associations between methylation at *SLC6A4* with cardiometabolic markers implies a potential mediating role for these sites with obesity and other cardiovascular or metabolic diseases. Taken all together, our findings suggest that methylation may be a pathway through which stressful experiences like discrimination can become embodied and ultimately affect cardiometabolic health.

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Chapter 3, in full, is an adaptation of a primary data paper in preparation for submission to a special issue on developmental embodiment at the journal *Frontiers in Systems Neuroscience*. Clausing, E.S. & Non, A.L. The dissertation author was the primary investigator and author of this paper.

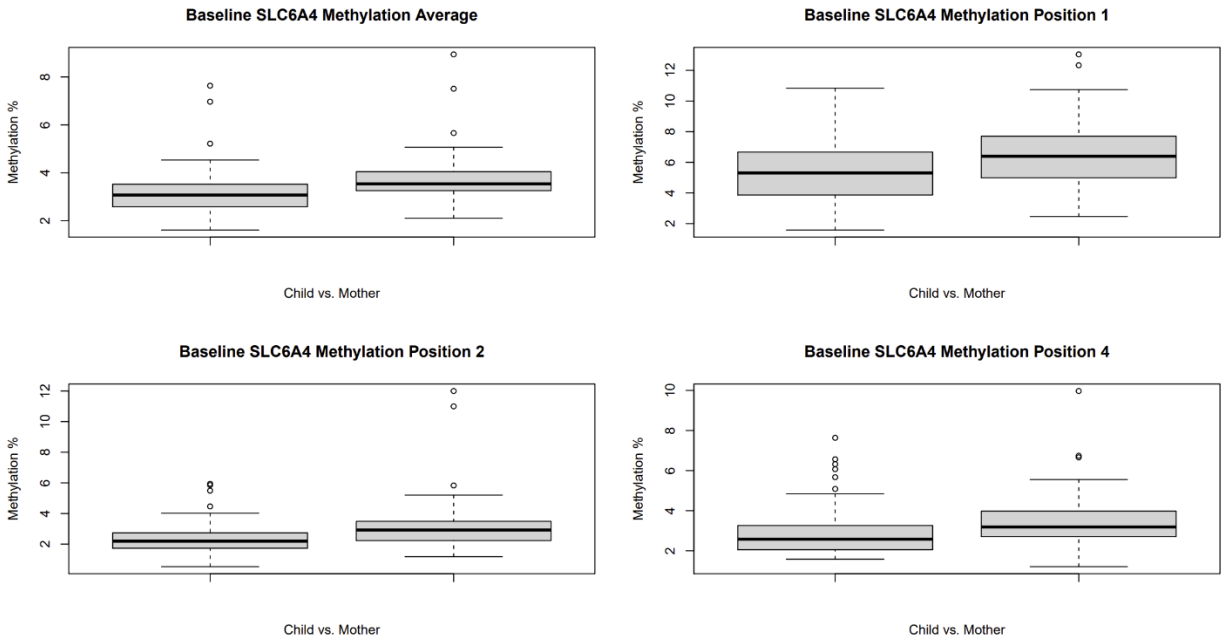

Figure 3.1: Comparison of child and mothers' methylation levels at baseline time point.

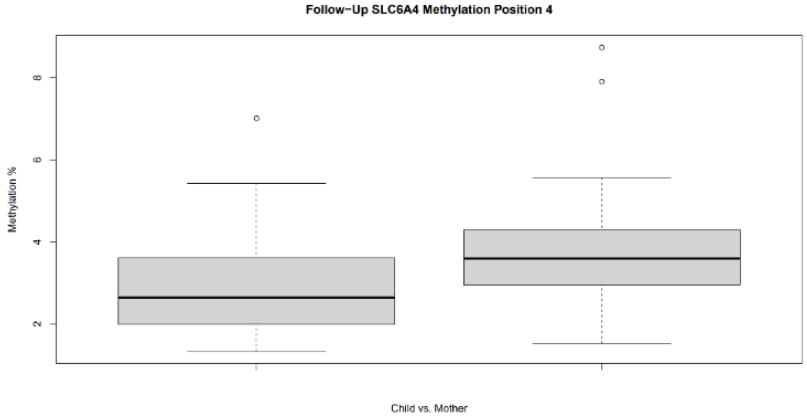

Figure 3.2: Comparison of child and mothers' methylation levels at the follow-up time point.

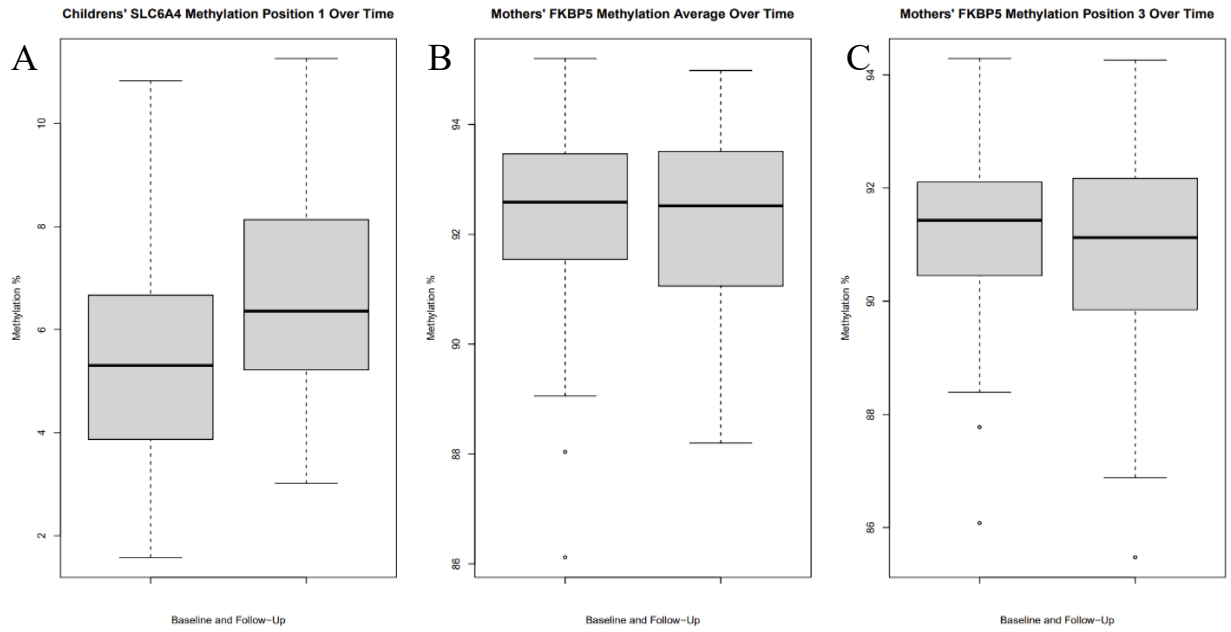

Figure 3.3: Mothers and children's methylation levels over time (baseline and follow-up). A represents children's methylation at CpG1 of *SLC6A4*. B represents mother's methylation levels of *FKBP5* average, and C represents mother's methylation levels of CpG3 of *SLC6A4*.

Table 3.1. Summary of coefficient alphas and questions in stress and resilience scales.

	α‡ (95% CI)	**# of Items**	**Questions (English Translations)**
Child Reported Stress Scales			
Total child stress scale	0.69 (0.6, 0.78)	16	(An additive composite of all stress scale questions below)
IRS	0.46 (0.28, 0.63)	5	How often is each of the following true? (never, sometimes, always)? 1. I get upset that we never go out. 2. I miss relatives that live in my parent's home country. 3. I hear my parents talk about problems with their family in their home country. 4. I see reports about police arresting Latinx people on TV. 5. **I am worried that my parents will be forced to return to their home country.**
Discrimination score	0.70 (0.59, 0.80)	4	Tell me how often the following things happen to you (never, sometimes, always). 1. My classmates make fun of me because I am from [parent's home country]. 2. My classmates make fun of me because of the clothes I wear or the food I bring to school. 3. My classmates make fun of me because I speak Spanish. 4. My classmates say mean things to me.
Everyday Discrimination Scale (EDS) (Williams et al. 1997)	0.83 (0.78, 0.87)	10	In your day-to-day life, how often do any of the following things happen to you? (Almost Everyday, At Least One A Week, A Few Times A Month, A Few Times A Year, Less Than Once A Year, Never) 1. You are treated with less courtesy than other people. 2. You are treated with less respect than other people. 3. You receive poorer service than other people at restaurants or stores. 4. People act as if they think you are not smart. 5. People act as if they are afraid of you. 6. People act as if they think you are dishonest. 7. People act as if they're better than you are. 8. You or your family members are called names or insulted. 9. You are threatened or harassed. 10. People ignore you or act as if you are not there.
School-related stress	0.49 (0.33, 0.65)	7	During this current school year, tell me how often the following things happen to you (never, 1-2 times, more than 2 times). 1. I had something stolen from me at school. 2. I got in trouble at school. 3. I got into a physical fight at school. 4. I was bullied (picked on, made fun of, etc.) at school. How often did the following things happen to you? (never sometimes, always) 5. I feel scared to go to school. 6. I worry about my grades. 5. Teachers are unfair to me.

(R) represents reverse coding.

Table 3.1. Summary of coefficient alphas and questions in stress and resilience scales, continued.

	α‡ (95% CI)	**# of Items**	**Questions (English Translations)**
Child Reported Resilience Scales			
Social Support from parents	0.76 (0.68, 0.84)	6	How often is each of the following true about your family? (never, sometimes, always) 1. We talk about our day. 2. My parents ask about my day at school. 3. My parents care about my feelings. 4. My parents pay attention to what I say. 5. I can talk to my parents if I am upset or have a problem. 6. My parents help me when I need it.
Youth Life Orientation Test (YLOT) (Ey et al. 2005)	0.71 (0.62, 0.80)	12	Please tell me whether you Agree A Lot, Agree A Little, Neither Agree nor Disagree, Disagree A Little, Disagree A Lot: 1. Each day I look forward to having a lot of fun. 2. I usually expect to have a good day. 3. When things are bad, I expect them to get better. 4. Overall, I expect more good things to happen to me than bad things. 5. When I am not sure what will happen next, I usually expect it to be something good. 6. I am lucky person. 7. Usually, I don't expect good things to happen to me. (R) 8. Each day I expect bad things to happen. (R) 9. No matter what I try, I do not believe anything is going to work. (R) 10. When things are good, I expect something to go wrong. (R) 11. Things usually go wrong for me. (R) 12. If something nice happens, chances are it won't be to me. (R)
Maternal Reported Stress Scales			
Total Stress Score	0.92 (0.89, 0.94)	63	(An additive composite of all questions in Maternal Stress Scales below)
Immigrant-related stress	0.64 (0.53, 0.76)	10	When I emigrated to the US, I felt stressed because: (yes/no) 1. Couldn't afford to bring family when emigrated 2. No legal documentation when emigrated 3. Separated from spouse or children when emigrated 4. Lost contact with my family when emigrating During the past year I felt stressed because: (yes/no) 5. I could not communicate with others 6. My partner or a close family member was arrested. 7. My partner or a close family member was deported. 8. My family or I had difficulty adjusting to American customs. 9. My family live far away. 10. My partner does not have legal documents.

(R) represents reverse coding.

Table 3.1. Summary of coefficient alphas and questions in stress and resilience scales, continued.

	α‡ (95% CI)	**# of Items**	**Questions (English Translations)**
Discrimination stress	0.69 (0.60, 0.78)	7	How often did you feel that you: (yes/no)? 1. Were discriminated against at your job? 2. Were treated as if you were less than other Americans 3. Were discriminated against at the doctor's office or hospital 4. Experienced discrimination in your neighborhood because you are an immigrant 5. Were treated unfairly because you are Latina? 6. Have seen friends treated badly because they are Latina? 7. People dislike you because you are Latina?
Everyday Discrimination Scale (EDS) (Williams et al. 1997)	0.82 (0.78, 0.87)	8	In your day-to-day life, how often do any of the following things happen to you? (Almost Everyday, At Least One A Week, A Few Times A Month, A Few Times A Year, Less Than Once A Year, Never) 1. You are treated with less courtesy than other people. 2. You are treated with less respect than other people. 3. You receive poorer service than other people at restaurants or stores. 4. People act as if they think you are not smart. 5. People act as if they are afraid of you. 6. People act as if they're better than you are. 7. You are called names or insulted. 8. You are threatened or harassed. You are followed around in stores.
Household Stress	0.63 (0.52, 0.74)	8	In the past year I felt stressed because: 1. My child spent too much time indoors/enclosed. 2. My child had to translate for me or other family members. 3. **Domestic violence happened in my close family.** 4. I had infidelity problems. 5. I had difficulty finding where to leave my child while working. 6. I fought frequently with my spouse/partner. 7. I separated from my spouse/partner. 8. My spouse/partner had a mental health problem.
Family economic stress	0.85 (0.80, 0.90)	16	In the past year, I felt stressed because: (yes/no) 1. I could not find a job. 2. I was overworked at my job. 3. I could not do the work I was trained for in my home country. 4. I was unemployed or lost my job. 5. I have to work night shifts. 6. I have to work very long shifts or multiple jobs to pay my bills. 7. Conditions at my work are not healthy/have caused painful injuries. 8. I could not find enough work. 9. People with less skills or education than me have better jobs. 10. I was given the lowest position at work. 11. I could not get a loan for a home. 12. I did not understand the American system of credit. **13. I frequently had problems paying basic bills.** 14. I lived in an overcrowded home. 15. I could not afford quality housing. 16. I could not afford childcare (or the type of childcare I wanted).

Table 3.1. Summary of coefficient alphas and questions in stress and resilience scales, continued.

	α‡ (95% CI)	**# of Items**	**Questions (English Translations)**
Family health stress	0.80 (0.74-0.86)	11	In the past year, I felt stressed because: 1. A member of my family had a major health problem. 2. I had a major health problem. 3. I did not have health insurance. 4. I had trouble communicating with my doctor. 5. I lacked information I needed about healthcare. 6. I needed medical care but did not receive it. 7. I had to go to an emergency room. 8. I had difficulty understanding and filling out medical forms. 9. I did not have dental insurance for myself. 10. There was no interpreter at the doctor. 11. I could not find a Hispanic doctor.
Maternal Resilience Scales			
Social Support and Connection (Berkman and Syme 1979)	0.59 (0.45, 0.72)	11	Please tell me whether you Strongly Agree, Agree, Disagree, Strongly Disagree: 1. I have had difficulty making friends in Nashville. 2. I have difficulty seeing my friends or family because I lack transportation. 3. I have found emotional support through my church. 4. I had family members near where I live but I had no relationship with them. 5. I have friends or family with whom I can talk about my feelings or problems. 6. I have friends or family who can help with financial troubles. 7. On average, how many times do you talk on the telephone with family, friends, or neighbors who live near you in the US? 8. On average, how many times do you talk on the telephone with family, friends, or neighbors who live in your country of origin? 9. On average, how often do you get together with friends or relatives? 10. On average, how often do you attend church or religious services? 11. On average, how often do you attend meetings of the clubs or organizations you belong to?
Life Orientation Test – Revised (LOT-R) [35]	0.43 (0.25, 0.61)	6	Please tell me whether you Agree A Lot, Agree A Little, Neither Agree nor Disagree, Disagree A Little, Disagree A Lot: 1. In Uncertain times, I usually expect the best. 2. If something can go wrong for me, it will. (R) 3. I'm always optimistic about my future. 4. I hardly ever expect things to go my way. (R) 5. I rarely count on good things happening to me. (R) 6. Overall, I expect more good things to happen to me than bad.

(R) represents reverse coding.

Table 3.2. Targeted regions of *FKBP5* and *SLC6A4* by bisulfite pyrosequencing.

Gene	Chromosome location (UCSC build hg19)	Amplicon	Primer Type	Primer sequence (5'→3')
FKBP5	chr6:35,558,488-35,558,514	342 bp	Forward	EpigenDx ADS3828 FS2 (proprietary)
			Reverse	EpigenDx ADS3828 FS2 (proprietary)
			Sequencing	5' TGGAGTTATAGTGTAGGTTTT 3'
			Unconverted Sequence to analyze	5' TTCGTGACTCCTGTGAAGGGTACAATCC 3'
			Converted Sequence to analyze	5' TTCGTGATTTTTGTGAAGGGTATAATTC 3'
SLC6A4	chr17:28,563,022-28,563,224	203 bp	Forward	5' GTATTGTTAGGTTTTAGGAAGAAAGAGAGA 3'
			Reverse	5' Biotin-AAAAATCCTAACTTTCCTACTCTTTAACTT 3'
			Sequencing	5' AAGAAAGAGAGAGTAGTT 3'
			Unconverted Sequence to analyze	5' TTCGGGATGGGGACGATGGGGAGGTGTCCGAGGTCAAG AGAAAGCGGCACGAGCAGACCCCTGTGTGCCGTCCTGTGGGCGCGGGGCGGCAGGGGAGGCGCACACCTGCTCCTTTGTGCAGCC 3'
			Converted Sequence to analyze ('-' strand)	5' TTCGGGATGGGGACGATGGGGAGGTGTTCGAGGTTAAG AGAAAGCGGTACGAGTAGATTTTTGTGTGTCGTTTTGTGGGCGCGGGGCGGTAGGGGAGGCGTATATTTGTTTTTTTGTGTAGTT 3'

Table 3.3. Demographics, social stressors, and resilience factors over time, complete case data.

	Baseline (n=79) n, % or mean (sd, range)	**Follow-up (n=39)** n, % or mean (sd, range)	**Missing data baseline/follow-up**	**p-value‡**
Child Demographics				
Age in years	8.67 (2.13, 5-13)	10.5 (2.10, 6-15)	1/2	**4.074e-15**
Gender (female)	44 (56.4%)	17 (47.2%)	1/1	--
Country of birth			0/2	--
United States	57 (72.2%)	27 (73.0%)		
Other	22 (27.8%)	10 (27.0%)		
Mother Demographics				
Age in years	34.61 (5.95, 23-52)	37.45 (4.84, 29-47)	3/0	**<2.2e-16**
Country of birth			3/1	--
Mexico	66 (86.8%)	35 (92.1%)		
Other Latinx country	10 (13.2%)	3 (7.9%)		
Years in US	12.59 (3.97, 4-27)	14.98 (3.46, 6.67-22.42)	4/2	**<2.2e-16**
Legal status			4/3	**2.214e-06**
Undocumented	64 (85.3%)	33 (91.7%)		
Documented	11 (14.7%)	3 (8.3%)		
Marital status			3/1	**0.04123**
Married	65 (85.5%)	29 (76.3%)		
Single	11 (14.5%)	9 (23.7%)		
Years of Education	9.39 (3.18, 2-18)	9.57 (3.24, 2-16)	3/1	--
Trouble paying basic bills (yes)	30 (39.5%)	10 (27.0%)	3/2	0.2278
Smoking frequency	2 (2.6%)	3 (7.9%)	3/1	0.6171
Child Psychosocial Stressors				
Total Child Stress	0.56 (0.26, 0.13-1.31)	0.43 (0.15, 0.12-0.75)	4/5	0.1956
Immigrant stress score	0.85 (0.38, 0-1.75)	0.99 (0.38, 0.2-1.8)	2/3	**0.008674**
Discrimination stress	0.27 (0.37, 0-2)	0.21 (0.31, 0-1.4)	2/3	0.4822
School-related stress	0.51 (0.32, 0-1.43)	0.55 (0.28, 0-1.43)	3/4	0.1261
Fear of parent deportation			2/3	*0.08508*
Never	27 (35.0%)	8 (22.2%)		
Sometimes	31 (40.3%)	19 (52.8%)		
Always	19 (24.7%)	9 (25%)		
Bullied at school			2/4	0.2136
Never	44 (57.1%)	23 (65.7%)		
Sometimes	12 (15.6%)	7 (20.0%)		
Always	21 (27.3%)	5 (14.3%)		
Child Resilience Factors				
SSS			15/5	0.5062
Richer	15 (23.4%)	16 (47.1%)		
Same	42 (65.6%)	14 (42.2%)		
Poorer	7 (11.0%)	4 (11.7%)		
Social support parents	1.41 (0.41, 0.5-2.0)	1.53 (0.34, 0.6-2.0)	2/3	**0.00243**
Optimism	--	32.83 (7.08, 20-46)	39/3	--
Mother report of Psychosocial Stressors				
Total maternal stress	0.30 (0.17, 0.02-0.78)	0.25 (0.12, 0.02-0.53)	8/5	**0.01917**
Immigrant stress score	0.46 (0.23, 0-0.9)	0.42 (0.21, 0-0.8)	8/1	**0.001468**

Table 3.3. Demographics, social stressors, and resilience factors over time, complete case data, continued.

	Baseline (n=79) n, % or mean (sd, range)	**Follow-up (n=39)** n, % or mean (sd, range)	**Missing data baseline/follow-up**	**p-value‡**
Discrimination score	0.43 (0.25, 0-1.0)	0.36 (0.24, 0-0.86)	6/2	*0.05259*
Child's school-related stress score	0.25 (0.21, 0-1.0)	0.20 (0.17, 0-0.57)	3/1	0.1381
Household stress	0.21 (0.21, 0.0-0.8)	0.23 (0.20, 0.0-0.8)	5/1	0.6097
Family economic stress	0.24 (0.24, 0.0-1.0)	0.17 (0.17, 0.0-0.63)	6/4	*0.05941*
Health stress	0.32 (0.26, 0.0-1.0)	0.27 (0.22, 0.0-1.0)	3/2	0.2237
Mother Resilience variables				
SSS	4.07 (1.88, 1-9)	4.32 (1.56, 1-8)	3/1	*0.07479*
Social support and connection	2.48 (0.58, 0.25-3.40)	2.19 (0.56, 1.0-3.40)	3/1	**0.01912**
Optimism	17.12 (3.05, 12-24)	13.66 (2.30, 8-18)	5/1	**1.041e-07**

‡ p-value based on paired t-tests for continuous variables, and McNemar (paired Chi Square) test for categorical variables. Comparisons were calculated only on the 36 individuals in both time points. **Bolded** values represent significant associations. *Italicized* values represent marginal associations.

Table 3.4. Children's psychosocial stressors, resilience factors, and cardiometabolic biomarkers.

		BMI	**Waist Circumference**
Baseline			
Child variables		n=75	n=65
Stress factors:			
	Total stress score	7.443 (14.877)	0.848 (6.614)
	School stress	5.428 (11.851)	3.721 (5.233)
	IRS	3.919 (9.851)	-2.442 (4.011)
	Fear of parent's deportation	0.787 (4.942)	-1.648 (2.058)
	Discrimination stress	4.373 (9.985)	1.499 (4.099)
Resilience factors:			
	Parental social support	8.771 (8.500)	0.954 (3.683)
Follow-Up			
Child variables		n=31	n=30
Stress factors:			
	Total stress score	19.551 (40.437)	*42.130 (21.086)*
	School stress	20.487 (19.307)	**22.152 (10.722)**
	IRS	0.208 (15.650)	4.755 (9.305)
	Fear of parent's deportation	8.865 (7.495)	1.607 (4.497)
	Everyday Discrimination	9.280 (6.417)	**9.920 (3.722)**
	Discrimination stress	18.411 (21.605)	*20.163 (10.876)*
Resilience factors:			
	Parental social support	-26.365 (14.496)	-6.144 (9.249)
	Optimism)	-0.545 (0.794)	-0.596 (0.454)

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal associations.

Table 3.5. Mothers' psychosocial stressors, resilience factors, and cardiometabolic biomarkers.

	BMI	**SBP**	**DBP**
Baseline			
Maternal variables	n=76	n=73	n=73
Stress factors:			
Total stress score	0.434 (3.553)	8.680 (9.145)	2.402 (6.556)
IRS	-0.257 (2.623)	*12.043 (6.570)*	0.654 (4.730)
Family Health Stress	1.764 (2.286)	2.557 (5.789)	-0.108 (4.080)
Household stress	-0.749 (2.845)	-3.476 (7.240)	-0.809 (5.102)
Family economic stress	-1.578 (2.580)	0.639 (6.575)	0.512 (4.682)
Discrimination stress	0.002 (2.491)	*10.923 (6.290)*	5.976 (4.489)
Resilience factors:			
SSS	-0.310 (0.309)	-0.909 (0.790)	-0.169 (0.560)
Social support/social connection	**-2.153 (0.004)**	1.319 (2.600)	1.533 (1.824)
Optimism	*-0.335 (0.197)*	0.792 (0.502)	*0.587 (0.351)*
Demographic/Immigrant-related Factors			
SASH	0.523 (1.130)	-0.473 (2.855)	0.168 (2.010)
Follow-Up			
Maternal variables	n=30	n=34	n=34
Stress factors:			
Total stress score	8.573 (10.141)	30.828 (19.445)	15.470 (16.110)
IRS	5.060 (6.957)	4.159 (12.073)	-1.290 (9.757)
Household stress	2.092 (5.425)	-15.870 (9.840)	-8.607 (8.110)
Family health stress	7.377 (6.092)	8.371 (9.175)	1.209 (7.525)
Family economic stress	-2.141 (7.240)	0.627 (13.676)	-5.010 (10.978)
Everyday Discrimination	-1.031 (2.014)	0.346 (3.771)	-0.650 (3.049)
Discrimination stress	2.585 (4.727)	*15.804 (8.372)*	7.766 (7.008)
Resilience factors:			
SSS	-0.300 (0.694)	**-2.706 (1.268)**	-1.302 (1.068)
Social support/social connection	0.350 (1.899)	1.968 (3.712)	*5.106 (2.873)*
Optimism	-0.257 (0.483)	0.930 (0.910)	0.277 (0.744)
Demographics/Immigrant-Related			
SASH	**-2.962 (1.438)**	1.364 (2.861)	3.486 (2.235)

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal associations.

Table 3.6. Psychosocial stressors and resilience factors and methylation levels at *FKBP5* of children and mothers at both time points.

	FKBP5		
	CpG1	**CpG2**	**Average**
Baseline			
Child variables			
Stress factors:			
Total stress score	-1.16 (1.62)	1.58 (1.14)	0.21 (1.19)
School stress	0.38 (1.30)	1.06 (0.91)	0.72 (0.95)
Immigrant-related stress	-0.21 (1.09)	0.97 (0.77)	0.38 (0.80)
Fear of parent's deportation	-0.10 (0.54)	*0.72 (0.37)*	0.31 (0.39)
Discrimination stress	*-1.93 (1.06)*	0.74 (0.76)	-0.60 (0.79)
Resilience factors:			
Parental social support	-1.27 (0.98)	-0.26 (0.70)	-0.77 (0.72)
Maternal variables			
Stress factors:			
Total stress score	-1.12 (1.52)	-0.84 (1.12)	-0.98 (1.25)
IRS	-1.26 (1.09)	-0.80 (0.80)	-1.03 (0.90)
Household stress	0.18 (1.21)	0.25 (0.88)	0.22 (0.99)
Family health stress	-0.69 (0.98)	-0.43 (0.71)	-0.56 (0.80)
Family economic stress	-1.29 (1.06)	-0.90 (0.78)	-1.09 (0.87)
Discrimination stress	0.85 (1.05)	-0.20 (0.77)	0.33 (0.87)
Resilience factors:			
SSS	0.07 (0.13)	-0.06 (0.09)	4.33e-03 (0.11)
Social support/social connection	0.23 (0.42)	0.17 (0.30)	0.20 (0.34)
Optimism	-0.08 (0.08)	0.01 (0.06)	-0.03 (0.07)
Demographic/Immigrant-related Factors			
SASH	**-1.19 (0.44)**	*-0.58 (0.33)*	**-0.89 (0.36)**
Follow-Up			
Child variables			
Stress factors:			
Total stress score	-1.86 (3.44)	-2.57 (2.57)	-2.21 (2.79)
School stress	1.54 (1.90)	-0.20 (1.46)	0.67 (1.56)
IRS	-1.79 (1.32)	-1.47 (0.98)	-1.63 (1.05)
Fear of parent's deportation	-0.86 (0.69)	0.12 (0.54)	-0.37 (0.57)
Everyday Discrimination	-0.83 (0.59)	**-1.03 (0.38)**	*-0.93 (0.45)*
Discrimination stress	2.15 (1.83)	0.34 (1.41)	1.24 (1.50)
Resilience factors:			
Parental social support	**2.86 (1.29)**	1.03 (1.03)	*1.94 (1.07)*
Optimism	-0.07 (0.07)	-0.02 (0.05)	-0.04 (0.06)

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal associations.

Table 3.6. Psychosocial stressors and resilience factors and methylation levels at *FKBP5* of children and mothers at both time points, continued.

	FKBP5		
	CpG1	**CpG2**	**Average**
Maternal variables			
Stress factors:			
Total stress score	-1.78 (3.80)	0.77 (3.30)	-0.50 (3.29)
IRS	-1.47 (2.43)	1.28 (2.15)	-0.10 (2.15)
Household stress	-0.41 (1.86)	-0.26 (1.65)	-0.33 (1.63)
Family health stress	-1.84 (0.70)	-0.67 (0.67)	*-1.25 (0.64)*
Family economic stress	2.44 (2.16)	1.37 (2.28)	1.90 (2.09)
Everyday Discrimination	0.69 (0.65)	-0.34 (0.58)	0.17 (0.58)
Discrimination stress	0.08 (1.56)	-0.45 (1.36)	-0.18 (1.35)
Resilience factors:			
SSS	-0.14 (0.26)	-0.14 (0.23)	-0.14 (0.23)
Social support/social connection	-0.39 (0.67)	4.71e-03 (0.59)	-0.19 (0.59)
Optimism	0.04 (0.17)	-0.10 (0.15)	-0.03 (0.15)
Demographics/Immigrant-Related			
SASH	0.46 (0.52)	0.10 (0.47)	0.29 (0.46)

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal associations.

Table 3.7. Psychosocial stressors and resilience factors and methylation levels at *SLC6A4* of children and mothers at both time points.

	SLC6A4						
	CpG1	**CpG2**	**CpG3**	**CpG4**	**CpG5**	**CpG6**	**Average**
Baseline							
Child variables							
Stress factors:							
Total stress score	-0.36 (1.01)	0.49 (0.51)	0.95 (0.52)	0.80 (0.59)	*0.98 (0.67)*	*1.34 (0.68)*	0.70 (0.46)
School stress	-0.60 (0.81)	0.20 (0.41)	0.75 (0.43)	*0.73 (0.47)*	*0.78 (0.53)*	0.74 (0.54)	0.43 (0.37)
Immigrant-related stress	-0.49 (0.68)	0.34 (0.34)	**0.77 (0.35)**	0.45 (0.40)	**0.89 (0.44)**	*0.89 (0.45)*	0.48 (0.31)
Fear of parent's deportation	-0.38 (0.33)	0.13 (0.17)	**0.38 (0.17)**	*0.34 (0.19)*	**0.55 (0.21)**	**0.49 (0.21)**	*0.25 (0.15)*
Discrimination stress	-0.03 (0.81)	0.09 (0.41)	0.15 (0.43)	-0.31 (0.47)	-0.24 (0.53)	0.61 (0.54)	0.04 (0.37)
Resilience factors:							
Parental social support	-0.37 (0.63)	-0.22 (0.32)	-0.05 (0.34)	0.03 (0.37)	-0.44 (0.41)	-0.22 (0.42)	-0.21 (0.29)
Maternal variables							
Stress factors:							
Total stress score	*2.72 (1.37)*	1.85 (1.19)	*2.17 (1.20)*	0.09 (0.91)	0.08 (0.73)	**2.10 (0.93)**	**1.50 (0.70)**
Immigrant-related stress	**2.74 (0.98)**	**1.83 (0.85)**	**2.11 (0.86)**	0.70 (0.66)	0.33 (0.53)	**1.65 (0.67)**	**1.56 (0.49)**
Household stress	1.17 (1.13)	1.18 (0.96)	0.12 (0.98)	0.28 (0.73)	-0.50 (0.58)	1.20 (0.76)	0.58 (0.574)
Family health stress	1.13 (0.91)	0.89 (0.77)	**1.92 (0.76)**	-0.22 (0.59)	0.44 (0.47)	**1.50 (0.60)**	**0.94 (0.45)**
Family economic stress	0.79 (2.02)	0.51 (0.87)	0.33 (0.89)	0.24 (0.66)	-0.59 (0.52)	0.56 (0.69)	0.30 (0.52)
Discrimination stress	**1.98 (0.95)**	1.30 (0.83)	1.32 (0.83)	0.38 (0.64)	-0.02 (0.52)	1.10 (0.66)	**1.01 (0.49)**
Resilience factors:							
Subjective social status	**-0.25 (0.12)**	-0.16 (0.10)	**-0.23 (0.10)**	*-0.13 (0.08)*	-0.02 (0.06)	**-0.24 (0.08)**	**-0.17 (0.06)**
Social support/social connection	0.26 (0.41)	0.24 (0.34)	-0.25 (0.25)	0.06 (0.26)	-0.12 (0.21)	-0.21 (0.28)	-2.60E-03 (0.21)
Optimism	-0.07 (0.08)	-0.05 (0.07)	-0.07 (0.07)	-0.08 (0.05)	-0.02 (0.04)	-0.05 (0.06)	-0.06 (0.04)
Demographic/Immigrant-related Factors							
SASH	**-0.88 (0.44)**	-0.50 (0.38)	-0.01 (0.39)	-0.29 (0.29)	0.07 (0.23)	-0.13 (0.30)	-0.29 (0.23)
Follow-Up							
Child variables							
Stress factors:							
Total stress score	1.56 (2.50)	0.14 (1.54)	1.24 (1.49)	0.22 (1.54)	-0.15 (1.22)	-0.13 (1.73)	0.48 (1.20)

Table 3.7. Psychosocial stressors and resilience factors and methylation levels at *SLC6A4* of children and mothers at both time points, continued.

	SLC6A4						
	CpG1	**CpG2**	**CpG3**	**CpG4**	**CpG5**	**CpG6**	**Average**
School stress	-2.19 (1.38)	-0.55 (0.94)	-0.77 (0.97)	0.97 (0.90)	0.59 (0.69)	0.14 (1.00)	-0.30 (0.75)
Immigrant-related stress	0.26 (1.06)	0.28 (0.66)	0.80 (0.69)	0.02 (0.66)	-0.15 (0.51)	0.57 (0.70)	0.30 (0.55)
Fear of parent's deportation	-0.08 (0.56)	0.21 (0.35)	0.46 (0.36)	-0.08 (0.35)	-0.08 (0.27)	-0.07 (0.37)	0.06 (0.29)
Everyday Discrimination	-0.09 (0.41)	-0.17 (0.25)	-0.20 (0.24)	0.05 (0.24)	-0.06 (0.19)	0.03 (0.25)	-0.07 (0.20)
Discrimination stress	-0.53 (1.46)	-1.13 (0.89)	-0.77 (0.96)	-0.06 (0.91)	-0.21 (0.71)	-1.13 (0.96)	-0.64 (0.75)
Resilience factors:							
Parental social support	-0.38 (1.09)	*-1.21 (0.65)*	-0.70 (0.71)	-0.30 (0.67)	0.14 (0.53)	-0.20 (0.73)	-0.44 (0.56)
Optimism	-0.08 (0.05)	**-0.07 (0.03)**	-8.94e-04 (0.04)	-0.05 (0.03)	-0.04 (0.03)	-0.01 (0.04)	-0.04 (0.03)
Maternal variables							
Stress factors:							
Total stress score	-2.96 (3.13)	-1.41 (1.79)	-0.87 (1.72)	-3.87 (2.08)	2.14 (2.09)	-0.90 (2.50)	-1.18 (1.63)
Immigrant-related stress	0.06 (2.05)	-0.66 (1.24)	-1.33 (1.11)	**-3.37 (1.30)**	-1.12 (1.41)	-2.01 (1.58)	-1.40 (1.10)
Household stress	-0.01 (1.56)	0.18 (0.95)	-0.56 (0.86)	**-2.64 (0.99)**	-0.50 (1.09)	-0.28 (1.24)	-0.64 (0.86)
Family health stress	-0.47 (0.63)	0.02 (0.40)	-0.32 (0.36)	-0.61 (0.45)	-0.64 (0.44)	-0.16 (0.52)	-0.36 (0.35)
Family economic stress	-0.13 (2.14)	-0.76 (1.35)	-0.46 (1.23)	-1.91 (1.54)	-0.03 (1.37)	-1.24 (1.70)	-0.76 (1.23)
Everyday Discrimination	0.35 (0.58)	-0.12 (0.34)	0.01 (0.33)	-0.27 (0.41)	0.28 (0.41)	-0.19 (0.46)	0.01 (0.32)
Discrimination stress	-1.09 (1.33)	-0.42 (0.78)	0.30 (0.76)	-0.55 (0.94)	1.45 (0.91)	-0.06 (1.07)	-0.06 (0.74)
Resilience factors:							
Subjective social status	0.28 (0.21)	0.21 (0.13)	0.13 (0.12)	0.04 (0.15)	0.12 (0.15)	0.17 (0.17)	0.16 (0.12)
Social support/social connection	0.48 (0.56)	0.42 (0.34)	0.07 (0.32)	0.08 (0.40)	-0.20 (0.39)	-0.14 (0.49)	0.12 (0.31)
Optimism	-3.48e-04 (0.14)	-0.01 (0.09)	0.08 (0.08)	0.08 (0.10)	0.13 (0.10)	0.14 (0.11)	0.07 (0.08)
Demographics/Immigrant-Related							
SASH	0.63 (0.43)	*0.51 (0.25)*	**0.54 (0.23)**	**0.84 (0.27)**	**0.61 (0.29)**	0.53 (0.34)	**0.61 (0.22)**

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal associations.

Table 3.8. Children's methylation levels and cardiometabolic biomarkers.

		BMI Percentile	p-value	Waist Circumference	p-value
Baseline					
Child variables		n=69		n=62	
SLC6A4					
	Average	-11.754 (3.631)	**0.001869**	-4.627 (1.544)	**0.00395**
	Position 1	-3.911 (1.730)	**0.02696**	-2.000 (0.709)	**0.00646**
	Position 2	-5.512 (3.474)	0.11724	-2.494 (1.393)	*0.078325*
	Position 3	-6.009 (3.269)	*0.07043*	-2.913 (1.335)	**0.03299**
	Position 4	-5.843 (2.950)	*0.05167*	-1.186 (1.306)	0.36745
	Position 5	-5.936 (2.596)	**0.02534**	-2.241 (1.079)	**0.042098**
	Position 6	-7.003 (2.521)	**0.00706**	-2.121 (1.198)	*0.081674*
FKBP5					
	Average	-1.998 (1.539)	0.198	-0.555 (0.638)	0.38817
	Position 1	-1.381 (1.130)	0.2258	-0.496 (0.464)	0.2898
	Position 2	-1.498 (1.585)	0.348	-0.189 (0.661)	0.775576
Follow-Up					
Child variables		n=29		n=28	
SLC6A4					
	Average	-0.544 (4.883)	0.912	-0.427 (3.051)	0.88984
	Position 1	0.400 (2.469)	0.873	-0.367 (1.593)	0.81954
	Position 2	-2.998 (4.011)	0.461	-0.2834 (2.556)	0.91252
	Position 3	0.431 (3.730)	0.909	-1.530 (2.400)	0.52925
	Position 4	-0.569 (4.027)	0.889	1.824 (2.580)	0.48551
	Position 5	-0.745 (5.122)	0.885	1.858 (3.525)	0.60238
	Position 6	0.190 (3.877)	0.961	-1.491 (2.462)	0.54992
FKBP5					
	Average	-2.450 (2.326)	0.301	0.574 (1.540)	0.712
	Position 1	-2.352 (1.867)	0.218	0.491 (1.230)	0.6928
	Position 2	-1.494 (2.517)	0.558	0.440 (1.662)	0.793

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal associations.

Table 3.9. Mother's methylation levels and cardiometabolic biomarkers.

		BMI	**p-value**	**SBP**	**p-value**	**DBP**	**p-value**
Baseline							
Maternal variables		n=70/69		n=68/66		n=68/66	
SLC6A4							
	Average	0.112 (0.601)	0.8527	2.041 (1.445)	0.162	0.353 (1.052)	0.7382
	Position 1	-0.222 (0.306)	0.4695	0.215 (0.757)	0.778	0.002 (0.544)	0.9973
	Position 2	-0.088 (0.360)	0.8072	1.235 (0.869)	0.16	0.572 (0.629)	0.3665
	Position 3	0.146 (0.354)	0.68	1.297 (0.849)	0.131	0.422 (0.619)	0.4971
	Position 4	0.312 (0.475)	0.514	0.629 (1.175)	0.594	0.224 (0.846)	0.7923
	Position 5	0.373 (0.593)	0.531	0.840 (1.485)	0.574	-1.244 (1.058)	0.2439
	Position 6	0.264 (0.449)	0.5587	1.411 (1.087)	0.199	0.098 (0.790)	0.9014
FKBP5							
	Average	-0.015 (0.375)	0.9687	0.716 (0.928)	0.443	0.756 (0.663)	0.2586
	Position 1	0.114 (0.306)	0.7114	0.528 (0.760)	0.49	0.621 (0.543)	0.2566
	Position 2	-0.255 (0.422)	0.5481	0.810 (1.040)	0.439	0.734 (0.745)	0.3285
Follow-Up							
Maternal variables		n=28/29		n=32/33		n=32	
SLC6A4							
	Average	-0.153 (1.189)	0.8988	1.343 (2.178)	0.5419	4.098 (1.610)	**0.01608**
	Position 1	-0.101 (0.651)	0.8777	-0.949 (1.199)	0.43476	0.082 (0.978)	0.933
	Position 2	-0.689 (1.061)	0.5218	-0.206 (2.001)	0.91873	3.463 (1.492)	**0.027**
	Position 3	0.357 (1.157)	0.7597	1.377 (2.145)	0.52571	3.642 (1.617)	**0.03148**
	Position 4	-0.282 (0.911)	0.7597	1.911 (1.688)	0.2664	3.549 (1.237)	**0.00735**
	Position 5	0.855 (0.891)	0.3455	2.780 (1.615)	*0.09516*	3.280 (1.232)	**0.0122**
	Position 6	-0.520 (0.812)	0.5273	1.090 (1.519)	0.47833	2.521 (1.151)	**0.03616**
FKBP5							
	Average	0.172 (0.572)	0.766	-0.281 (1.069)	0.7946	-0.181 (0.874)	0.837
	Position 1	-0.120 (0.508)	0.816	-0.287 (0.941)	0.763	-0.135 (0.770)	0.862
	Position 2	0.497 (0.566)	0.387	-0.192 (1.073)	0.8588	-0.190 (0.876)	0.83

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal association.

Table 3.10. Mother's psychosocial stressors and resilience factors with child's methylation at *FKBP5*.

		FKBP5	
		CpG2	**Average**
Baseline			
Maternal variables			
Stress factors:			
	Health stress		*-1.87 (1.10)*
Resilience factors:			
	SSS		*0.26 (0.14)*
	Social support/social connection	**1.49 (0.46)**	**1.18 (0.48)**

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal associations.

Table 3.11. Mother's psychosocial stressors and resilience factors with child's methylation at *SLC6A4*.

	SLC6A4						
	CpG1	**CpG2**	**CpG3**	**CpG4**	**CpG5**	**CpG6**	**Average**
Baseline							
Maternal variables							
Stress factors:							
Legal Status	**-1.34 (0.62)**						
SASH			**0.50 (0.24)**			**0.65 (0.30)**	
Health stress		*-0.81 (0.47)*					
Resilience factors:							
Education			**0.09 (0.04)**				
SSS	**-0.33 (0.12)**						
Follow-Up							
Maternal variables							
Stress factors:							
Total stress score			**5.96 (2.27)**	*4.02 (2.17)*			
Immigrant-related stress			*2.82 (1.47)*				
Household stress		**2.54 (1.01)**	**3.23 (1.02)**	**2.19 (1.03)**	*1.52 (0.81)*		**2.13 (0.83)**
Family economic stress				**3.19 (1.52)**	*2.14 (1.21)*		
Resilience factors:							
Education	*-0.20 (0.11)*						
SSS			*-0.30 (0.15)*			*-0.28 (0.15)*	
Social support/social connection					**-0.73 (0.28)**	*-0.73 (0.41)*	*-0.64 (0.31)*

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal associations.

Supplemental Table S3.1. Child psychosocial stressors, resilience factors, and methylation correlation table at baseline.

	Total Stress	School Stress	IRS	DS	FPD	SSP	BMI %	WC	FKBP5 average	CpG1	CpG2	SLC6A4 average	CpG1	CpG2	CpG3	CpG4	CpG5	CpG6
Total Stress	1.00																	
School Stress	**0.83**	1.00																
IRS	**0.66**	**0.27**	**1.00**															
DS	**0.70**	**0.48**	**0.22**	**1.00**														
FPD	**0.56**	**0.37**	**0.69**	0.19	1.00													
SSP	**0.30**	**0.26**	**0.30**	0.12	**0.19**	1.00												
BMI %	0.06	0.07	-0.01	0.11	0.04	0.08	1.00											
WC	0.15	0.22	0.05	0.03	0.10	0.11	**0.61**	1.00										
FKBP5 average	-0.01	0.03	0.01	-0.05	0.04	-0.16	-0.13	-0.18	1.00									
CpG1	-0.08	0.00	-0.02	-0.17	-0.03	-0.17	-0.14	-0.16	**0.90**	1.00								
CpG2	0.10	0.05	0.05	0.14	0.11	-0.09	-0.08	-0.14	**0.80**	**0.46**	1.00							
SLC6A4 average	0.22	0.15	**0.25**	0.04	0.20	-0.04	**-0.39**	**-0.32**	0.21	0.19	0.19	1.00						
CpG1	-0.03	-0.07	-0.06	-0.01	-0.14	-0.06	**-0.28**	**-0.36**	0.01	0.09	-0.10	**0.52**	1.00					
CpG2	0.16	0.09	0.19	0.04	0.12	-0.04	-0.21	-0.18	0.10	0.12	0.04	**0.78**	**0.45**	1.00				
CpG3	0.22	0.17	**0.29**	0.03	0.22	0.05	**-0.24**	-0.24	**0.23**	0.15	**0.28**	**0.78**	0.13	**0.56**	1.00			
CpG4	**0.23**	0.21	0.22	-0.01	**0.24**	0.03	**-0.25**	-0.11	0.17	0.12	0.19	**0.73**	0.10	**0.49**	**0.54**	1.00		
CpG5	0.22	0.19	**0.29**	-0.02	**0.31**	-0.09	**-0.29**	-0.20	**0.25**	0.20	**0.25**	**0.82**	0.08	**0.58**	**0.77**	**0.64**	1.00	
CpG6	**0.26**	0.15	**0.28**	0.15	**0.25**	-0.03	**-0.32**	-0.18	0.20	0.13	**0.24**	**0.71**	0.06	**0.37**	**0.57**	**0.55**	**0.66**	1.00

Bolded values represent significant associations. Key: IRS: immigrant-related stress; DS: discrimination stress; FPD: fear of parent deportation; SSP: social support from parents; BMI: body mass index; WC: waist circumference.

Supplemental Table S3.2. Child psychosocial stressors, resilience factors, and methylation correlation table at follow-up.

	Total Stress	School Stress	IRS	DS	FPD	EDS	SSP	YLOT	BMI %	WC	FKBP5 average	CpG1	CpG2	SLC6A4 average	CpG1	CpG2	CpG3	CpG4	CpG5	CpG6
Total Stress	1.00																			
School Stress	0.17	1.00																		
IRS	**0.65**	-0.20	1.00																	
DS	**0.51**	**0.58**	-0.19	1.00																
FPD	**0.38**	-0.25	**0.65**	-0.16	1.00															
EDS	**0.48**	**0.45**	0.35	0.24	0.11	1.00														
SSP	-0.31	-0.18	-0.06	-0.13	-0.19	**-0.46**	1.00													
YLOT	-0.12	-0.20	-0.11	0.10	-0.13	**-0.37**	**0.38**	1.00												
BMI %	0.05	0.26	-0.07	0.18	0.13	0.27	**-0.36**	-0.18	1.00											
WC	0.25	0.13	0.17	0.00	0.11	**0.40**	-0.09	-0.26	0.32	1.00										
FKBP5 average	-0.22	0.16	**-0.43**	0.29	-0.29	**-0.39**	0.21	0.02	-0.11	0.00	1.00									
CpG1	-0.18	0.19	**-0.39**	**0.33**	-0.37	-0.30	0.28	0.02	-0.16	0.00	**0.95**	1.00								
CpG2	-0.24	0.10	**-0.42**	0.21	-0.15	**-0.47**	0.08	0.01	-0.03	-0.01	**0.91**	**0.75**	1.00							
SLC6A4 average	0.11	0.11	0.04	0.04	0.00	-0.08	-0.19	-0.30	0.07	-0.10	0.27	0.27	0.23	1.00						
CpG1	0.17	-0.01	0.01	0.12	-0.05	-0.07	-0.14	**-0.34**	0.14	-0.09	0.23	0.27	0.13	**0.73**	1.00					
CpG2	0.02	0.02	-0.01	-0.01	0.03	-0.14	-0.32	-0.27	-0.09	-0.15	0.31	0.32	0.26	**0.83**	**0.53**	1.00				
CpG3	0.14	0.00	0.12	0.04	0.13	-0.18	-0.20	0.00	0.08	-0.16	0.11	0.06	0.17	**0.78**	**0.37**	**0.59**	1.00			
CpG4	0.09	**0.35**	-0.04	0.18	-0.08	0.05	-0.14	-0.29	0.07	-0.01	0.32	0.31	0.29	**0.91**	**0.59**	**0.76**	**0.65**	1.00		
CpG5	0.01	0.22	-0.02	-0.04	-0.01	-0.03	-0.01	**-0.37**	0.04	0.08	0.30	0.26	0.31	**0.78**	**0.45**	**0.59**	**0.51**	**0.79**	1.00	
CpG6	-0.02	0.03	0.14	-0.17	-0.01	0.04	-0.05	-0.09	0.02	-0.10	-0.02	0.00	-0.04	**0.59**	0.07	**0.42**	**0.56**	**0.48**	**0.42**	1.00

Bolded values represent significant associations. Key: IRS: immigrant-related stress; DS: discrimination stress; FPD: fear of parent deportation; SSP: social support from parents; YLOT: Youth Life Orientation Test; BMI: body mass index; WC: waist circumference.

Supplemental Table S3.3. Maternal psychosocial stressors, resilience factors, and methylation correlation table at baseline.

	Total Stress	IRS	DS	Household stress	Health stress	FES	SASH	SSS	SSC	LOT-R	BMI	SBP	DBP	FKBP5 average	CpG1	CpG2	SLC6A4 average	CpG1	CpG2	CpG3	CpG4	CpG5	CpG6
Total Stress	1.00																						
IRS	**0.74**	1.00																					
DS	**0.63**	**0.45**	1.00																				
Household stress	**0.72**	**0.35**	**0.31**	1.00																			
Health stress	**0.85**	**0.55**	**0.43**	**0.49**	1.00																		
FES	**0.87**	**0.50**	**0.50**	**0.69**	**0.59**	1.00																	
SASH	0.13	-0.03	-0.06	0.06	0.14	0.01	1.00																
SSS	**-0.31**	**-0.39**	-0.19	-0.13	**-0.30**	-0.15	-0.06	1.00															
SSC	-0.13	-0.11	0.03	-0.10	-0.18	-0.02	-0.13	**0.29**	1.00														
LOT-R	-0.13	-0.21	0.16	**-0.24**	-0.13	-0.13	0.11	0.06	**0.27**	1.00													
BMI	0.01	0.00	-0.02	-0.06	0.09	-0.08	0.01	-0.09	**-0.23**	-0.22	1.00												
SBP	0.11	0.21	0.20	-0.08	0.05	0.01	-0.04	-0.12	0.06	0.17	**0.35**	1.00											
DBP	0.04	0.03	0.15	-0.07	0.00	0.00	-0.04	-0.02	0.10	0.16	**0.30**	**0.74**	1.00										
FKBP5 average	-0.10	-0.14	0.03	0.04	-0.09	-0.15	**-0.26**	0.01	0.07	-0.06	0.00	0.09	0.12	1.00									
CpG1	-0.09	-0.14	0.08	0.03	-0.09	-0.15	**-0.29**	0.07	0.07	-0.12	0.04	0.08	0.11	**0.96**	1.00								
CpG2	-0.09	-0.13	-0.06	0.05	-0.08	-0.14	-0.18	-0.06	0.07	0.02	-0.06	0.09	0.10	**0.93**	**0.79**	1.00							
SLC6A4 average	0.23	**0.33**	0.22	0.10	0.21	0.06	-0.15	**-0.32**	0.01	-0.16	0.01	0.16	0.04	0.14	0.18	0.08	1.00						
CpG1	**0.24**	**0.32**	**0.23**	0.12	0.15	0.09	-0.22	**-0.24**	0.07	-0.11	-0.06	0.05	0.03	0.17	0.19	0.12	**0.51**	1.00					
CpG2	0.15	**0.23**	0.17	0.12	0.11	0.06	-0.17	-0.17	0.09	-0.09	-0.03	0.17	0.12	0.13	0.14	0.10	**0.86**	**0.28**	1.00				
CpG3	0.18	**0.26**	0.16	-0.01	**0.25**	0.03	-0.03	**-0.24**	-0.06	-0.12	0.05	0.18	0.09	0.06	0.08	0.03	**0.83**	0.14	**0.73**	1.00			
CpG4	0.01	0.11	0.09	0.08	-0.04	0.06	-0.08	-0.21	0.01	-0.14	-0.02	0.02	-0.05	0.05	0.09	-0.01	**0.49**	-0.12	**0.41**	**0.39**	1.00		
CpG5	0.00	0.06	0.00	-0.10	0.10	-0.13	0.03	-0.04	-0.06	-0.05	0.04	0.05	-0.16	-0.06	-0.02	-0.09	**0.40**	0.12	0.18	**0.23**	**0.21**	1.00	
CpG6	0.23	**0.25**	0.15	0.16	**0.24**	0.08	-0.06	**-0.31**	-0.07	-0.13	0.08	0.16	0.03	0.10	0.08	0.11	**0.81**	**0.23**	**0.73**	**0.79**	**0.26**	**0.15**	1.00

Bolded values represent significant associations. Key: IRS: immigrant-related stress; DS: discrimination stress; FES: Family Economic Stress; SASH: Short Acculturation Scale for Hispanics; SSS: Subjective Social Status; SSC: social support/social connection; LOT-R: Life Orientation Test – Revised; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Supplemental Table S3.4: Maternal psychosocial stressors, resilience factors, and methylation correlation table at follow-up.

	Total Stress	IRS	DS	Household stress	Health stress	FES	EDS	SASH	SSS	SSC	LOT-R	BMI	SBP	DBP	FKBP5 average	CpG1	CpG2	SLC6A4 average	CpG1	CpG2	CpG3	CpG4	CPG5	CpG6
Total Stress	1.00																							
IRS	0.41	1.00																						
DS	**0.77**	0.09	1.00																					
Household stress	0.43	0.03	0.07	1.00																				
Health stress	0.39	0.14	-0.12	**0.63**	1.00																			
FES	**0.90**	0.24	**0.83**	0.26	0.04	1.00																		
EDS	**0.68**	0.14	**0.93**	-0.03	-0.32	**0.82**	1.00																	
SASH	-0.22	0.12	-0.02	-0.37	-0.34	-0.22	0.10	1.00																
SSS	-0.51	-0.26	**-0.52**	-0.06	0.04	**-0.50**	-0.48	-0.31	1.00															
SSC	**-0.59**	-0.05	**-0.64**	-0.32	-0.01	**-0.64**	**-0.65**	-0.09	**0.65**	1.00														
LOT-R	0.00	-0.16	0.33	-0.44	**-0.54**	0.14	0.48	0.29	-0.13	-0.20	1.00													
BMI	0.02	-0.04	0.06	0.12	0.16	-0.15	-0.19	-0.30	-0.12	-0.03	-0.16	1.00												
SBP	0.15	-0.06	0.27	-0.25	0.14	-0.15	-0.13	0.07	**-0.32**	0.07	0.07	**0.37**	1.00											
DBP	0.02	-0.03	0.18	-0.18	-0.02	-0.20	-0.09	0.25	-0.27	0.25	-0.05	**0.23**	**0.64**	1.00										
FKBP5 average	-0.09	-0.15	0.02	-0.03	-0.13	0.12	0.07	0.03	-0.05	-0.05	-0.05	0.07	-0.01	-0.05	1.00									
CpG1	-0.16	-0.21	0.06	-0.05	-0.20	0.11	0.17	0.07	-0.07	-0.09	-0.01	-0.03	0.00	-0.01	**0.94**	1.00								
CpG2	0.00	-0.05	-0.03	-0.01	-0.04	0.11	-0.07	-0.02	-0.01	-0.01	-0.09	0.17	-0.01	-0.08	**0.92**	**0.74**	1.00							
SLC6A4 average	-0.16	-0.05	0.04	-0.13	-0.13	-0.10	0.11	**0.37**	0.04	0.06	0.04	-0.06	-0.04	**0.45**	-0.05	0.04	-0.14	1.00						
CpG1	-0.10	0.12	-0.08	-0.05	-0.25	0.07	0.21	0.21	0.16	0.19	0.04	-0.12	-0.24	0.01	**0.35**	**0.36**	0.29	**0.57**	1.00					
CpG2	-0.17	0.06	-0.03	0.00	-0.07	-0.09	0.06	0.28	0.08	0.19	-0.12	-0.14	-0.14	**0.43**	-0.08	0.01	-0.16	**0.90**	**0.47**	1.00				
CpG3	-0.13	-0.10	0.12	-0.13	-0.11	-0.10	0.09	0.31	0.05	0.03	0.03	0.02	0.00	**0.43**	-0.15	-0.04	-0.25	**0.92**	**0.40**	**0.80**	1.00			
CpG4	**-0.37**	-0.25	-0.03	**-0.34**	-0.25	-0.24	-0.01	**0.38**	-0.12	0.01	-0.03	-0.04	0.06	**0.51**	-0.01	0.10	-0.14	**0.86**	**0.33**	**0.72**	**0.86**	1.00		
CpG4	0.12	0.03	0.26	-0.08	0.08	-0.05	0.15	**0.35**	-0.04	-0.08	0.12	0.14	0.18	**0.48**	-0.22	-0.18	-0.23	**0.78**	0.16	**0.61**	**0.70**	**0.66**	1.00	
CpG6	-0.11	-0.11	0.02	-0.03	0.03	-0.10	0.00	0.26	0.05	-0.06	0.13	-0.12	0.01	**0.40**	-0.29	-0.21	**-0.34**	**0.83**	0.17	**0.78**	**0.77**	**0.66**	**0.76**	1.00

Bolded values represent significant associations. Key: IRS: immigrant-related stress; DS: discrimination stress; FES: Family Economic Stress; EDS: Everyday Discrimination Score; SASH: Short Acculturation Scale for Hispanics; SSS: Subjective Social Status; SSC: social support/social connection; LOT-R: Life Orientation Test – Revised; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Supplemental Results

Children Baseline:

In testing correlations between all children's variables and methylation sites at baseline, no significant correlations were found with *FKBP5* in children. However, total child stress, immigrant related stress, and fear of parent deportation correlated positively with several sites in *SLC6A4* (Table 3.6).

Mothers Baseline: In mothers at baseline, negative correlations were also found between SASH and average methylation at *FKBP5* and position 1. Also, total mother stress, immigrant related stress, discrimination, and health stress all correlated positively with various positions of *SLC6A4*. Maternal SSS also correlated negatively with several positions of *SLC6A4* (Table 3.7).

Children Follow-up:

At follow-up time point in children, immigrant related stress and everyday discrimination were negatively correlated with average *FKBP5* and at least one methylation site. Discrimination stress was positively correlated with position 1 at *FKBP5*. School stress associated positively with position 4 of *SLC6A4* and optimism correlated negatively with positions 1 and 5 of *SLC6A4* (Table 3.8).

Mothers Follow-up:

In mothers at follow-up, no variables associated with *FKBP5*. Total maternal stress and household stress negatively correlated with position 4 of *SLC6A4*. SASH was positively correlated with several positions of *SLC6A4* (Table 3.9).

Supplemental Table S3.5: Fully adjusted models of psychosocial stressors and resilience factors and methylation levels at *FKBP5* of children and mothers at both time points.

	FKBP5		
	CpG1	**CpG2**	**Average**
Baseline			
Child variables			
Stress factors:			
Total stress score	-1.03 (1.709)	1.707 (1.175)	0.337 (1.236)
School stress	0.260 (1.419)	0.833 (0.982)	0.546 (1.022)
Immigrant-related stress	-0.034 (1.151)	1.200 (0.787)	0.583 (0.827)
Fear of parent's deportation	-0.043 (0.573)	*0.726 (0.388)*	0.341 (0.411)
Discrimination stress	-1.786 (1.099)	0.991 (0.771)	-0.398 (0.807)
Resilience factors:			
Parental social support	-1.237 (1.036)	-0.155 (0.729)	-0.696 (0.75)
Maternal variables			
Stress factors:			
Total stress score	-0.841 (1.485)	-1.040 (1.141)	-0.940 (1.456)
IRS	-0.986 (1.111)	-0.920 (0.844)	-0.953 (0.928)
Household stress	0.497 (1.193)	0.334 (0.910)	0.415 (0.999)
Family health stress	-0.063 (0.997)	-0.505 (0.757)	-0.284 (0.834)
Family economic stress	-1.449 (0.510)	-1.072 (0.791)	-1.260 (0.867)
Discrimination stress	0.043 (1.039)	-0.682 (0.798)	-0.320 (0.877)
Resilience factors:			
SSS	0.040 (0.137)	-0.048 (0.104)	-0.004 (0.115)
Social support/social connection	-0.189 (0.427)	0.080 (0.326)	-0.054 (0.358)
Optimism	-0.117 (0.083)	0.014 (0.066)	-0.051 (0.071)
Demographic/Immigrant-related Factors			
SASH	*-1.014 (0.535)*	-0.503 (0.414)	*-0.759 (0.451)*
Follow-Up			
Child variables			
Stress factors:			
Total stress score	-0.594 (3.975)	-0.829 (2.946)	-0.712 (3.226)
School stress	1.708 (2.103)	-0.142 (1.588)	0.783 (1.712)
IRS	-1.055 (1.646)	-1.273 (1.211)	-1.164 (1.317)
Fear of parent's deportation	-0.413 (0.853)	0.457 (0.633)	0.022 (0.691)
Everyday Discrimination	-0.697 (0.674)	**-1.005 (0.418)**	-0.851 (0.505)
Discrimination stress	2.694 (2.262)	1.529 (1.707)	2.112 (1.826)
Resilience factors:			
Parental social support	2.258 (1.529)	0.818 (1.178)	1.538 (1.248)
Optimism	-0.105 (0.078)	-0.028 (0.060)	-0.067 (0.064)

Supplemental Table S3.5. Fully adjusted models of psychosocial stressors and resilience factors and methylation levels at *FKBP5* of children and mothers at both time points, continued.

	FKBP5		
	CpG1	**CpG2**	**Average**
Maternal variables			
Stress factors:			
Total stress score	-2.508 (4.056)	-0.172 (3.302)	-1.340 (3.379)
IRS	-1.019 (2.706)	1.862 (2.258)	0.421 (2.316)
Household stress	-0.315 (1.999)	-0.046 (1.686)	-0.180 (1.708)
Family health stress	-1.121 (1.979)	0.671 (1.652)	-0.225 (1.689)
Family economic stress	1.839 (2.443)	-0.252 (2.533)	0.794 (2.333)
Everyday Discrimination	0.786 (0.697)	-0.313 (0.592)	0.237 (0.602)
Discrimination stress	0.037 (1.677)	-0.485 (1.394)	-0.224 (1.417)
Resilience factors:			
SSS	-0.149 (0.330)	0.013 (0.280)	-0.068 (0.283)
Social support/social connection	-0.555 (0.811)	0.204 (0.689)	-0.175 (0.698)
Optimism	0.096 (0.180)	-0.048 (0.152)	0.024 (0.154)
Demographics/Immigrant-Related			
SASH	0.639 (0.650)	0.063 (0.558)	0.351 (0.561)

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal association.

Supplemental Table S3.6. Fully adjusted models of psychosocial stressors and resilience factors and methylation levels at *SLC6A4* of children and mothers at both time points.

	SLC6A4						
	CpG1	**CpG2**	**CpG3**	**CpG4**	**CpG5**	**CpG6**	**Average**
Baseline							
Child variables							
Stress factors:							
Total stress score	-0.167 (1.066)	0.214 (0.544)	0.501 (0.549)	0.820 (0.614)	1.084 (0.729)	*1.263 (0.653)*	0.619 (0.482)
School stress	-0.496 (0.854)	-0.090 (0.434)	0.302 (0.451)	0.727 (0.489)	0.799 (0.584)	0.676 (0.529)	0.320 (0.387)
Immigrant-related stress	-0.379 (0.698)	0.269 (0.357)	*0.678 (0.357)*	0.452 (0.400)	*0.926 (0.466)*	*0.823 (0.423)*	0.462 (0.311)
Fear of parent's deportation	-0.361 (0.345)	0.062 (0.178)	0.246 (0.180)	0.303 (0.198)	**0.576 (0.228)**	*0.357 (0.212)*	0.197 (0.156)
Discrimination stress	0.042 (0.834)	-0.070 (0.428)	-0.127 (0.439)	-0.256 (0.481)	-0.121 (0.574)	0.666 (0.513)	0.022 (0.378)
Resilience factors:							
Parental social support	0.088 (0.639)	-0.186 (0.327)	-0.067 (0.336)	0.074 (0.369)	-0.523 (0.434)	-0.192 (0.398)	-0.134 (0.289)
Maternal variables							
Stress factors:							
Total stress score	**3.077 (1.368)**	1.700 (1.256)	2.074 (1.260)	0.026 (0.954)	0.202 (0.751)	**2.036 (0.970)**	**1.519 (0.731)**
IRS	**3.334 (0.982)**	*1.821 (0.934)*	**2.136 (0.932)**	0.698 (0.707)	0.568 (0.566)	**1.485 (0.738)**	**1.674 (0.526)**
Household stress	1.310 (1.128)	1.034 (1.020)	0.206 (1.037)	0.463 (0.761)	-0.445 (0.608)	1.120 (0.800)	0.628 (0.600)
Family health stress	*1.780 (0.923)*	0.856 (0.850)	**1.911 (0.831)**	-0.308 (0.634)	0.634 (0.502)	**1.425 (0.654)**	**1.050 (0.487)**
Family economic stress	0.586 (1.011)	0.338 (0.908)	0.279 (0.928)	0.212 (0.678)	-0.591 (0.529)	0.471 (0.711)	0.216 (0.538)
Discrimination stress	1.501 (0.974)	1.247 (0.891)	1.287 (0.887)	0.144 (0.668)	-0.103 (0.538)	1.131 (0.705)	0.868 (0.521)
Resilience factors:							
SSS	**-0.335 (0.126)**	-0.163 (0.118)	**-0.236 (0.117)**	-0.135 (0.087)	-0.078 (0.070)	**-0.266 (0.089)**	**-0.202 (0.066)**
Social support/social connection	-0.099 (0.419)	0.274 (0.377)	-0.210 (0.380)	0.035 (0.280)	-0.249 (0.222)	-0.166 (0.298)	-0.069 (0.222)
Optimism	-0.115 (0.085)	-0.047 (0.077)	-0.056 (0.078)	-0.076 (0.057)	-0.023 (0.044)	-0.028 (0.062)	-0.057 (0.045)
Demographic/Immigrant-related Factors							
SASH	-0.609 (0.532)	-0.671 (0.478)	0.198 (0.488)	-0.120 (0.359)	0.409 (0.283)	0.068 (0.384)	-0.121 (0.285)

Values represent betas (sd). **Bolded** values represent significant associations. *Italicized* values represent marginal association.

Supplemental Table S3.6. Fully adjusted models of psychosocial stressors and resilience factors and methylation levels at *SLC6A4* of children and mothers at both time points, continued.

	SLC6A4						
	CpG1	**CpG2**	**CpG3**	**CpG4**	**CpG5**	**CpG6**	**Average**
Follow-Up							
Child variables							
Stress factors:							
Total stress score	1.602 (2.775)	0.895 (1.672)	0.393 (1.427)	0.942 (1.678)	0.609 (1.318)	-1.571 (1.645)	0.478 (1.291)
School stress	-1.882 (1.474)	-0.327 (1.030)	-0.097 (0.988)	1.485 (0.954)	0.822 (0.721)	1.120 (0.942)	0.187 (0.805)
IRS	0.658 (1.219)	0.201 (0.813)	0.017 (0.792)	-0.061 (0.789)	0.095 (0.594)	-0.579 (0.758)	0.055 (0.651)
Fear of parent's deportation	0.151 (0.633)	0.077 (0.420)	0.238 (0.406)	-0.253 (0.405)	-0.086 (0.306)	-0.517 (0.383)	-0.065 (0.336)
Everyday Discrimination	0.060 (0.399)	-0.098 (0.280)	-0.274 (0.250)	0.174 (0.239)	0.043 (0.191)	-0.065 (0.240)	-0.027 (0.212)
Discrimination stress	-0.944 (1.708)	-0.472 (1.136)	-0.354 (1.107)	0.933 (1.090)	0.266 (0.831)	-0.635 (1.068)	-0.201 (0.912)
Resilience factors:							
Parental social support	-1.416 (1.144)	*-1.387 (0.731)*	-0.769 (0.745)	-0.591 (0.749)	-0.170 (0.570)	-0.006 (0.737)	-0.723 (0.609)
Optimism	**-0.117 (0.055)**	*-0.065 (0.037)*	0.005 (0.038)	-0.046 (0.037)	-0.039 (0.028)	-0.018 (0.037)	-0.047 (0.030)
Maternal variables							
Stress factors:							
Total stress score	-2.804 (3.302)	-0.765 (1.494)	0.574 (1.647)	-2.969 (1.870)	2.299 (1.994)	-0.095 (2.513)	-0.627 (1.573)
IRS	1.775 (2.120)	0.562 (1.113)	-0.587 (1.172)	*-2.561 (1.259)*	-0.949 (1.551)	-1.456 (1.698)	-0.536 (1.140)
Household stress	0.172 (1.613)	0.921 (0.820)	-0.083 (0.884)	*-1.704 (0.961)*	-0.155 (1.172)	0.316 (1.291)	-0.089 (0.859)
Family health stress	-1.535 (1.537)	-0.057 (0.828)	-0.265 (0.869)	*-1.661 (0.938)*	0.484 (1.128)	0.182 (1.267)	-0.475 (0.832)
Family economic stress	-1.262 (2.431)	-0.319 (1.245)	0.131 (1.307)	-1.109 (1.547)	0.619 (1.545)	-0.310 (1.848)	-0.375 (1.289)
Everyday Discrimination	0.456 (0.586)	0.071 (0.292)	0.130 (0.328)	-0.073 (0.374)	0.403 (0.426)	-0.119 (0.473)	0.145 (0.311)
Discrimination stress	-1.066 (1.352)	-0.077 (0.676)	0.527 (0.751)	-0.170 (0.864)	*1.804 (0.932)*	0.301 (1.091)	0.220 (0.719)
Resilience factors:							
SSS	0.225 (0.261)	0.055 (0.138)	0.008 (0.145)	-0.096 (0.166)	0.084 (0.192)	0.047 (0.212)	0.054 (0.141)
Social support/social connection	0.438 (0.655)	-0.194 (0.342)	-0.364 (0.355)	-0.498 (0.406)	-0.722 (0.458)	-0.756 (0.507)	-0.349 (0.345)
Optimism	0.065 (0.146)	0.046 (0.076)	0.108 (0.077)	0.109 (0.090)	*0.173 (0.101)*	0.180 (0.112)	0.114 (0.075)
Demographics/Immigrant-Related							
SASH	0.742 (0.505)	0.383 (0.263)	*0.516 (0.269)*	**0.769 (0.295)**	*0.685 (0.357)*	0.354 (0.416)	**0.575 (0.256)**

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Chapter 4

Epigenetic age associates with psychosocial stress and resilience in children of Latinx immigrants

ABSTRACT

Aim: To investigate associations of psychosocial stressors and resilience factors with DNA methylation age in saliva of Latinx children of immigrants before and after the 2016 presidential election (2015-2018).

Materials and Methods. We compared psychosocial exposures with four distinct measures of epigenetic age assessed in saliva of children (6-13 years, n=71 pre-election; n=35 post-election). Exploratory genome-wide analyses were also conducted.

Results: We found distinct associations across some epigenetic clocks and time points: e.g., greater maternal social status pre-election and fear of parent deportation post-election both associated with decreased Hannum age (p's≤0.01).

Conclusion: Though limited in size, our unique study design provides novel hypotheses regarding how social environment may influence epigenetic aging and genome-wide methylation, potentially contributing to racial/ethnic health inequalities.

INTRODUCTION

Latinx immigrants and their children represent one of the fastest growing, yet most vulnerable groups of the US population, with high rates of chronic diseases. Mexican Americans, for example, tend to have very high rates of metabolic disorders, with almost 100% of adults projected to be obese or overweight by 2030, and the highest rates of childhood obesity compared with White or Black children (Wang et al. 2020). Evidence is also emerging that Latinx women experience more depressive symptoms than White or Black women, and this disparity may emerge early in adolescence (Hargrove et al. 2020).

One explanation for the rising disparities in health is the exposure to high burdens of psychosocial stressors in daily life which affect mothers and children, including financial stressors (Mendoza et al. 2017), fear of deportation (Barajas-Gonzalez et al. 2018; Becerra 2016), family separation, (Dreby 2015) and racism/discrimination (Cervantes et al. 2019; Molina et al. 2019). While these stressors have always existed for Latinx families, they have demonstrably increased in recent years (Barajas-Gonzalez et al. 2018). A number of executive orders and policies have threatened the stability of immigrant families (Torres et al. 2018) and there has been an upsurge in hate crimes and even fatal shootings against Latinx immigrants (FitzGerald 2019). This toxic environment has been linked with increasing rates of health problems for a whole generation of Latinx American children, including increased anxiety, sleep problems, elevated blood pressure (Eskenazi et al. 2019), and higher rates of preterm births since the last presidential election (Gemmill et al. 2019; Krieger et al. 2018). It is not yet clear which mechanisms link these stressors with disease outcomes.

Severe social stressors or adversities experienced in childhood may become embodied by leaving lasting signatures on the epigenomes of children (Silberman et al. 2016). There is growing evidence of an association of social stressors and DNA methylation at specific sites throughout the genome in both adults and children. DNA methylation has been associated with low socioeconomic status (McDade et al. 2019), racism/discrimination (de Mendoza et al. 2017; Santos et al. 2018), and exposure to prenatal depression (Cardenas et al. 2019; Non et al. 2014). The largest study of this kind focused on cumulative exposure to different facets of adversity across childhood and adolescence in British adolescents (n=1658). This large epigenome-wide association study (EWAS) found limited evidence of site-specific associations in blood at age 18 (Marzi et al. 2018). While less research has been conducted with Latinx children, we propose

that they are particularly vulnerable to stress exposures, especially in recent years. Thus, stress-induced epigenetic changes may underlie dysregulated metabolic systems, immune function, or contribute to risk for psychopathology, thereby contributing to the documented erosion of health over time and across generations evidenced by Latinx populations in the US (Fox et al. 2018).

A novel way to measure stress effects on the epigenome is through examining associations with estimates of DNA methylation age (DNAmAge), also known as an "epigenetic clock." Epigenetic clock estimates are composites of DNA methylation sites that correlate with chronological age across different tissues (Hannum et al. 2013; Horvath 2013), and associate with different biological aspects of aging (Horvath et al. 2018; McEwen et al. 2019). In adults, deviation between chronologic and estimated epigenetic age has been predictive of all-cause mortality, cancer, and cardiovascular disease, independent of chronological age or other risk factors, such as smoking or diet (Perna et al. 2016). Various psychosocial stressors have been linked with accelerated epigenetic aging in adults, including lifetime stress exposures (Zannas et al. 2015), chronic financial stress (Simons et al. 2016), and retrospective reports of childhood traumas (Wolf et al. 2018). Fewer studies have examined associations with stress or adversity on epigenetic age in children, despite the fact that accelerated epigenetic aging correlates well with chronological age in youth (Simpkin et al. 2017). Epigenetic age potentially contributes to emergence of health disparities early in development, but more longitudinal epigenomic studies are needed across diverse racial/ethnic groups who may disproportionately experience higher rates of childhood adversities.

More attention is also needed on the role of resilience factors for epigenetic age, as they can be important buffers of psychosocial stressors. For example, one study found that supportive families reduced epigenetic aging in African American adolescents exposed to high levels of

discrimination (Brody et al. 2016a). Latinx communities traditionally exhibit high levels of social support, through close family ties and social relationships (Perreira et al. 2019). Additionally, optimism can be a powerful buffer for mental and cardiovascular health outcomes among Latinx youth and adults (Hernandez et al. 2018). It is important to consider these types of positive psychosocial factors alongside stress factors in examining associations with children's epigenetic age and epigenomes.

The current study examined associations of psychosocial stressors and resilience factors with epigenetic age estimates and epigenome-wide patterns of DNA methylation in the saliva of children of Latinx immigrants at two time points spanning the 2016 US Presidential election. We used data from the study of Children of Immigrants Collaborating to Overcome Stress (CHICOS), a sample of primarily Mexican immigrant families in Nashville, TN. We examined all psychosocial factors in relation to four different measures of epigenetic age – Horvath's DNAmAge, Hannum, Pediatric-Buccal-Epigenetic (PedBE), and the Skin & Blood clocks – at each time point, as well as change in age estimates over time. We hypothesized that higher psychosocial stressors and lower resilience factors would associate with increased epigenetic age. We also posited that changes in epigenetic age over time may be moderated by these psychosocial exposures. We additionally conducted an exploratory epigenome-wide association analysis and examined stress-regulatory candidate genes at both time points. While the longitudinal aspect of our study is limited in sample size, our study is unique in straddling a period of rapid policy changes towards immigrants in the US. Thus, our project provides a glimpse into epigenetic patterns of a vulnerable population over time in a shifting and uncertain political context.

MATERIALS/METHODS

Study Population

Data analyzed here are drawn from a sample of Latinx mothers enrolled in the CHICOS study based in Nashville, TN, a quickly expanding destination for immigrants (2017). The overall goals of the longitudinal study are focused on identifying associations between Latinx immigrant stress and cardiometabolic health in mothers and children. Recruitment began shortly before the recent Presidential election between June 2015 and September 2016, and subjects were revisited a year after the inauguration, between March and September of 2018. Participants were recruited from immigrant serving community centers and subsequent snowball sampling. Eligibility criteria were: 1) women above age 18 had to self-identify as Latinx foreign-born immigrant mothers and 2) have a child between the ages of 6-13 (limiting to childhood and early adolescence). In total, 81 mothers and their children participated pre-election and 38 post-election. The Vanderbilt and UCSD Institutional Review Boards approved all protocols for the CHICOS study. Oral informed consent was obtained from all participants.

Exposures: Psychosocial stressors and resilience factors

Exposures: psychosocial stressors & resilience factors

All exposure data were collected in person with mothers in Spanish (1.5-2 hours) and children primarily in English (45 min). Surveys were a combination of validated scales and new interview questions developed following a set of 10 initial individual interviews with children, and focus groups with 32 Latinx immigrant mothers in Nashville, TN (Non et al. 2019).

Psychosocial Stressors

Measures of psychosocial stress focused on factors that impacted children directly (e.g., discrimination, bullying) or indirectly by affecting the family environment of the child (e.g.,

family economic stress). Measures reported at both time points separately by children and mothers included new indices created for this study of *immigrant-related stress, discrimination stress, child's school-related stress,* and a *total stress score* for mothers and separately for children. Measures additionally reported by only mothers included *family economic stress, family health stress,* and *household stress*. The questions included in each stress scale and Cronbach's alpha score for internal reliability are listed in Table 4.1. The previously validated *everyday discrimination* scale was also reported separately for mothers and children at the post-election time point (Williams et al. 1997). Thus, we include two different measures of discrimination at the post-election time point. All indices were calculated by taking the mean of responses for those not missing more than two questions, and higher scores indicate more stress across all measures. Outside of the scales, we also examined a few individual questions of interest, including *child fear of parent deportation,* child's and mothers' reports of the *child being bullied at school,* and mothers' report of *domestic violence in the close family*. We also included one qualitative open-ended question asked of children: "what is your biggest worry on an average day?" Responses of the child's biggest daily worry question were coded into two categories, related to family separation or not, based on the most common theme across responses.

Resilience Measures

Measures of resilience pre-election included *social support* and *optimism* reported separately by mothers and children. Maternal social support was measured with a combined index of social support and social connection scales at pre- and post-election time points, including questions from the Berkman Syme Social Network Index (Berkman and Syme 1979) in addition to questions stemming from our focus groups (Non et al. 2019). We developed child-

focused social support questions developmentally appropriate to our sample population based on support reported by children from their parents (Table 4.1). Generalized dispositional optimism was measured in the mothers using the revised version of the Life Orientation Test (LOT-R), a 10-item version of the original LOT (Carver et al. 2010). Optimism was measured in children only at the post-election time point, using the Y-LOT, the youth version of the LOT-R, which has been validated in a racially diverse set of 3rd to 6th grade children (Ey et al. 2005). Measures of *subjective social status* (SSS) were also considered a resilience factor, as higher scores indicate better social standing. SSS has been linked with self-reported health among Latinx immigrants, and has been hypothesized to capture immigrant experiences that may alter perceived self-worth (Garza et al. 2017). Maternal SSS was measured at pre- and post-election time points with the MacArthur SSS scale, which asks mothers to report where they felt they fit on a social ladder (range 1-10) in relation to others in the US (Adler et al. 2000). For children we used a modified SSS scale, which asked them to report how their family fit on a social ladder in relation to other families in the US (poorer, same, or richer for children).

Covariates

Mothers self-reported at both time points their own age, marital status, number of years lived in the US, legal status, country of birth for themselves and their children, and maternal smoking status. Children reported their own age and gender. We collected multiple measures of objective socioeconomic status (SES), and include in all analyses maternal education (years) and problems paying basic bills. Cell composition was estimated using a hierarchical Robust Partial Correlations-RPC approach (Teschendorff et al. 2017), using epithelial, fibroblast, and immune cell data sets (Reinius et al. 2012; Zheng et al. 2018). We collapsed all immune cell types into a composite immune type score, to reduce loss of degrees of freedom in adding all cell types to the

models. As fibroblast estimates were extremely low, we present our primary models adjusted for proportion of epithelial cells.

Outcome: DNA methylation

Sample Collection. At pre- and post-election time points, up to 4ml of saliva were collected from 81 participants pre-election and 38 participants post-election using Oragene saliva collectors (DNA Genotek, Ottawa, Ontario, Canada). Saliva was stored at room temperature in Oragene kits, per manufacturer recommendation until DNA extractions. DNA was isolated from 500ul of children's saliva using prepIT-L2P (Zymo Research, CA, USA) and stored at -20^{o}C until time of analysis. We excluded DNA from three samples at pre-election and two samples collected post-election due to low quality or low concentration of DNA.

Epigenomic Data

Genome-wide DNA methylation measures were generated on the children's DNA with high enough quality/concentration (n=79 pre-election and n=36 post-election) using the Illumina Infinium Methylation Epic (850k) BeadChip. In brief, 750ng of DNA were sent to Institute of Genomic Medicine, where they were bisulfite converted using EZ DNA Methylation-Gold Kit (Zymo Research, CA) and sequenced. Control samples of known methylation (0%, 50%, and 100% methylated DNA, Zymo Research, CA), plus two duplicate samples were also included for a total of 120 samples. Samples were distributed randomly across the chips, but longitudinal matched pairs were kept in the same column to control for batch effects. All but one sample passed quality control procedures; this sample was removed for having outlying global unmethylated and methylated signal intensities, which may indicate incomplete bisulfite conversion. Additionally, after removing those missing data on mothers' legal status, ability to pay basic bills, and/or years in the US, our complete case analytical sample was n=71 pre-

election and 35 post-election (33 overlapping both time points). The raw data was processed using SeSAMe, which implements background subtraction based on normal-exponential deconvolution using out-of-band probes (noob), dye-bias correction using nonlinear scaling, and low intensity-based detection calling based on out-of-band array hybridization (Triche et al. 2013; Zhou et al. 2018). Data were produced for 865,859 CpG sites. After removing 105,454 probes (12.2%) that either overlapped with SNPs, were flagged for non-specific binding, on sex chromosomes, or that failed to pass the intensity-based detection threshold for any of the 113 samples, 760,405 sites were included in the EWAS. To adjust for batch effects across chips, we applied the ComBat package in R (Johnson et al. 2006).

Epigenetic age calculations

For analysis of epigenetic age, we calculated four different DNAmAge estimates. Because saliva is a mix of epithelial and blood cells, proportions of which vary with age (Theda et al. 2018), it is not clear which is the most appropriate aging clock. First, we calculated the original pan-tissue measure of DNAmAge estimate on all samples using Horvath's epigenetic clock of 353 CpG sites, which has been validated across multiple tissue types, including saliva (Horvath 2013). We also calculated the Hannum clock, based on 71 CpG sites (Hannum et al. 2013). Both clocks were trained with a wide range of age samples (e.g., Hannum clock in blood 19-101 years, Horvath pan tissue clock, birth-101 years), and have been validated with the new EPIC array platform (McEwen et al. 2018). Third, we calculated the newer PedBE age estimate, which is based on 94 CpG sites optimized for pediatric populations (ranging from birth to 21 years) with buccal epithelial cells (McEwen et al. 2019). Fourth, we estimated the Skin & Blood clock, based on 391 CpG sites, optimized for skin, saliva and blood samples, and other related cell types, based on a training sample ranging in age from 3 days to 96 years (Horvath et al.

2018). We also calculated a rate change variable for all four clocks, as the difference in estimated DNAmAge at post- minus pre-election time points, divided by the difference in years between saliva collection time points.

Data analyses

We analyzed each of the epigenetic age estimates in relation to each psychosocial stress and resilience factor listed in Table 4.1 (each modeled separately) at pre- and post-election time points using multivariable linear regressions. The rate of change estimates was analyzed only in relation to pre-election factors. All minimally adjusted models included child's age, gender, and maternal smoking, which are known confounders in epigenetic studies (Kaur et al. 2019). In fully adjusted models, we additionally included socioeconomic and immigrant-related demographic factors as covariates, including mother's years in the US, mother's legal status, marital status, maternal education level, and problems paying basic bills. While these variables could contribute to psychosocial stress effects, we included them as potential confounders separate from the stressors, in part because we were interested in the effects of each type of stressor independent of these factors. We also examined legal status as a primary predictor in models adjusted for all the same covariates, given its role in contributing to the immigrant-related stress context. For determining significance in epigenetic age analyses, we used a Bonferroni threshold of (0.05/4 clocks) is 0.0125.

For epigenome-wide analyses, we used limma to investigate the linear association between each psychosocial stressor or resilience factor and DNA methylation at pre- and post-election time points (Ritchie et al. 2015). All models controlled for the same covariates used in epigenetic age models. Results are presented in units of beta-values. We present all results that pass a p-threshold of 6e-8 for genome-wide significance, based on a Bonferroni correction

(0.05/760,405 analyzed probes). We note that these corrections are highly conservative given that many of the CpG sites are correlated with each other, and not independent tests. Thus, for exploratory purposes we also present some results that do not pass these strict criteria in supplemental tables.

For analysis of candidate genes, we examined all CpG sites included in a pre-selected set of stress-regulatory candidate genes: *CRHBP* (n=26 sites); *CRHR1* (n=70); *CRHR2* (n=41); *FKBP5* (n=53); *IGF2* (n=151); *LEP* (n=24); *MAO-A* (n=24); *MAO-B* (n=16); *MEST* (n=90); *NR3C1* (n=89); *OXTR* (n=22); *PACAP* (n=76); *POMC* (n=27); *SLC6A3* (n=81); *SLC6A4* (n=31). Of these 821 unique CpG sites, we removed any missing data for any sample, leaving a total of 709 sites for analyses. Some of these genes, such as *CRHBP, CRHR1, FKBP5* and *NR3C1* are part of the hypothalamic pituitary adrenal (HPA) axis. Other genes included are relevant to multiple regulatory systems beyond stress, such as metabolic or cardiovascular pathways, but were selected here as they have been implicated in studies of early life adversity (Barnett Burns et al. 2018; Misra et al. 2019; Morrison et al. 2019; Nothling et al. 2019; Papadopoulou et al. 2019; Tian et al. 2019). Multivariable linear models were used to model site-specific DNA methylation as a function of each stress/resilience factor separately, adjusting for the same covariates listed for epigenetic age and EWAS. We present only results that pass a p significance threshold of 7e-5 (0.05/709 sites) for candidate gene analyses.

To assess changes in genome-wide methylation and candidate genes over time in the 33 samples with complete data at both time points, we calculated a rate of change in DNA methylation by dividing the difference in DNA methylation level at post-election from pre-election by the number of years between saliva collection points (average=1.9 years). We

regressed this rate of change in DNA methylation against all the same psychosocial stress and resilience factors at the pre-election time point, adjusting for the same set of covariates.

In sensitivity analyses for all outcome measures (epigenetic age, site by-site methylation, and candidate gene sites), we tested for associations without adjusting for potential heterogeneity in cell proportions for all models. All analyses were conducted in R (http://www.R-project.org) using packages from Bioconductor.

RESULTS

Characteristics of our analytical sample of 71 pre-election and 35 post-election CHICOS participant children are displayed in Table 4.2. At the pre-election time point, the children ranged in age from 6-13, with a mean of 8.7 years. Slightly more than half were female (56.3%), and the majority of the children were born in the US (76.1%). Most participant's mothers were born in Mexico (87.3%), were undocumented (84.5%), were married (84.5%), and were not smokers (97.8%). Mothers were generally of low SES, with an average of 9.46 years of education, and on average reported a low mean subjective social status of 4.11 out of 10. At the post-election time point, children were on average 1.9 years older than at pre-election, with a mean age of 10.5 years, and all other demographics were largely similar over time. Children that were lost to follow-up or did not provide a saliva sample at the post-election time point were more likely to have mothers with slightly higher social support at the pre-election time point (T-test, $p=0.038$). No other measured psychosocial stressors, resilience factors, or demographic characteristics at baseline differed between those that had DNAm assayed at the post-election time point and those that did not.

To view distributions across all stress measures and demographic characteristics, see Table 4.2 and Supp Figure S4.1-S4.4. Correlations between all continuous covariates and stress

measures pre-election are shown in Supp Tables S4.1 and S4.2. In brief, the majority of reports of psychosocial stressors or resilience factors were consistent over time (Table 4.2, Supp Figure S4.1-S4.4). For example, children reported low levels of total stress, discrimination stress, and school stress at both time points. Mothers reported relatively low levels of total stress at both time points. However, some measures changed over time: e.g., levels of immigrant-related stress increased in children but decreased in mothers at post-election (p's≤0.021). Maternal perceived discrimination significantly decreased post-election (p=0.037). Among resilience factors, social support increased in children but decreased in mothers (p's<0.008), and optimism decreased over time in the mothers (p<0.0001).

Epigenetic age analyses

Epigenetic age estimates were all strongly correlated with chronological age (Table 3.0), with the Skin & Blood clock showing the highest correlation (r=0.875), and Hannum showing the lowest (r=0.513). All clocks were also significantly correlated with each other, though none higher than r=0.559 (Table 4.3). Horvath's DNAmAge score was most highly correlated with the Skin & Blood clock (r=0.803) and least with the Hannum clock (r=0.423). We report distinct patterns of associations between exposure variables and each of the different epigenetic age estimates, adjusting for child's chronological age, as well as gender, maternal smoking, mothers' years in the US, maternal legal status, marital status, maternal education level, problems paying basic bills, and immune cell proportions (Figure 4.1, Table 4.4). Specifically, <u>at pre-election</u>, none of the child-reported variables associated with any of the epigenetic clocks. However, increased levels of maternal discrimination associated with decreased epigenetic age in the PedBE clock (β=-0.716 years, 95%CI: -1.387, -0.045), and increased levels of family health stress associated with increased epigenetic age in the Skin and Blood Clock (β=1.038 95%CI:

0.146, 1.930 years). Increased maternal subjective social status associated with decreased epigenetic age in the Hannum clock (β=-0.438 years, 95%CI: -0.723, -0.152). After Bonferroni adjustment, only the association between higher maternal subjective social status and decreased Hannum DNAmAge estimate remained significant.

At the post-election time point, greater child's fear of parent deportation was significantly associated with decreased age based on the Hannum clock (β=-1.882 years, 95%CI: -3.220, -0.544). Among the maternal variables, increased levels of discrimination and total stress both associated with decreased epigenetic age in the Skin and Blood Clock (β=-1.668 years, 95%CI: -3.111, -0.225; β=-4.468 years, 95% CI: -8.208, -0.728, respectively). In contrast to the observed pre-election association, increased maternal subjective social status was associated with *increased* epigenetic age in the Hannum clock (β=0.755 years, 95%CI: 0.126, 1.383; Figure 4.1A). We note sample size in these analyses was much smaller than at pre-election, and the only post-election association that passed Bonferroni adjustment was that between child's fear of parent deportation and decreased Hannum epigenetic age.

In assessing rate of change in each epigenetic clock per chronological year, maternal report of stress factors showed more associations than child's reports (Figure 4.1, Table 4.4). Specifically, maternal report of discrimination stress, immigrant-related stress, family health stress, and total stress were all associated with a decreased Hannum DNAmAge per year (all βs between –5.942 and -0.148 age/year), and decreasing Skin & Blood DNAm age per year with maternal report of child school stress (β=-1.268 age/year, 95%CI: -2.332, -0.204). The only child-reported stressor associated with rate of change in epigenetic age was child's fear of parent deportation, where greater frequency of fears was associated with a decreasing PedBE DNAm age per year (β=-0.148 age/year, 95%CI: -0.269, -0.027). Among resilience factors, increased

maternal social support/connection was associated with an increase in the DNAmAge per year (β =0.985 age/year, 95%CI: 0.0642, 1.907). Only the associations between Hannum epigenetic age with mothers' total stress, family health stress, and discrimination passed Bonferroni adjustment.

EWAS and candidate gene analyses

In exploratory analyses, we also analyzed all psychosocial stress and resilience factors in a site-by-site epigenome-wide association analysis. We detected two associations at the pre-election time point with genome-wide significance following Bonferroni threshold p<6e-8 (Supp Figure 2.0A, Supp Table 2.0). Increased levels of maternal report of their child's school stress associated with decreased methylation at one site in the intron of *TNK2* (cg20697427: β=-0.069 beta-value, 95%CI: -0.090, -0.048). Undocumented maternal legal status was also significantly associated with increased methylation at one site in a CpG island within an exon of *ZNF205* (cg01093395: β = 0.025 beta-value, 95%CI: 0.017, 0.032). At post-election, undocumented maternal legal status was associated with increased levels of methylation at two CpG sites post-election (Supp Figure S4.5A, Supp Table 2.0), both in the body of *HLA-DPB1* gene after adjusting for cell types (cg02692313: β=0.334 beta-value, 95%CI: 0.255, 0.414; cg25511667: β=0.271 beta-value, 95%CI; 0.205, 0.337). In assessing rate of methylation change over time across the genome, no site-specific associations met the genome-wide threshold of 6e-8. For exploratory purposes, all results are reported in Supp Table S4.4 and Supp Figure S4.5.

In a second set of exploratory analyses, we examined candidate genes in relation to all stress and resilience factors across time points (Supp Tables S4.5, S4.6, and Supp Figures S4.6). In brief, we found limited evidence for associations across time points. Of the 709 sites in 14 genes interrogated, only 3 sites within 3 genes showed significant associations (at a p-value threshold of 7e-5) with any of our exposures across time points. Specifically, the only pre-

election associations that passed Bonferroni adjustment included child's report of social support from parents with one site in the open sea of *LEP*, and maternal report of their child's school stress with one site in the CpG island shelf of *IGF2*. When analyzing rate of change over time, after Bonferroni adjustment, increased maternal immigrant-related stress significantly associated with a decrease in methylation per year at one site in the *CRHR2* gene. Additionally, we found increased maternal report of their child's school stress was associated with an increase in methylation per year at one site in *NR3C1*. All associations are shown in Supp Table S4.6 for exploratory purposes.

In comparing broad patterns across all analyses, we found no overlap in significant associations detected between maternal and child reports of similar stress domains (Figure 4.1; Supp Figures S4.5 and S4.6). For epigenetic clocks and genome-wide results, more associations were generally found with maternal-reported variables than child-reported variables. In comparing associations across time points, none of the same exposures showed significant associations both pre- and post-election with epigenetic clocks or CpG sites, with the exception of legal status in the epigenome-wide analysis.

For all sensitivity analyses that did not adjust for cell type proportions, we report findings in the supplemental materials (Supp Tables 4.7-4.10). In brief, while strength of associations changed, the direction of associations among the significant findings were the same. For example, stronger and more significant associations were seen pre-election linking increased epigenetic age with stressors in the Hannum clock analyses that did not adjust for the proportion of epithelial cells (e.g., with child's immigrant related stress and fear of parent deportation). For both EWAS and candidate gene analyses at pre-election, models unadjusted for cell type

revealed the same top hits as adjusted models. Fewer associations were identified in the change over time analyses in models unadjusted for cell type.

DISCUSSION

This study offers, to our knowledge, the first analysis of epigenetic age and genome-wide DNA methylation patterns in Latinx children in relation to their social environments. In this exploratory study, we examined associations of psychosocial stressors and resilience factors with multiple measures of DNA methylation age in saliva of Latinx children of immigrants before and after the 2016 presidential election (2015-2018, n's=71 and 35). While we did not find very high overall levels of stress reported at either time point, there was sufficient variation across exposures reflecting differing experiences among families. After Bonferroni adjustment, we found one significant association with maternal subjective status and decreased Hannum DNAmAge pre-election, while at post-election, we found increased stress generally associated with decreased epigenetic age, and higher resilience was associated with increased epigenetic age across many clock measures. In exploratory epigenome-wide analyses, we found some evidence for associations with genome-wide significance at both time points, and in relation to change over time, in some genes potentially relevant to immune and other functions. Below we describe the directions of association, the potential functional relevance of findings, and how our results relate to similar studies, focusing only on the most significant findings.

Epigenetic age

Various clocks have recently been optimized for calculating epigenetic age within specialized populations, such as the Pediatric-Buccal-Epigenetic (PedBE) clock for child buccal samples (McEwen et al. 2018), or the Skin & Blood clock, developed for skin, saliva, and blood samples across age groups (Horvath et al. 2018). Along with the original Hannum and Horvath

clocks, it remains an open question as to which of these clocks are most appropriate for study of accelerated aging in children across tissues, and in relation to which exposures. For example, one of the only longitudinal studies of epigenetic aging in blood samples from British children found abuse, financial hardship, and neighborhood disadvantage associated with the Hannum but not the Horvath clock measured at age 7.5 years (Marini et al. 2019). However, other studies have found significant associations using the Horvath clock, such as accelerated aging with stressors, such as lifetime exposure to violence, as found in a salivary sample from African American children, aged 6-13 (Jovanovic et al. 2017). One of the only multi-racial studies of epigenetic aging in children found early life exposure to violence (but not neglect or food insecurity) to be associated with an accelerated Horvath's clock estimate in saliva from children aged 8-16, though no racial differences were detected (Sumner et al. 2019). We tested multiple epigenetic clocks because it is unclear which clock is best for children's saliva, particularly as saliva has a variable mix of blood and epithelial cells (microscopy estimates for 6-7 year old children's saliva estimate 70% epithelial cells, but with high between-subject variation (Theda et al. 2018)).

In comparing our results across clocks, we note that the Hannum estimate of DNAmAge is the least strongly associated with chronological age in our sample and was associated strongly with the most measures of stress and resilience across time points. This result implies that Hannum DNAmAge estimates may be more sensitive to stress and resilience than the other clock measures in the saliva of children. Notably, two recent studies also found the Hannum's DNAmAge estimates to show more significant associations with child adversity measures than Horvath's DNAmAge estimates (Marini et al. 2019; Wolf et al. 2017). The differences across clock results may be due to different tissues and ages of subjects used to develop these clocks, and largely different sets of CpG sites used in the clocks. In fact, it is possible that these clocks

are relevant to different aspects of biological aging, as they have been shown to related to different disease-related phenotypes (Lu et al. 2018).

In our study, the association between mothers' subjective social status and estimated Hannum DNAm age was inconsistent across time. These results should be taken with caution, given the risk of false positives with the smaller post-election sample size. The differences across time points could also be a product of distinct age distributions pre- and post-election. Despite the small size of our longitudinal analyses, the strongest associations we detected were in analyses of the rate of change in epigenetic age over time, where decreased rate of change associated with many stressors, primarily for the Hannum clock. While these results must be replicated in larger studies, the overall trends may indicate age-dependent associations between social exposures and epigenetic clocks, and a reduced rate of change in epigenetic age for children exposed to higher levels of stress.

Prior studies are inconsistent in direction of associations reported with epigenetic clocks, and in how they interpret the meaning of epigenetic age in children. Many studies find accelerated aging in blood and saliva of children associated with higher levels of stressors, such as discrimination, exposure to violence, or childhood trauma (Brody et al. 2016b; Jovanovic et al. 2017; Marini et al. 2019; Wolf et al. 2018). An additional longitudinal study showed associations between greater economic hardship (e.g., pre- and post-2008 recession) and epigenetic age acceleration in blood of African American adolescents at age 19 (Chen et al. 2016). A study of epigenetic aging in Latinx adults has shown inconsistent directions of associations relative to white populations in blood, depending on cell type adjustment (Horvath et al. 2016). The few studies to examine epigenetic aging over time in children have shown inconsistent associations across time points. For example, faster epigenetic aging with prenatal

smoking exposure was found over time, though slower epigenetic aging with prenatal alcohol exposure at birth (but not later in childhood), and slower aging with prenatal selenium exposure both at birth and age 7 (Simpkin et al. 2016). Simpkin et al. suggest accelerated epigenetic aging as an index of child development after finding associations with accelerated growth and development in childhood and adolescence (e.g., changes in weight, BMI, pubertal stage) (Simpkin et al. 2016; Suarez et al. 2018). However, the same study also found negative associations with changes in height and fat mass, and no association with age of puberty onset, so it is yet unclear if accelerated aging universally implies faster child development. The health relevance of accelerated aging in childhood is still unclear, though studies suggest epigenetic age acceleration in early adolescence is associated with pubertal stage and other physiological and even psychiatric aging-related outcomes (Suarez et al. 2018; Sumner et al. 2019). Future studies are needed to fully determine if faster aging in childhood is beneficial or harmful to children's health, and if epigenetic age scores mediate associations between stress exposures and higher morbidity or mortality in Latinx populations.

The biological pathways underlying these associations are complex and difficult to determine, given the number of interrelated environmental, hormonal, and genetic forces simultaneously acting on children. Increased epigenetic age may be related to disrupted HPA axis functioning, as evidenced by associations between accelerated aging and higher cortisol awakening response (Suarez et al. 2018), though a causal relationship has yet to be determined. Similarly, epigenetic aging may relate to disrupted immune system functioning, as immune cells such as CD4 T and natural killer cells (found in blood *and* saliva) may play a role in pacing the epigenetic clock (Wolf et al. 2018). Further functional study of the sites involved in the DNAmAge estimates will be important to understand these pathways.

Pre- and post-election EWAS and candidate gene analyses

Maternal legal status was the most consistent exposure associated with methylation across time points, and with the largest effect sizes genome-wide. At the pre-election time point, we found undocumented mothers had higher levels of methylation at a site in *ZNF205*, a gene related to transcriptional regulation (Stelzer G 2016), as well as relevant to Herpes viral infection (Belinky F 2015). At post-election, undocumented mothers also had much higher levels of methylation at two sites in the *HLA-DBP1* gene, which encodes a major histocompatibility complex protein, and thus plays a role in immune function. Because these loci differed across time points, and the sample size post-election was much smaller, these results should be interpreted with caution. However, if replicated, these methylation differences may be relevant to immune function within the blood cells in saliva. Maternal (but not child's) report of child's school stress was the only other measured exposure that showed an association of genome-wide significance at pre-election, specifically at a CpG site in an N-shelf within the body of the *TNK2* gene. This gene encodes the tyrosine kinase non-receptor 2, a protein important for cell growth and proliferation, and related to protein kinase activity (Stelzer G 2016). Like the *ZNF205* gene, *TNK2* plays a fundamental role in cellular mechanisms, but has unclear health implications.

We were surprised to find that legal status was the only factor among all analyzed exposures that associated with sites across time points. Given that most families were of mixed status, where US citizen children had mothers with undocumented status, we had predicted that many children would also face discrimination and other immigrant-related stressors, regardless of their mothers' legal status. It may be that children were not able or willing to fully articulate their experiences of discrimination, or fears of parent deportation, but these stressors were detectable through the measure of their maternal legal status. Legal status may also serve as a

proxy for other negative economic and social consequences for children. We were also surprised that maternal but not child's report of school stress was the relevant exposure measure. It is possible children were more reluctant than their mothers to admit to adverse experiences at school, or potentially the questions we asked of mothers captured aspects of school stress that were more relevant than those asked of children.

The difficulty detecting associations with methylation change over time was not unexpected because many of the psychosocial stressors showed similar reported levels before and after the 2016 presidential election. The only significant change over time in exposures was a small increase for children (but small decrease for mothers) in immigrant-related stress. We were in fact surprised to see relatively low reported levels of maternal and child total stress both before and after the election. We suspect this may in part be due to reticence or stoicism, which has been documented both in Latinx women and boys (Bauer et al. 2000; Santos et al. 2013) or potentially even an act of defiance to deny levels of stress. The reductions we report in immigrant-related stress and total stress over time may in part be explained by attrition of the most vulnerable participants in the study, though frequency of undocumented mothers did not decrease post-election. Regardless of the low reported stress levels, we acknowledge that objective burdens on the Latinx community have been high for decades, and the Latinx families are not facing a unique historical moment of anti-immigrant policies and sentiments in the US (Rosa and Bonilla 2017). High levels of racism have been reported by many of these same mothers since 2014 (Non et al. 2014). When qualitatively discussing conditions for immigrants in Nashville, many mothers reported exacerbated levels of racism and discrimination. One mother in our study said, "Sometimes they belittle us. They've blamed us of being responsible for the decline of the United States of America." Future qualitative studies will be needed to

determine whether women and children are potentially reluctant to report stressors, or if conditions have truly not changed over time.

We note that among the few significant genome-wide associations we identified at the pre-election time point where we had the largest sample size, the magnitude of significant effect sizes was minimal (ranging from -0.069 to 0.025 beta-value). However, these magnitudes are on par with the small effect sizes for prenatal maternal smoking and SES found in other studies (Joubert et al. 2012; Laubach et al. 2019). The functional relevance of small effect sizes is yet to be determined, but if they are replicable across settings, they may prove to be important for contributing to disease risk in children (Breton et al. 2017). We also note that our lack of consistent findings across the exposures is similar to another recent study that also failed to find consistent associations with early life stressors, in a much larger dataset (Marzi et al. 2018). While it is possible our results are false negatives, even strongly powered studies have been unable to detect convincing findings, potentially indicating that peripheral tissues like blood and saliva may not be ideal for investigation of social environmental exposures (Marzi et al. 2018). Alternatively, epigenetic associations with these exposures may be too small and nuanced; careful attention to appropriate and comprehensive measurement of the social environment will be required to detect subtle interaction effects, which usually cannot be achieved with larger sample sizes. Despite these limitations, we detected some interesting trends, and we believe this exploratory study generated hypotheses that justify further study.

Lack of many significant findings among all the hundreds of sites tested in the candidate genes may be a result of small sample size, but also ascertainment bias and limited coverage of the Epic BeadChip. Though it is the largest microarray available, it only assays ~3% of the 28 million CpG sites in the genome, and was originally designed to target cancer-related regions

(Bibikova et al. 2011). Thus, many candidate sites identified in prior studies within these genes were not covered on the array. Additionally, this array was not optimized for diverse populations, and thus may miss population-specific methylation variants.

In comparing our overall findings to the few other epigenetic studies of perceived racial/ethnic discrimination (de Mendoza et al. 2017; Santos et al. 2018), no previously identified sites in adult blood in our study were associated with our measures of maternal or child discrimination. The study by Santos et al. used a pyrosequencing candidate gene approach and identified everyday discrimination to associate with sites in *NR3C1*, *BDNF*, and *FKBP5* in blood of mothers during pregnancy and 4-6 weeks postpartum (Santos et al. 2018). The lack of associations at the same sites in our candidate gene analyses could be a product of difference in tissue type, life stage, or potentially because they targeted sites that are not included on the microarray, with the exception of a single site at chr5:1427836 (hg19) in *NR3C1*. The study by de Mendoza et al. used the same microarray to analyze epigenomic marks in blood with two discrimination measures in 147 African American adult women (de Mendoza et al. 2017). They observed significant associations with the major life discrimination but not the race-related events scale, at nine CpG sites, none of which were associated with discrimination or any other psychosocial stressor in our study. Taken together, these findings may imply that different measures of discrimination vary significantly in how they associate with epigenomic patterns. Alternatively, discrepancies across studies could be a result of different tissue types, race/ethnicities, age/life stage, cohort effects, or potentially false positive results.

We believe our models adjusted for proportions of cell types are more informative than unadjusted models because they reveal intrinsic methylation differences irrespective of cell type proportions. However, the unadjusted models may also be important for consideration, as they

reveal associations reflective of differences in cell proportions in children's saliva. Children with greater proportions of blood versus epithelial cells may be suffering from higher rates of gum disease or other aspects of poor oral health. Poor oral health is often a symptom of poor overall health, and by contributing to systemic inflammation, it has been shown as a risk factor for chronic diseases such as diabetes, cardiovascular disease, preterm birth, cancer, and increased mortality (Dörfer et al. 2017). Thus, any methylation differences in unadjusted models may be driven by differences in oral health and therefore may still be relevant to disease processes.

Strengths and limitations

Our study contains a number of unique strengths. First, we believe our study offers the first analyses of psychosocial stress in relation to epigenomes of Latinx children. Our analysis of change over time before and after the 2016 presidential election also represents the first natural experiment of epigenomic associations influenced by a national election, which led to dramatic increases in threats to Latinx immigrant families. Second, our longitudinal design allowed for prospective collection of a comprehensive set of psychosocial stressors in childhood at pre-election, without much risk of recall bias (beyond a month, or a year for some questions), and to assess the persistence of these stressors and epigenetic marks into early adolescence. Third, despite a small sample size, our study was unique in the depth of data we collected on each participant, including rich and comprehensive psychosocial measures on social and cultural experiences, obtained through extensive 2–3-hour interviews with mothers and nearly hour-long interviews with children. This allowed us to measure psychosocial stressors across multiple domains of the household, work, and school environments, and to create a comprehensive total stress score for both mothers and children. Fourth, we controlled for potential confounders such as maternal smoking, multiple measures of SES, mothers' years in the US, and documentation

status. Fifth, we designed our questions following prior focus groups with a subset of the same population, which allowed us to tailor our study to the specific cultural group and current local conditions. Sixth, we uniquely included perspectives of mothers and children, and in fact found that mother and child reports differed on many measures (e.g., bullying and school stress). While we included more questions asked of mothers than children, we believe maternal stressors can be relevant to child's health (O'Connor et al. 2017), potentially even more so than child's perspective when children are very young. This is partly because maternal stress can influence parenting behavior, family economic circumstances, and children may overhear (or have direct discussion with mothers) about these stressors. In fact, we found that maternal stressors associated with children's epigenetic age while none of the child-reported factors did. Seventh, our study included resilience factors in mothers and children, which are often neglected in studies of stress. While our sample size was not sufficient to assess how these resilience factors may buffer stress effects, we were able to generate hypotheses about how they may relate to epigenomic patterns. Finally, our study was strengthened by the comprehensive analysis approach, where we assessed multiple epigenetic age scores, epigenome wide patterns, and candidate genes, in addition to changes in all of these measures over time.

We recognize that our study has some limitations. First, the small sample size was the major limitation, particularly for the epigenome wide analyses. A recent study has presented a power analysis suggesting sample sizes of 1000 are necessary to detect small effects at most sites using the EPIC array (Mansell et al. 2019), which is unlikely to be achieved in most studies. Like many studies of vulnerable populations, our sample size was unavoidably limited by inherent difficulties in recruiting a largely undocumented immigrant population (Hacker et al. 2015), and the difficulties in re-contacting participants who were reluctant to be found post-election. Despite

this limitation, we were able to identify some suggestive trends to pursue in future studies. Second, our use of salivary DNA raises concerns about cellular heterogeneity that can be difficult to account for with bioinformatic adjustment (McGregor et al. 2016), though we saw similar results in our sensitivity analyses for many models. Fortunately, cellular heterogeneity should not greatly affect epigenetic age analyses, as pan-tissue DNAmAge score has been validated across tissue types (Horvath 2013), and we investigated clocks that have been optimized for saliva and buccal cells. Further, even for genome-wide results that were not significantly independent of cellular heterogeneity, methylation changes due to variation in cell type proportions could be causally relevant to disease risk (Holbrook et al. 2017). Third, our study participants largely were low SES undocumented immigrant mothers, and thus our sample may have insufficient variation on some psychosocial stress and socioeconomic factors, though wide variation was seen in reports of immigrant-related stress levels and discrimination stress, as well as all maternal resilience factors. Fourth, our participants came only from Nashville, TN, and thus findings are not widely generalizable. However, this study site represents an important site for immigration studies, particularly because interior US cities have been newly targeted by the anti-immigrant policies of the current administration (Holbrook et al. 2017; Farzan 2019). Fifth, we did not interview fathers in our study, whose perspectives are also relevant in shaping the social environments of the children. However, we surmise that their socioeconomic contribution is captured, to some extent, by the mothers' reports of family SES factors, and their role in shaping the household environment was partly accounted for through mothers' reports of partner documentation status, domestic violence, partner drug use, and partner's mental health, included in our household stress scale. We also speculate that elementary aged children largely spend more time with mothers, particularly in Latinx households, where many mothers are

homemakers. Sixth, we do not have any data on prenatal or perinatal factors, which for some genes may have more relevance in shaping epigenomes than childhood exposures. Finally, we note that we may be underestimating the effects of stress measures given that our models adjusted for many covariates that may be on the pathway between stress and epigenetic outcomes.

CONCLUSION

We present the first longitudinal study of epigenetic age and epigenomes in relation to psychosocial stress or resilience factors in children of immigrants. Some pre-election findings supported associations with increased epigenetic age with stress and decreased with resilience. However, post-election, we found decreased epigenetic age (and decreased rate of change in epigenetic age) with some stressors and increased epigenetic age (and increased rate of change in epigenetic age) with some resilience factors. These findings possibly indicate slower child development with more stress exposures at the later time point. We also identified limited evidence for associations with stress or resilience factors genome-wide (e.g., only 4 sites associated with any exposure across both time points) or with candidate genes (e.g., only two sites associated at both time points). We found minimal changes in DNA methylation over time. If replicated across racial/ethnic groups, our findings suggest both psychosocial stress and resilience factors may be relevant contributors to racial disparities in health and aging through epigenetic mechanisms.

Future perspective

More research in larger samples is needed to validate the trends we identified. Functional studies in animal models and in vitro will be necessary to confirm if any gene-specific findings we report contribute to racial health disparities. In particular, gene editing technologies could be

used to potentially alter methylation states in cell lines and across tissue types, to validate effects of any findings on cortisol response or other cellular phenotypes (Kang et al. 2019). More longitudinal research is especially important to understand how the social environment impacts epigenetic aging across childhood, and if faster or slower aging in children predisposes them to heightened chronic disease risk. Future studies could also examine epigenetic aging across generations (in both mothers and children). Studies may also compare immigrant families to non-immigrant but underserved communities, to tease apart the burden of immigrant-relevant stressors specifically, and to learn more about processes that lead to embodiment of stress. However, in addition to focusing on epigenetic mechanisms of embodiment, it is also important not to lose sight of the structural forces that shape stressful environments and access to resilience resources for immigrant families in the first place, and to address policies to reduce inequalities in stress exposures before they impact future generations of children.

Summary points

- Children of immigrants are at risk for adverse health outcomes, exacerbated since the 2016 Presidential election, potentially through epigenetic pathways.
- Our analysis of the CHICOS study, a Nashville-based longitudinal study of immigrant mothers and children, is the first to examine psychosocial stress or resilience in relation to epigenetic age or epigenome wide patterns in Latinx children.
- At post-election and over time, we generally found increased stress and decreased resilience associated with decreased epigenetic age (and rate of change over time), suggesting stress may slow child development.
- Very few significant genome-wide or candidate gene sites were associated with stress or resilience measures.

- Future studies are necessary to validate our findings and ascertain if methylation in these CpGs regions relates to health outcomes and racial disparities in health.

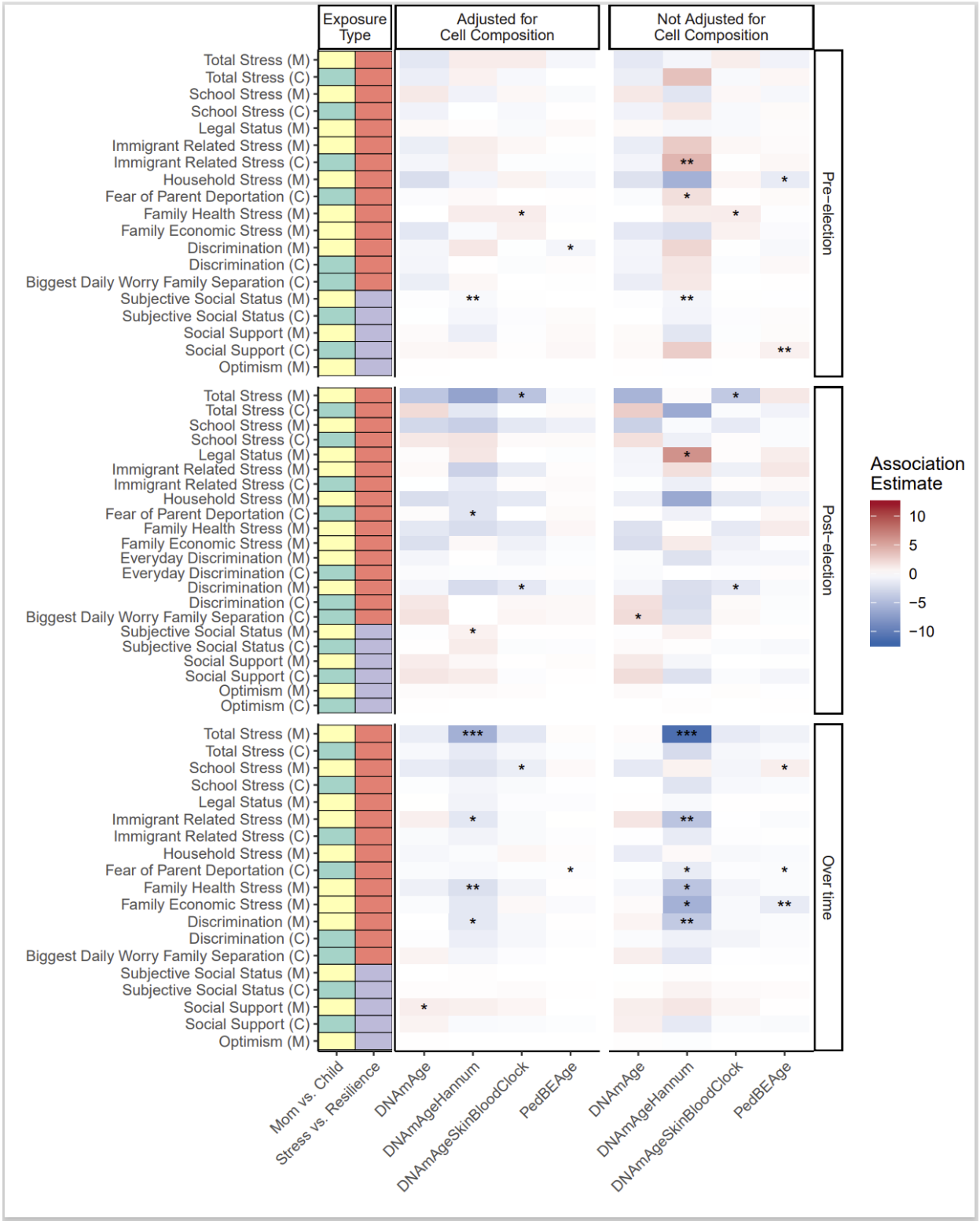
ACKNOWLEDGEMENTS

Chapter 4 examines associations of psychosocial stressors and resilience factors with epigenetic age estimates and epigenome-wide patterns of DNA methylation in the saliva of children of Latinx immigrants at two time points spanning the 2016 US Presidential election. We examined all psychosocial factors in relation to four different measures of epigenetic age – at each time point, as well as change in age estimates over time. Chapter 4 was originally published in part as an invited submission for a special issue on racial disparities in epigenetics research in the journal *Epigenomics*, and I served as first author, with Drs. Alexandra Binder and Amy L. Non as co-authors.

Citation: Clausing, E.S., Binder, A.M., and Non, A.L. Epigenetic age associates with psychosocial stress and resilience in children of Latinx immigrants. *Epigenomics*.

Figure 4.1. Results of all epigenetic clock analyses with psychosocial stress and resilience factors.

Associations of each epigenetic age estimate are shown in relation to all mother and child stress and resilience factors at pre-election, post-election, and change over time. The left side of the figure shows models adjusted for cell type composition, and the right side shows results without cell type adjustment. Yellow indicates maternal-reported variable, green indicates child-reported variable. Red under exposure type indicates psychosocial stressor, and purple under exposure type indicates resilience factor. The colors of the association estimate indicate direction of association, with blue as decreased epigenetic aging, and red as increased aging. ***$p<0.001$, **$p<0.01$, *$p<0.05$.
(M): mother reported variable; (C): child reported variables


Exposure Type
Adjusted for Cell Composition
Not Adjusted for Cell Composition
Pre−election
Post−election
Over time
Total Stress (M)
Total Stress (C)
School Stress (M)
School Stress (C)
Legal Status (M)
Immigrant Related Stress (M)
Immigrant Related Stress (C)
Household Stress (M)
Fear of Parent Deportation (C)
Family Health Stress (M)
Family Economic Stress (M)
Discrimination (M)
Discrimination (C)
Biggest Daily Worry Family Separation (C)
Subjective Social Status (M)
Subjective Social Status (C)
Social Support (M)
Social Support (C)
Optimism (M)
Everyday Discrimination (M)
Everyday Discrimination (C)
Optimism (C)
Mom vs. Child
Stress vs. Resilience
DNAmAge
DNAmAgeHannum
DNAmAgeSkinBloodClock
PedBEAge
Association Estimate
10
5
0
−5
−10

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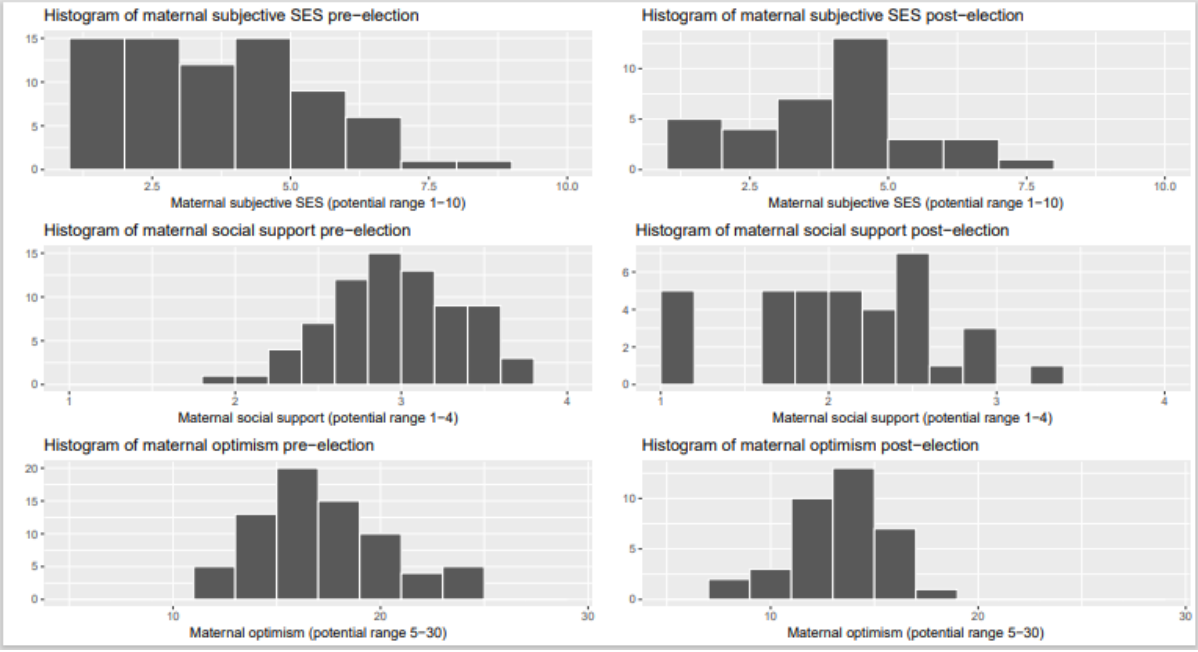
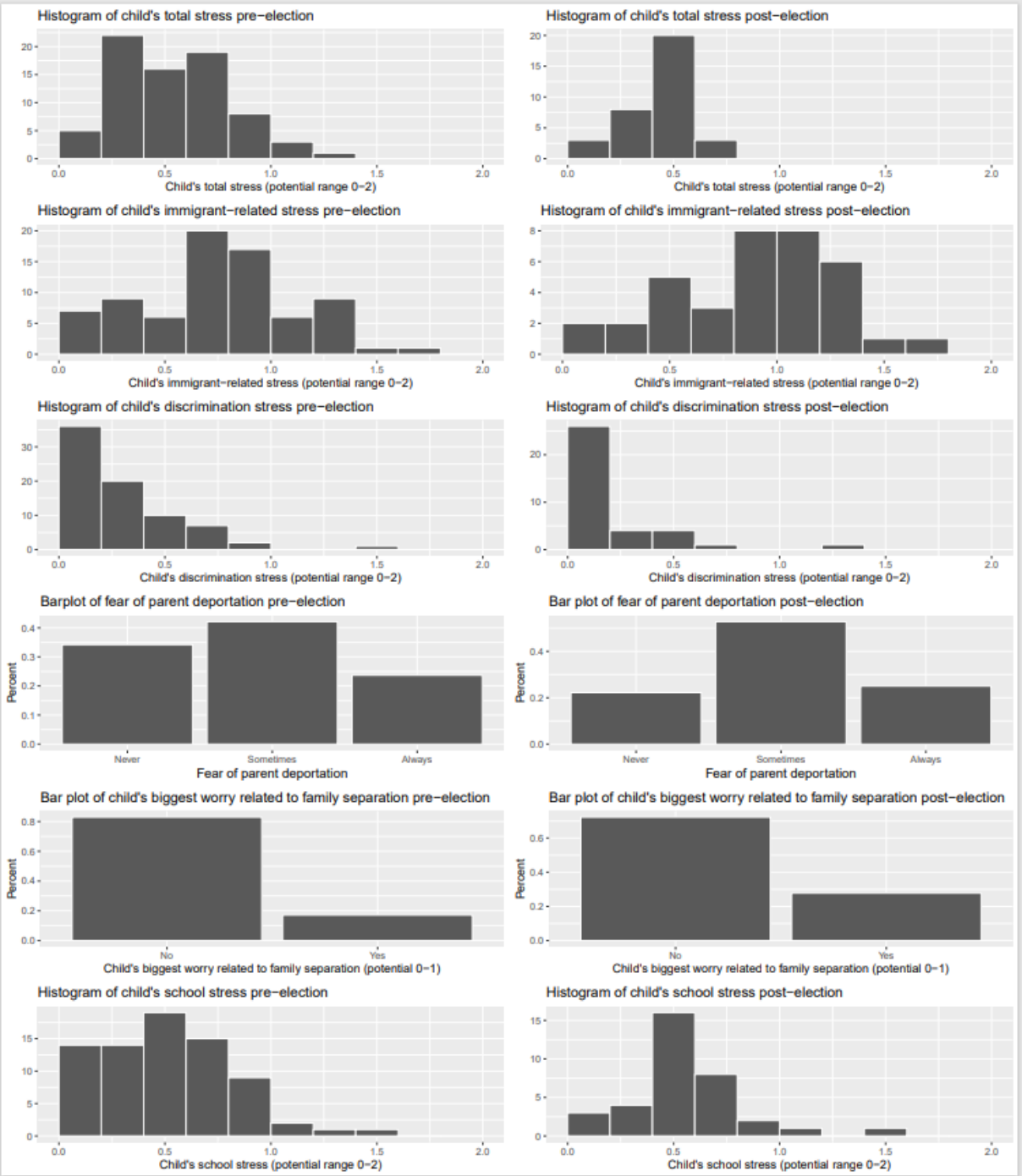
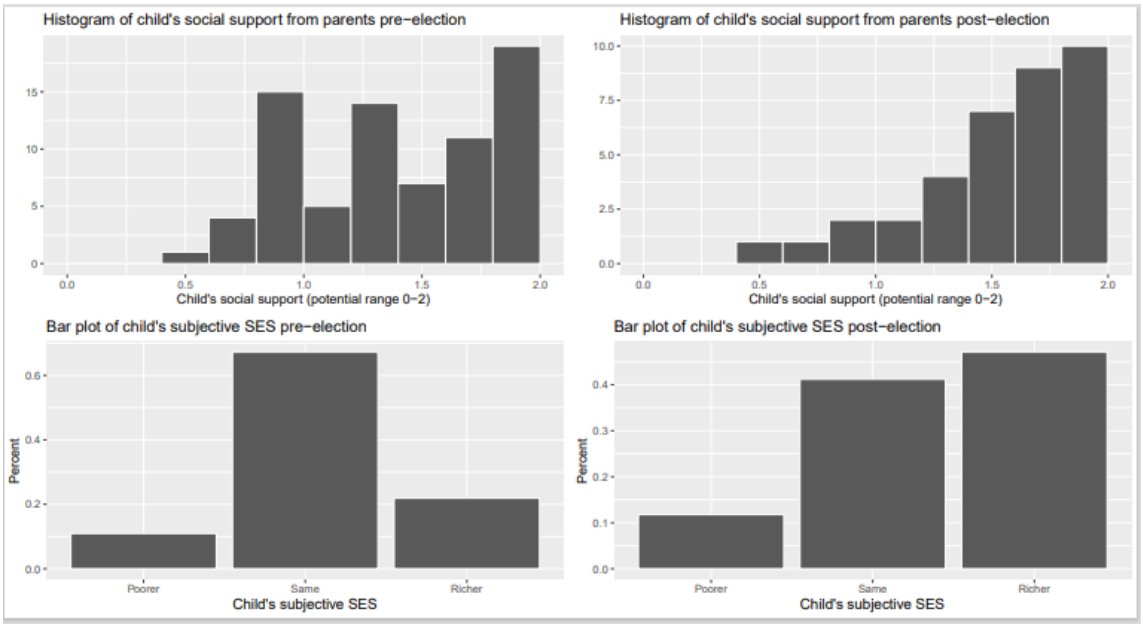
Supplemental Figure S4.1: Histograms and bar plots showing maternal psychosocial stressors. Pre-election exposures are on the left and post-election exposures are on the right.



Supplemental Figure S4.2: Histograms and bar plots showing maternal resilience factors. Pre-election exposures are on the left and post-election exposures are on the right.



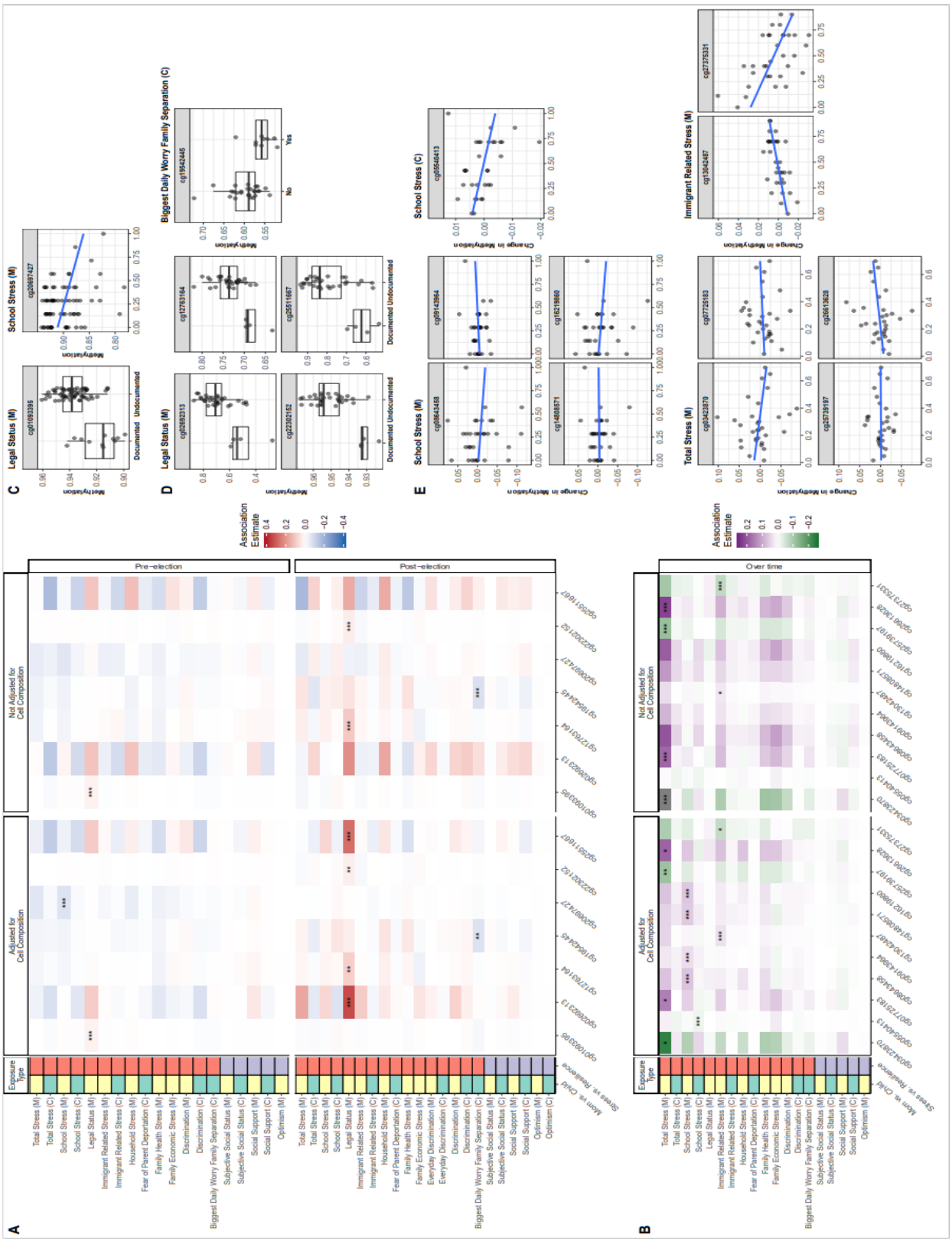
Supplemental Figure S4.3: Histograms and bar plots showing psychosocial stressors in children. Pre-election exposures are on the left and post-election exposures are on the right.



Supplemental Figure S4.4: Histograms and bar plots showing resilience factors in children. Pre-election exposures are on the left and post-election exposures are on the right.

Supplemental Figure S4.5: EWAS results of all psychosocial stress and resilience factors.

Section A displays EWAS results for pre- and post-election DNA methylation levels across all mother and child stress and resilience factors. CpG sites are shown for any associations that were significant at either time point. The left side of the figure shows models adjusted for cell type composition, and the right side shows results without cell type adjustment. Section B displays EWAS results in relation to change in methylation levels over time. ***p-value<1e-7, **p-value<1e-6, *p-value<1e-5. Top hits in the pre-election analyses are shown in C, at the post-election analyses in D, and change over time in E. Yellow indicates maternal-reported variable, green indicates child-reported variable. Red under exposure type indicates psychosocial stressor, and purple under exposure type indicates resilience factor.
EWAS: Epigenome-wide association study; (M): mother reported variable; (C): child reported variables; CpG: cytosine-phosphate-guanine site.


A
B
C
D
E
Pre−election
Post−election
Over time
Adjusted for Cell Composition
Not Adjusted for Cell Composition
Exposure Type
Association Estimate
Change in Methylation
Methylation
School Stress (M)
Legal Status (M)
Biggest Daily Worry Family Separation (C)
School Stress (C)
Total Stress (M)
Immigrant Related Stress (M)
Mom vs. Child
Spouse vs. Respondent

Supplemental Figure S4.6: Results of all analyses of candidate genes with psychosocial stress and resilience factors.

Section A displays candidate gene results for pre- and post-election DNA methylation levels across all mother and child stress and resilience factors. CpG sites are shown for any associations that were significant at either time point. The left side of the figure shows models adjusted for cell type composition, and the right side shows results without cell type adjustment. Section B displays candidate gene results in relation to change in methylation levels over time. Yellow indicates maternal-reported variable, green indicates child-reported variable. Red under exposure type indicates psychosocial stressor, and purple under exposure type indicates resilience factor. ***$p<0.0001$, **$p<0.001$, *$p<0.01$.
(M): mother reported variable; (C): child reported variables; CpG: cytosine-phosphate-guanine site.

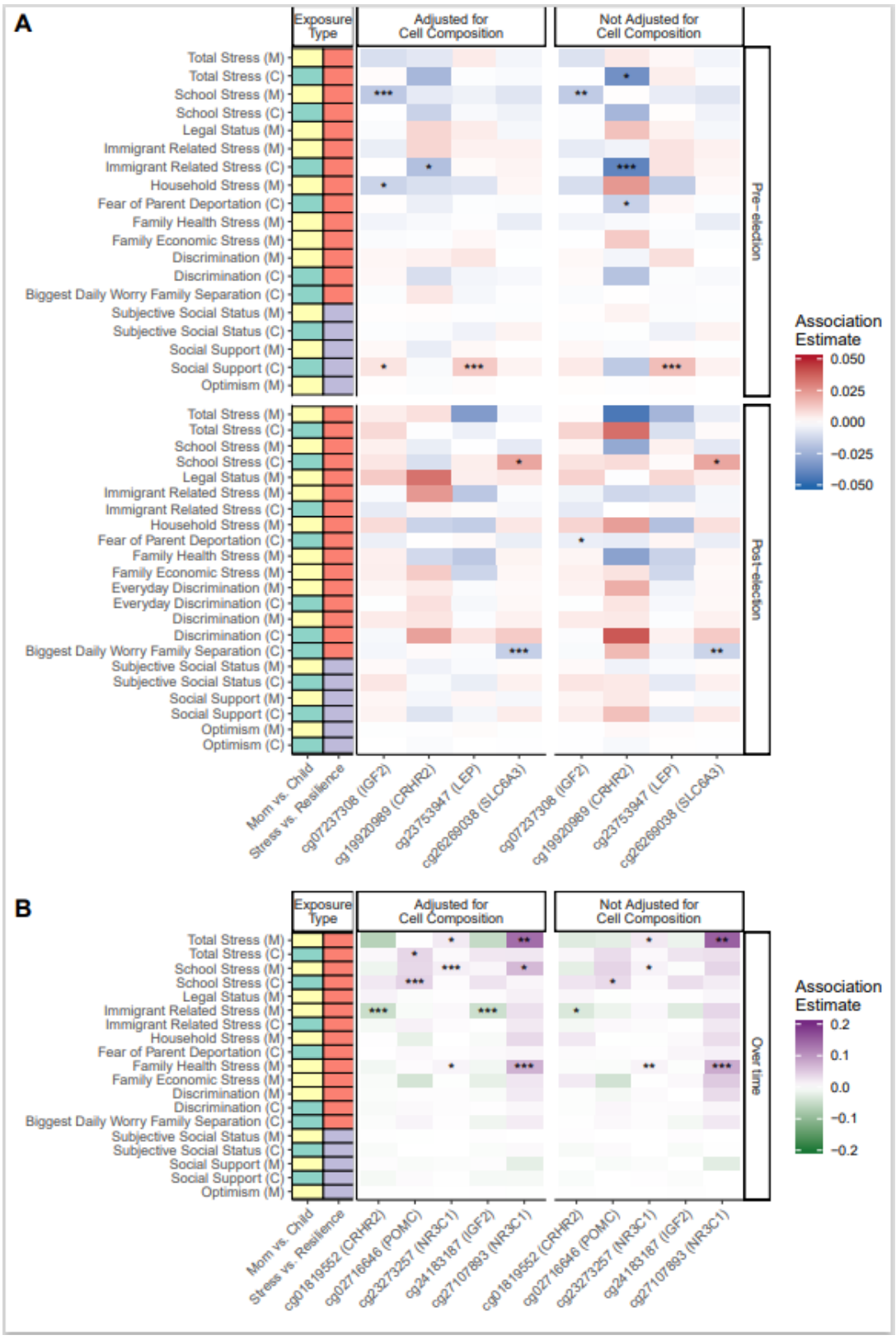

A
Exposure Type
Adjusted for Cell Composition
Not Adjusted for Cell Composition
Total Stress (M)
Total Stress (C)
School Stress (M)
School Stress (C)
Legal Status (M)
Immigrant Related Stress (M)
Immigrant Related Stress (C)
Household Stress (M)
Fear of Parent Deportation (C)
Family Health Stress (M)
Family Economic Stress (M)
Discrimination (M)
Discrimination (C)
Biggest Daily Worry Family Separation (C)
Subjective Social Status (M)
Subjective Social Status (C)
Social Support (M)
Social Support (C)
Optimism (M)
Everyday Discrimination (M)
Everyday Discrimination (C)
Optimism (C)
Pre−election
Post−election
Association Estimate
0.050
0.025
0.000
−0.025
−0.050
Mom vs. Child
Stress vs. Resilience
cg07237308 (IGF2)
cg19920989 (CRHR2)
cg23753947 (LEP)
cg26269038 (SLC6A3)
B
cg01819552 (CRHR2)
cg02716646 (POMC)
cg23273257 (NR3C1)
cg24183187 (IGF2)
cg27107893 (NR3C1)
Over time
0.2
0.1
0.0
−0.1
−0.2

Table 4.1. Summary of coefficient alphas and questions in stress and resilience scales.

	α‡ (95% CI)	**# of Items**	**Questions (English Translations)**
Child Reported Stress Scales			
Total child stress scale	0.69 (0.6, 0.78)	16	(An additive composite of all stress scale questions below)
Immigrant-related stress	0.46 (0.28, 0.63)	5	How often is each of the following true? (never, sometimes, always)? 6. I get upset that we never go out. 7. I miss relatives that live in my parent's home country. 8. I hear my parents talk about problems with their family in their home country. 9. I see reports about police arresting Latinx people on TV. 10. **I am worried that my parents will be forced to return to their home country.**
Discrimination score	0.70 (0.59, 0.80)	4	Tell me how often the following things happen to you (never, sometimes, always). 6. My classmates make fun of me because I am from [parent's home country]. 7. My classmates make fun of me because of the clothes I wear or the food I bring to school. 8. My classmates make fun of me because I speak Spanish. 9. My classmates say mean things to me.
Everyday Discrimination Scale (EDS) [33]	0.83 (0.78, 0.87)	10	In your day-to-day life, how often do any of the following things happen to you? (Almost Everyday, At Least One A Week, A Few Times A Month, A Few Times A Year, Less Than Once A Year, Never) 11. You are treated with less courtesy than other people. 12. You are treated with less respect than other people. 13. You receive poorer service than other people at restaurants or stores. 14. People act as if they think you are not smart. 15. People act as if they are afraid of you. 16. People act as if they think you are dishonest. 17. People act as if they're better than you are. 18. You or your family members are called names or insulted. 19. You are threatened or harassed. 20. People ignore you or act as if you are not there.
School-related stress	0.49 (0.33, 0.65)	7	During this current school year, tell me how often the following things happen to you (never, 1-2 times, more than 2 times). 7. I had something stolen from me at school. 8. I got in trouble at school. 9. I got into a physical fight at school. **10. I was bullied (picked on, made fun of, etc.) at school.** How often did the following things happen to you? (never sometimes, always) 11. I feel scared to go to school. 12. I worry about my grades. 10. Teachers are unfair to me.
Child Reported Resilience Scales			
Social Support from parents	0.76 (0.68, 0.84)	6	How often is each of the following true about your family? (never, sometimes, always) 7. We talk about our day. 8. My parents ask about my day at school. 9. My parents care about my feelings. 10. My parents pay attention to what I say. 11. I can talk to my parents if I am upset or have a problem. 12. My parents help me when I need it.

Table 4.1. Summary of coefficient alphas and questions in stress and resilience scales, continued.

	α‡ (95% CI)	**# of Items**	**Questions (English Translations)**
Youth Life Orientation Test (YLOT) [36]	0.71 (0.62, 0.80)	12	Please tell me whether you Agree A Lot, Agree A Little, Neither Agree nor Disagree, Disagree A Little, Disagree A Lot: 13. Each day I look forward to having a lot of fun. 14. I usually expect to have a good day. 15. When things are bad, I expect them to get better. 16. Overall, I expect more good things to happen to me than bad things. 17. When I am not sure what will happen next, I usually expect it to be something good. 18. I am lucky person. 19. Usually, I don't expect good things to happen to me. (R) 20. Each day I expect bad things to happen. (R) 21. No matter what I try, I do not believe anything is going to work. (R) 22. When things are good, I expect something to go wrong. (R) 23. Things usually go wrong for me. (R) 24. If something nice happens, chances are it won't be to me. (R)
Maternal Reported Stress Scales			
Total Stress Score	0.92 (0.89, 0.94)	63	(An additive composite of all questions in Maternal Stress Scales below)
Immigrant-related stress	0.64 (0.53, 0.76)	10	When I emigrated to the US, I felt stressed because: (yes/no) 11. Couldn't afford to bring family when emigrated 12. No legal documentation when emigrated 13. Separated from spouse or children when emigrated 14. Lost contact with my family when emigrating During the past year I felt stressed because: (yes/no) 15. I could not communicate with others 16. My partner or a close family member was arrested. 17. My partner or a close family member was deported. 18. My family or I had difficulty adjusting to American customs. 19. My family live far away. 20. My partner does not have legal documents.
Discrimination stress	0.69 (0.60, 0.78)	7	How often did you feel that you: (yes/no)? 8. Were discriminated against at your job? 9. Were treated as if you were less than other Americans 10. Were discriminated against at the doctor's office or hospital 11. Experienced discrimination in your neighborhood because you are an immigrant 12. Were treated unfairly because you are Latina? 13. Have seen friends treated badly because they are Latina? 14. People dislike you because you are Latina?
Everyday Discrimination Scale (EDS) [33]	0.82 (0.78, 0.87)	8	In your day-to-day life, how often do any of the following things happen to you? (Almost Everyday, At Least One A Week, A Few Times A Month, A Few Times A Year, Less Than Once A Year, Never) 9. You are treated with less courtesy than other people. 10. You are treated with less respect than other people. 11. You receive poorer service than other people at restaurants or stores. 12. People act as if they think you are not smart. 13. People act as if they are afraid of you. 14. People act as if they're better than you are. 15. You are called names or insulted. 16. You are threatened or harassed. 17. You are followed around in stores.

Table 4.1. Summary of coefficient alphas and questions in stress and resilience scales, continued.

	α‡ (95% CI)	**# of Items**	**Questions (English Translations)**
Maternal report of school-related stress	0.61 (0.48, 0.73)	7	In the past year I felt stressed because: (yes/no) 1. **My child was bullied.** 2. My child was discriminated against at school. 3. I could not help my child with homework. 4. There was violence at my child's school. 5. Drugs were sold at my child's school. 6. I did not have money to buy my child's books or school supplies. I have had difficulty communicating with my child's teacher or principal.
Household Stress	0.63 (0.52, 0.74)	8	In the past year I felt stressed because: 9. My child spent too much time indoors/enclosed. 10. My child had to translate for me or other family members. 11. **Domestic violence happened in my close family.** 12. I had infidelity problems. 13. I had difficulty finding where to leave my child while working. 14. I fought frequently with my spouse/partner. 15. I separated from my spouse/partner. 16. My spouse/partner had a mental health problem.
Family economic stress	0.85 (0.80, 0.90)	16	In the past year, I felt stressed because: (yes/no) 17. I could not find a job. 18. I was overworked at my job. 19. I could not do the work I was trained for in my home country. 20. I was unemployed or lost my job. 21. I have to work night shifts. 22. I have to work very long shifts or multiple jobs to pay my bills. 23. Conditions at my work are not healthy/have caused painful injuries. 24. I could not find enough work. 25. People with less skills or education than me have better jobs. 26. I was given the lowest position at work. 27. I could not get a loan for a home. 28. I did not understand the American system of credit. **29. I frequently had problems paying basic bills.** 30. I lived in an overcrowded home. 31. I could not afford quality housing. 32. I could not afford childcare (or the type of childcare I wanted).
Family health stress	0.80 (0.74-0.86)	11	In the past year, I felt stressed because: 12. A member of my family had a major health problem. 13. I had a major health problem. 14. I did not have health insurance. 15. I had trouble communicating with my doctor. 16. I lacked information I needed about healthcare. 17. I needed medical care but did not receive it. 18. I had to go to an emergency room. 19. I had difficulty understanding and filling out medical forms. 20. I did not have dental insurance for myself. 21. There was no interpreter at the doctor. 22. I could not find a Hispanic doctor.

Table 4.1. Summary of coefficient alphas and questions in stress and resilience scales, continued.

	α‡ (95% CI)	# of Items	Questions (English Translations)
Maternal Resilience Scales			
Social Support and Connection [34]	0.59 (0.45, 0.72)	11	Please tell me whether you Strongly Agree, Agree, Disagree, Strongly Disagree: 12. I have had difficulty making friends in Nashville. 13. I have difficulty seeing my friends or family because I lack transportation. 14. I have found emotional support through my church. 15. I had family members near where I live but I had no relationship with them. 16. I have friends or family with whom I can talk about my feelings or problems. 17. I have friends or family who can help with financial troubles. 18. On average, how many times do you talk on the telephone with family, friends, or neighbors who live near you in the US? 19. On average, how many times do you talk on the telephone with family, friends, or neighbors who live in your country of origin? 20. On average, how often do you get together with friends or relatives? 21. On average, how often do you attend church or religious services? On average, how often do you attend meetings of the clubs or organizations you belong to?
Life Orientation Test – Revised (LOT-R) [35]	0.43 (0.25, 0.61)	6	Please tell me whether you Agree A Lot, Agree A Little, Neither Agree nor Disagree, Disagree A Little, Disagree A Lot: 7. In Uncertain times, I usually expect the best. 8. If something can go wrong for me, it will. (R) 9. I'm always optimistic about my future. 10. I hardly ever expect things to go my way. (R) 11. I rarely count on good things happening to me. (R) 12. Overall, I expect more good things to happen to me than bad.

Table 4.2. Demographics, social stressors, and resilience factors pre- and post-election complete case data.

	Pre-election (n=71) n, % or mean (sd, range)	**Post-election (n=35)** n, % or mean (sd, range)	**Missing data pre-/post-**	**p-value‡**
Child Demographics				
Age in years	8.69 (2.09, 6-13)	10.51 (2.13, 6-15) †	0/0	**<0.0001**
Gender (female)	40 (56.3%)	17 (48.6%)	0/0	--
Country of birth			0/0	
United States	54 (76.1%)	25 (71.4 %)		--
Other	17 (23.9%)	10 (28.6%)		
Mother Demographics				
Country of birth			0/0	
Mexico	62 (87.3%)	33 (94.3%)		--
Other Latinx country	9 (12.7%)	2 (5.7%)		
Years in US	12.55 (4.0, 4-27)	15.14 (3.53, 6.67-22.42)	0/0	**<0.0001**
Legal status			0/0	
Undocumented	60 (84.5%)	31 (88.6%)		--
Documented	11 (15.5%)	4 (11.4%)		
Marital status			0/0	
Married	60 (84.5%)	30 (85.7%)		0.2482
Single	11(15.5%)	5 (14.3%)		
Years of Education	9.46 (3.1, 2-18)	9.69 (3.22, 2-16)	0/0	--
Trouble paying basic bills (yes)	24 (33.8%)	9 (25.7%)	0/0	0.7237
Smoking frequency	2 (2.8 %)	3 (8.6%)	0/0	0.6171
Child Psychosocial Stressors				
Total Child Stress	0.55 (0.26, 0.12-1.31)	0.42 (0.15, 0.12-0.75)	2/1	0.0561
Immigrant stress score	0.86 (0.38, 0.00-1.75)	0.99 (0.39, 0.20-1.80)	0/0	**0.0207**
Discrimination stress	0.25 (0.31, 0.00-1.50)	0.21 (0.31, 0.00-1.40)	0/0	0.3337
School-related stress	0.52 (0.32, 0.00-1.43)	0.55 (0.29, 0.00-1.43)	0/0	0.2729
Fear of parent deportation			0/0	
Never				
Sometimes	25 (35.2%)	7 (20.0%)		0.1804
Always	28 (39.4%)	19 (54.3%)		
	18 (25.4%)	9 (25.7%)		
Bullied at school			0/1	
Never	40 (56.3%)	23 (67.6%)		0.3496
Sometimes	11 (15.5%)	6 (17.6%)		
Always	20 (28.2%)	5 (14.7%)		
Child Resilience Factors				
Subjective SES			11/2	
Richer	14 (23.3 %)	16 (48.5%)		NA
Same	40 (66.7%)	14 (42.4 %)		
Poorer	6 (10%)	3 (9.1 %)		
Social support parents	1.43 (0.41, 0.50-2.00)	1.51 (0.35, 0.60-2.00)	0/0	**0.0081**
Optimism	--	32.91 (7.16, 20.00-46.00)	71/0	
Mother report of Psychosocial Stressors				
Total maternal stress	0.29 (0.17, 0.02-0.78)	0.24 (0.12, 0.02-0.53)	4/3	0.0549
Immigrant stress score	0.46 (0.23, 0.12-0.90)	0.40 (0.20, 0.00-0.80)	0/0	**0.0096**
Discrimination score	0.40 (0.26, 0.00-1.00)	0.34 (0.24, 0.00-0.71)	0/0	**0.0371**
Child's school-related stress score	0.26 (0.22, 0.00-1.00)	0.18 (0.16, 0.00-0.57)	0/0	0.1343
Household stress	0.20 (0.20, 0.00-0.80)	0.23 (0.21, 0.00-0.8)	0/1	0.1966
Family economic stress	0.23 (0.24, 0.00-1.00)	0.16 (0.17, 0.00-0.63)	3/2	0.3621
Family health stress	0.31 (0.27, 0.00-1.00)	0.24 (0.18, 0.73)	0/1	0.2676
Domestic violence in the family	8 (11.3%)	4 (11.4%)	0/0	0.3711
Mother Resilience variables				
Subjective SES	4.11 (1.92, 1.00-9.00)	4.43 (1.67, 1.00-8.00)	0/0	0.1315
Social support and connection	2.98 (0.38, 1.88- 3.70)	2.19 (0.58, 1.00-3.40)	0/0	**<0.0001**
Optimism	17.68 (3.02, 12.00-24.00)	13.60 (2.35, 8.00-18.00)	2/0	**<0.0001**

Table 4.2. Demographics, social stressors, and resilience factors pre- and post-election complete case data, continued.

‡Subset enrolled through post-election with DNA methylation data. ǂ p-value based on paired t-tests for continuous variables, and McNemar (paired Chi Square) test for categorical variables. Comparisons were calculated only on the 33 individuals with methylation data in both time points (significant associations shown in bold). †Age range overlaps with pre-election time point as a younger child in one family was added post-election in place of original participant. This child was excluded from all change over time analyses.

Table 4.3: Pearson correlations of all age acceleration scores at pre-election

	Chronological age	DNAm Age	Hannum Age	Skin & Blood Age	PedBE Age
Chronological age	1				
DNAmAge	0.718	1			
Hannum Age	0.513	0.423	11		
Skin & Blood Age	0.875	0.803	0.551	1	
PedBE Age	0.758	0.686	0.703	0.773	1

Table 4.4. Association between stress/resilience factors and epigenetic clocks pre- and post-election, and change over time.

	DNAmAge			DNAmAgeHannum			DNAmAgeSkinBloodClock			PedBE_age		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Pre-Election												
Child Variables												
Stress Factors:												
Total stress score	-1.204	1.001	0.234	0.756	1.158	0.516	-0.502	0.450	0.269	0.020	0.359	0.955
School stress	-0.913	0.819	0.269	-0.033	0.967	0.972	-0.508	0.365	0.170	0.048	0.293	0.872
Immigrant-related stress	-0.746	0.696	0.288	0.827	0.796	0.303	-0.163	0.308	0.598	-0.157	0.240	0.517
Fear of parent's deportation	-0.267	0.342	0.439	0.324	0.390	0.410	0.021	0.151	0.887	0.032	0.118	0.786
Discrimination	-0.738	0.789	0.354	0.057	0.908	0.951	-0.245	0.348	0.484	0.144	0.272	0.600
Biggest daily worry	-1.257	0.673	0.067	0.444	0.789	0.576	-0.013	0.304	0.967	-0.086	0.237	0.719
Resilience factors:												
Subjective social status	-0.032	0.500	0.950	-0.617	0.534	0.253	-0.204	0.220	0.360	0.239	0.177	0.183
Parental social support	0.438	0.683	0.524	0.512	0.781	0.515	0.126	0.301	0.677	0.421	0.229	0.071
Mother's variables												
Stress Factors:												
Total stress score	-1.761	2.018	0.387	1.075	2.362	0.651	1.053	0.880	0.236	-0.625	0.704	0.379
Child's school stress	1.220	1.349	0.369	-0.909	1.547	0.559	0.444	0.594	0.458	-0.368	0.464	0.430
Legal Status	0.332	0.699	0.636	0.154	0.799	0.848	-0.389	0.307	0.210	0.329	0.240	0.175
Immigrant-related stress	-1.267	1.236	0.309	0.942	1.420	0.509	0.436	0.545	0.427	-0.086	0.428	0.842
Household stress	-2.442	1.508	0.111	-0.797	1.758	0.652	0.687	0.671	0.310	-0.564	0.524	0.286
Family health stress	-0.013	1.080	0.991	1.038	1.227	0.401	**1.038**	**0.455**	**0.026**	-0.127	0.370	0.734
Family economic stress	-1.752	1.377	0.208	-0.358	1.621	0.826	0.815	0.604	0.182	0.026	0.486	0.957
Discrimination	-0.661	1.029	0.523	1.343	1.167	0.254	-0.103	0.453	0.821	**-0.716**	**0.342**	**0.041**
Resilience factors:												
Subjective social status	-0.139	0.136	0.308	**-0.438**	**0.146**	**0.004**	-0.080	0.059	0.182	-0.010	0.047	0.836
Social support/connection	0.259	0.700	0.713	-1.225	0.785	0.124	-0.152	0.307	0.623	0.347	0.237	0.148
Optimism	0.032	0.077	0.680	0.015	0.101	0.885	-0.025	0.036	0.479	0.010	0.029	0.742
Post-Election												
Child Variables												
Stress Factors:												
Total stress score	2.030	1.866	0.288	-1.677	2.330	0.479	-0.092	1.018	0.929	0.290	0.617	0.643
School stress	1.272	1.673	0.455	1.506	1.918	0.440	0.274	0.900	0.763	0.294	0.534	0.588
Immigrant-related stress	-0.035	1.082	0.974	-1.502	1.290	0.256	0.146	0.575	0.801	0.277	0.343	0.427
Fear of parent's deportation	0.206	0.638	0.750	**-1.882**	**0.683**	**0.011**	-0.015	0.340	0.966	0.289	0.197	0.155
Everyday Discrimination	-0.267	0.435	0.548	-0.175	0.417	0.679	-0.125	0.201	0.544	0.117	0.134	0.395
Discrimination	1.314	1.457	0.376	0.020	1.816	0.991	0.425	0.784	0.592	0.400	0.469	0.402
Biggest daily worry	1.618	0.925	0.093	0.014	1.204	0.991	0.537	0.511	0.304	0.372	0.306	0.236
Resilience factors:												
Subjective social status	0.068	0.795	0.933	1.047	0.981	0.297	-0.233	0.417	0.581	-0.195	0.241	0.428
Parental social support	1.377	1.186	0.257	1.072	1.478	0.475	-0.205	0.648	0.755	0.032	0.392	0.935
Optimism	0.028	0.059	0.639	0.012	0.073	0.867	0.003	0.032	0.917	0.009	0.019	0.659
Mother's variables												
Stress Factors:												
Total stress score	-4.248	4.005	0.301	-6.898	4.370	0.129	**-4.468**	**1.908**	**0.029**	-0.441	1.358	0.749
Child's school stress	-2.881	2.153	0.193	-3.538	2.639	0.193	-1.690	1.137	0.150	-1.066	0.684	0.132

Table 4.4. Association between stress/resilience factors and epigenetic clocks pre- and post-election, and change over time, continued.

	DNAmAge			DNAmAgeHannum			DNAmAgeSkinBloodClock			PedBE_age		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Legal Status	0.222	1.403	0.875	1.371	1.720	0.433	-0.026	0.747	0.972	-0.160	0.451	0.726
Immigrant-related stress	0.347	2.190	0.875	-3.380	2.595	0.205	-1.399	1.131	0.228	0.168	0.703	0.813
Household stress	-2.440	2.006	0.236	-1.918	2.569	0.463	-1.614	1.121	0.163	0.150	0.709	0.834
Family health stress	-1.696	2.271	0.463	-2.513	2.735	0.368	-1.755	1.105	0.126	0.475	0.701	0.505
Family economic stress	-2.295	2.843	0.428	0.378	3.278	0.909	-1.027	1.570	0.520	-0.315	0.997	0.755
Everyday Discrimination	-0.728	0.712	0.317	0.057	0.813	0.945	-0.593	0.355	0.109	-0.161	0.234	0.498
Discrimination	-0.725	1.517	0.637	-2.536	1.795	0.171	**-1.668**	**0.736**	**0.033**	-0.413	0.482	0.400
Resilience factors:												
Subjective social status	-0.144	0.289	0.623	**0.755**	**0.321**	**0.027**	0.074	0.154	0.633	0.041	0.093	0.661
Social support/connection	1.036	0.676	0.139	0.426	0.864	0.627	0.067	0.377	0.860	0.182	0.225	0.426
Optimism	0.201	0.162	0.226	0.267	0.197	0.189	0.146	0.084	0.094	0.004	0.054	0.935
Change over time												
Child Variables												
Stress Factors:												
Total stress score	-0.495	0.869	0.575	-1.516	0.896	0.106	-0.615	0.510	0.241	-0.166	0.201	0.419
School stress	-0.176	0.758	0.818	-0.694	0.814	0.404	-0.366	0.450	0.425	-0.062	0.177	0.729
Immigrant-related stress	-0.364	0.519	0.491	-0.847	0.541	0.131	-0.377	0.307	0.232	-0.114	0.120	0.351
Fear of parent's deportation	-0.298	0.291	0.318	-0.495	0.306	0.120	-0.178	0.176	0.324	**-0.148**	**0.062**	**0.025**
Discrimination	-0.117	0.705	0.870	-1.233	0.720	0.101	-0.570	0.409	0.177	-0.110	0.163	0.506
Biggest daily worry	0.668	0.570	0.253	-0.752	0.617	0.236	-0.191	0.352	0.592	-0.024	0.136	0.863
Resilience factors:												
Subjective social status	0.159	0.305	0.607	0.096	0.352	0.788	0.227	0.197	0.266	0.051	0.077	0.514
Parental social support	0.670	0.490	0.185	-0.362	0.548	0.516	-0.296	0.302	0.338	-0.164	0.113	0.161
Mother's variables												
Stress Factors:												
Total stress score	-1.340	1.844	0.476	**-5.942**	**1.529**	**0.001**	-1.736	1.049	0.114	0.185	0.430	0.672
Child's school stress	-1.478	0.954	0.135	-2.046	0.999	0.053	**-1.268**	**0.543**	**0.029**	0.317	0.224	0.171
Legal Status	0.027	0.594	0.964	-0.867	0.644	0.192	-0.202	0.359	0.579	-0.184	0.138	0.197
Immigrant-related stress	0.865	0.843	0.316	**-1.779**	**0.857**	**0.050**	-0.366	0.515	0.485	0.028	0.201	0.892
Household stress	-0.587	1.324	0.662	-0.319	1.442	0.827	0.488	0.796	0.547	0.174	0.307	0.576
Family health stress	-1.093	0.794	0.183	**-2.289**	**0.754**	**0.006**	-0.804	0.469	0.101	0.031	0.192	0.875
Family economic stress	-0.306	1.564	0.847	-1.680	1.656	0.322	0.363	0.934	0.702	-0.331	0.355	0.362
Discrimination	0.011	0.646	0.986	**-1.684**	**0.603**	**0.011**	-0.515	0.375	0.183	0.057	0.150	0.708
Resilience factors:												
Subjective social status	0.001	0.088	0.994	0.085	0.094	0.371	0.017	0.053	0.757	0.015	0.020	0.463
Social support/connection	**0.985**	**0.470**	**0.048**	0.856	0.528	0.119	0.541	0.289	0.074	-0.009	0.120	0.944
Optimism	0.050	0.070	0.486	-0.030	0.077	0.706	0.013	0.043	0.758	-0.013	0.016	0.412

Supplemental Table S4.1. Correlations between continuous covariates and maternal psychosocial factors.

	Mothers' education	Mothers' years in US	Child age	Mother's Subj SES	Total Maternal Stress	Maternal Discrimination Stress	Immigrant-related Stress	Child's School stress	Household Stress	Family Economic Stress	Health-related stress	Social Support
Mothers' years in US	0.09	1										
Child age	-0.12	0.19	1									
Maternal subj SES	0.16	0.11	-0.06	1								
Total maternal stress	-0.02	-0.03	0.04	**-0.29**	1							
Maternal discrimination Stress	**0.25**	0.13	-0.08	-0.15	**0.63**	1						
Immigrant-related stress	-0.15	-0.1	-0.04	**-0.38**	**0.74**	**0.46**	1					
Child school stress	-0.12	0.04	**0.26**	**-0.23**	**0.66**	0.19	**0.40**	1				
Household stress	-0.09	-0.14	0.02	-0.09	**0.72**	**0.29**	**0.34**	**0.49**	1			
Family economic stress	0.05	0.06	0.08	-0.16	**0.88**	**0.51**	**0.52**	**0.50**	**0.68**	1		
Health stress	-0.21	-0.04	0.15	0.15	0.15	-0.19	0.04	0.08	0.25	0.12	1	
Social support	0.17	0.14	-0.12	**0.34**	**-0.32**	-0.09	**-0.31**	**-0.31**	**-0.28**	-0.19	0.12	1
Optimism	**0.26**	0.11	-0.01	0.05	-0.13	0.16	-0.23	-0.20	-0.22	-0.11	-0.18	**0.44**

Bold values indicate significant correlations ($p<0.05$).

Supplemental Table S4.2. Correlations between continuous covariates and child psychosocial factors.

	Child age	Mothers' education	Mother's years in US	Total child stress	Child Discrimination stress	Child's school stress	Immigrant-related stress	Child's subjective SES	Social support	Optimism
Child age	1									
Mothers' education	-0.12	1								
Mothers' years in US	0.19	0.09	1							
Total child stress	0.19	0.16	-0.04	1						
Child's discrimination stress	-0.06	0.11	-0.11	**0.79**	1					
Child's school stress	0.15	**0.29**	0.04	**0.85**	**0.63**	1				
Immigrant-related stress	**0.26**	-0.03	-0.08	**0.66**	**0.32**	**0.25**	1			
Child's subjective SES	-0.1	-0.02	**-0.30**	0.16	0.1	0.16	0.07	1		
Social support	0.22	0.2	0.12	**0.28**	0.17	0.21	**0.33**	0.17	1	
Optimism	**-0.45**	-0.17	-0.25	-0.17	-0.2	-0.17	-0.09	**0.43**	0	1

Bold values indicate significant correlations ($p<0.05$).

Supplemental Table S4.3. EWAS between stress/resilience factors and genome-wide DNA methylation pre- and post-election.

	cg01093395: Body of *ZNF205* CpG island			cg20697427: Body of *TNK2* CpG island shelf			cg02692313: Body of *HLA-DPB1* Island			cg25511667: Body of *HLA-DPB1* Island		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Pre-election												
Child variables												
Stress factors:												
Total stress score	-0.010	0.005	0.066	-0.014	0.010	0.186	-0.077	0.053	0.155	-0.124	0.046	0.009
School stress	-0.004	0.005	0.383	-0.012	0.009	0.188	-0.061	0.043	0.167	-0.085	0.038	0.031
Immigrant-related stress	-0.003	0.004	0.465	-0.007	0.007	0.316	-0.013	0.036	0.729	-0.041	0.032	0.208
Fear of parent's deportation	-0.001	0.002	0.688	-0.006	0.003	0.111	-0.016	0.018	0.036	-0.022	0.016	0.174
Discrimination	-0.008	0.004	0.086	-0.005	0.008	0.533	-0.076	0.040	0.066	-0.103	0.035	0.005
Biggest daily worry	-0.008	0.004	0.040	-0.010	0.007	0.152	0.006	0.036	0.866	0.006	0.032	0.860
Resilience factors:												
Subjective social status	-0.002	0.003	0.413	-0.008	0.005	0.127	-0.002	0.027	0.949	-0.023	0.024	0.341
Parental social support	-0.002	0.004	0.587	0.004	0.007	0.592	-0.020	0.035	0.583	0.005	0.032	0.877
Mother's variables												
Stress factors:												
Total stress score	0.002	0.011	0.987	-0.061	0.018	0.001	-0.032	0.105	0.762	-0.038	0.095	0.697
Child's school stress	0.005	0.008	0.532	**-0.069**	**0.011**	**1.83e-8**	-0.002	0.070	0.976	-0.034	0.063	0.594
Legal Status	**0.025**	**0.004**	**2.98e-8**	0.003	0.007	0.660	0.094	0.036	0.012	0.097	0.033	0.005
Immigrant-related stress	-0.005	0.007	0.472	-0.020	0.012	0.116	0.005	0.065	0.939	0.012	0.058	0.842
Household stress	0.005	0.009	0.529	-0.044	0.015	0.004	-0.001	0.080	0.986	0.031	0.072	0.666
Family health stress	4.12e-4	0.008	0.946	-0.033	0.010	0.002	-0.056	0.056	0.323	-0.083	0.049	0.097

Supplemental Table S4.3. EWAS between stress/resilience factors and genome-wide DNA methylation pre- and post-election, continued.

	cg01093395: Body of *ZNF205* CpG island			cg20697427: Body of *TNK2* CpG island shelf			cg02692313: Body of *HLA-DPB1* Island			cg25511667: Body of *HLA-DPB1* Island		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Family economic stress	-0.002	0.007	0.790	-0.023	0.013	0.084	-0.028	0.073	0.707	0.018	0.066	0.782
Discrimination	0.001	0.006	0.897	-0.012	0.010	0.253	-0.016	0.053	0.767	0.042	0.048	0.385
Resilience factors:												
Subjective social status	-1.74e-4	0.001	0.821	0.002	0.001	0.077	0.002	0.007	0.772	0.002	0.006	0.732
Social support/connection	-0.003	0.004	0.471	0.013	0.007	0.060	0.044	0.036	0.232	0.026	0.032	0.436
Optimism	-3.67e-4	4.93e-4	0.461	1.45e-4	0.001	0.864	-0.001	0.005	0.835	0.002	0.004	0.579
Post-election												
Children's variables												
Stress factors:												
Total stress score	-0.011	0.012	0.373	-0.003	0.015	0.830	-0.054	0.054	0.322	-0.036	0.043	0.406
School stress	0.010	0.011	0.348	0.012	0.011	0.312	-0.067	0.045	0.140	-0.031	0.038	0.427
Immigrant-related stress	0.001	0.007	0.845	-0.013	0.008	0.114	-0.21	0.030	0.493	-0.039	0.024	0.118
Fear of parent's deportation	0.001	0.004	0.757	-0.008	0.005	0.113	0.009	0.018	0.613	-0.013	0.015	0.370
Everyday Discrimination	-2.92e-4	0.003	0.910	4.03e-5	0.003	0.988	-0.011	0.009	0.228	-0.003	0.008	0.657
Discrimination	0.007	0.009	0.491	-0.004	0.012	0.718	0.030	0.041	0.466	0.021	0.034	0.547
Biggest daily worry	-0.016	0.006	0.010	-0.009	0.007	0.216	0.005	0.028	0.851	-0.023	0.022	0.320
Resilience factors:												
Subjective social status	-0.005	0.005	0.316	-0.006	0.005	0.302	0.010	0.023	0.649	0.021	0.017	0.225
Parental social support	-0.001	0.008	0.857	-0.001	0.009	0.950	-0.007	0.034	0.843	-0.039	0.027	0.163

Supplemental Table S4.3. EWAS between stress/resilience factors and genome-wide DNA methylation pre- and post-election, continued.

	cg01093395: Body of *ZNF205* CpG island			cg20697427: Body of *TNK2* CpG island shelf			cg02692313: Body of *HLA-DPB1* Island			cg25511667: Body of *HLA-DPB1* Island		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Optimism	2.0e-4	3.82e-4	0.612	-0.001	4.50e-4	0.220	0.001	0.002	0.427	-0.002	0.001	0.192
Mother's variables:												
Stress factors:												
Total stress score	-0.009	0.024	0.723	-1.01e-5	0.033	1.00	0.166	0.112	0.149	-0.008	0.098	0.939
Child's school stress	-0.008	0.014	0.577	-0.002	0.017	0.919	0.076	0.061	0.223	0.076	0.050	0.140
Legal Status	0.006	0.009	0.545	0.003	0.011	0.818	**0.334**	**0.040**	**4.96e-9**	**0.271**	**0.033**	**8.00e-9**
Immigrant-related stress	-0.006	0.014	0.663	-0.001	0.017	0.938	0.097	0.059	0.110	0.010	0.051	0.844
Household stress	-0.002	0.014	0.871	4.29e-4	0.017	0.98	0.043	0.061	0.487	0.047	0.050	0.363
Family health stress	-0.009	0.013	0.508	0.009	0.018	0.597	-0.004	0.063	0.947	-0.077	0.049	0.132
Family economic stress	0.006	0.019	0.771	0.001	0.024	0.965	0.048	0.085	0.572	0.003	0.072	0.969
Everyday Discrimination	9.63e-5	0.005	0.984	-0.004	0.006	0.449	0.023	0.020	0.252	0.007	0.017	0.676
Discrimination	7.28e-4	0.010	0.943	0.003	0.012	0.796	0.083	0.040	0.044	0.038	0.035	0.284
Resilience factors:												
Subjective social status	1.50e-4	0.002	0.938	-0.001	0.002	0.611	-0.005	0.008	0.523	-0.001	0.007	0.901
Social support/connection	-0.007	0.004	0.142	-3.68e-5	0.006	0.995	0.035	0.019	0.069	0.004	0.016	0.790
Optimism	-1.58e-4	0.001	0.887	-0.002	0.001	0.081	0.002	0.005	0.668	-0.003	0.004	0.411

The table reports all sites with an unadjusted p-value<1e-7 in adjusted models in at least one of the tests (significant associations shown in bold). Underlined values indicate associations that pass the Bonferroni adjustment. Multivariable linear models adjusted for child's age, child's gender, mothers' marital status, problems paying basic bills, mothers' education, mothers' years in the U.S., mothers' legal status, mothers' smoking status, and estimated epithelial cell composition.

Supplemental Table S4.4. EWAS between stress/resilience factors and genome-wide rate of change in DNA methylation over time.

	cg13042487: TSS1500 of *ZFYVE21* 5'UTR of *XRCC3* CpG Island			cg05540413: TSS200 of *ZNF32* CpG Island			cg09143964: 5'UTR of *FAM196B* Body of *DOCK2* OpenSea		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Change over time									
Child variables									
Stress factors:									
Total stress score	-0.003	0.008	0.704	-0.017	0.004	3.57e-4	0.017	0.007	0.033
School stress	-0.010	0.006	0.114	**-0.019**	**0.002**	**9.73e-8**	0.015	0.006	0.021
Immigrant-related stress	0.006	0.005	0.219	-0.005	0.003	0.112	0.004	0.005	0.384
Fear of parent deportation	0.002	0.003	0.571	-0.002	0.002	0.222	0.003	0.003	0.343
Discrimination	0.004	0.007	0.516	-0.007	0.004	0.106	0.009	0.006	0.190
Biggest daily worry	0.004	0.006	0.520	-0.003	0.004	0.369	0.004	0.005	0.430
Resilience factors:									
Subjective social status	0.002	0.003	0.420	0.002	0.002	0.448	-2.86e-4	0.003	0.928
Parental social support	0.003	0.005	0.589	-0.003	0.003	0.369	0.003	0.005	0.507
Mother's variables									
Stress factors:									
Total stress score	0.049	0.014	0.002	0.017	0.011	0.130	0.027	0.016	0.096
Child's School stress	0.012	0.009	0.222	-0.007	0.006	0.244	**0.038**	**0.005**	**7.72e-8**
Legal Status	0.003	0.006	0.601	-0.001	0.004	0.883	0.005	0.005	0.372
Immigrant-related stress	**0.034**	**0.004**	**8.08e-8**	0.006	0.005	0.234	0.007	0.008	0.395
Household stress	0.005	0.013	0.677	0.004	0.008	0.649	0.001	0.012	0.952
Family health stress	0.014	0.007	0.079	0.003	0.005	0.539	0.020	0.006	0.004
Family economic stress	0.008	0.014	0.606	0.023	0.008	0.014	-0.015	0.014	0.272
Discrimination	0.006	0.006	0.354	-1.24e-4	0.004	0.976	0.004	0.006	0.557

Supplemental Table S4.4. EWAS between stress/resilience factors and genome-wide rate of change in DNA methylation over time, continued.

	cg13042487: TSS1500 of *ZFYVE21* 5'UTR of *XRCC3* CpG Island			cg05540413: TSS200 of *ZNF32* CpG Island			cg09143964: 5'UTR of *FAM196B* Body of *DOCK2* OpenSea		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Resilience factors:									
Subjective social status	-0.001	0.001	0.220	4.45e-5	0.001	0.937	-0.001	0.001	0.479
Social support/connection	-0.005	0.005	0.331	-0.001	0.003	0.735	-0.006	0.005	0.216
Optimism	-0.001	0.001	0.202	-0.001	4.34e-4	0.204	1.06e-4	0.001	0.875

The table reports all sites with an unadjusted p-value<1e-7 in adjusted models in at least one of the tests (significant associations shown in bold). Underlined values indicate associations that pass the Bonferroni adjustment. Multivariable linear models of rate of change over time (in years) adjusted for child's age, child's gender, mothers' marital status, problems paying basic bills, mothers' education, mothers' years in the U.S., mothers' legal status, mothers' smoking status, and estimated epithelial cell composition.

Supplemental Table S4.5. Associations between stress/resilience factors and DNA methylation in proximity to candidate genes pre- and post-election.

	cg07237308: 3'UTR/Body of *IGF2* CpG island shelf			cg23753947: 5'UTR of *LEP* Open sea			cg26269038: Body of *SLC6A3* Open sea		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Pre-election									
Child variables									
Stress factors:									
Total stress score	0.001	0.003	0.805	-0.001	0.004	0.873	-0.001	0.005	0.768
School stress	-2.14e-4	0.003	0.937	-0.002	0.004	0.642	-0.004	0.004	0.318
Immigrant-related stress	3.15e-4	0.002	0.887	0.001	0.003	0.696	0.003	0.003	0.425
Fear of parent's deportation	4.44e-4	0.001	0.681	-0.001	0.001	0.660	0.001	0.002	0.552
Discrimination	0.002	0.002	0.486	-0.003	0.003	0.359	-0.002	0.004	0.594
Biggest daily worry	-0.001	0.002	0.654	-0.002	0.003	0.413	0.001	0.003	0.867
Resilience factors:									
Parental social support	0.006	0.002	0.002	**0.012**	**0.003**	**8.82e-6**	0.003	0.003	0.375
Subjective social status	-0.001	0.001	0.661	-0.004	0.002	0.063	0.003	0.002	0.249
Mother's variables									
Stress factors:									
Total stress score	-0.010	0.006	0.113	0.005	0.009	0.601	-0.003	0.010	0.751
Child's school stress	**-0.017**	**0.004**	**3.38e-5**	-0.004	0.006	0.499	-0.008	0.006	0.212
Legal Status	-0.001	0.002	0.548	0.004	0.003	0.146	-0.002	0.003	0.456
Immigrant-related stress	-0.005	0.004	0.174	0.003	0.005	0.551	0.003	0.006	0.594
Household stress	-0.013	0.005	0.005	-0.008	0.007	0.225	0.002	0.007	0.767
Family health stress	-0.003	0.003	0.334	-0.001	0.005	0.915	-0.006	0.005	0.270

Supplemental Table S4.5. Associations between stress/resilience factors and DNA methylation in proximity to candidate genes pre- and post-election, continued.

	cg07237308: 3'UTR/Body of *IGF2* CpG island shelf			cg23753947: 5'UTR of *LEP* Open sea			cg26269038: Body of *SLC6A3* Open sea		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Family economic stress	-0.001	0.004	0.784	0.002	0.006	0.771	-0.001	0.007	0.934
Discrimination	0.002	0.003	0.503	0.006	0.004	0.187	-1.44e-4	0.005	0.976
Resilience factors:									
Subjective social status	3.70e-4	4.26e-4	0.388	-4.94e-4	0.001	0.405	-0.001	0.001	0.278
Social support/social connection	0.002	0.002	0.466	0.002	0.003	0.602	-3.49e-4	0.003	0.916
Optimism	0.001	2.70e-4	0.069	0.001	3.68e-4	0.027	-1.11e-4	4.17e-4	0.797
Post-election									
Child variables									
Stress factors:									
Total stress score	0.009	0.006	0.156	-0.005	0.008	0.587	-5.43e-5	0.008	0.995
School stress	0.006	0.005	0.293	0.004	0.007	0.591	0.021	0.006	0.001
Immigrant-related stress	-0.006	0.003	0.073	0.001	0.005	0.830	-0.002	0.005	0.637
Fear of parent's deportation	-0.005	0.002	0.015	0.001	0.003	0.645	-0.005	0.003	0.054
Everyday Discrimination	-3.94e-4	0.001	0.764	-0.002	0.002	0.219	0.002	0.002	0.297
Discrimination	-0.002	0.005	0.650	0.006	0.006	0.341	0.012	0.006	0.045
Biggest daily worry	-0.003	0.003	0.398	-0.001	0.004	0.776	**-0.015**	**0.003**	**8.85e-5**
Resilience factors:									
Parental social support	0.003	0.004	0.485	-0.003	0.005	0.608	0.004	0.005	0.407
Optimism	-1.23e-4	1.93e-4	0.530	8.09e-5	2.60e-4	0.758	-2.04e-4	2.58e-4	0.437
Subjective social status	0.006	0.002	0.016	-0.005	0.003	0.134	0.003	0.003	0.346

Supplemental Table S4.5. Associations between stress/resilience factors and DNA methylation in proximity to candidate genes pre- and post-election, continued.

	cg07237308: 3'UTR/Body of *IGF2* CpG island shelf			cg23753947: 5'UTR of *LEP* Open sea			cg26269038: Body of *SLC6A3* Open sea		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Mother's variables									
Stress factors:									
Total stress score	0.004	0.013	0.751	-0.031	0.018	0.088	-0.003	0.015	0.863
Child's school stress	0.004	0.007	0.633	-1.94e-4	0.010	0.984	-0.006	0.010	0.528
Legal Status	0.012	0.005	0.013	0.004	0.006	0.538	0.005	0.006	0.382
Immigrant-related stress	-0.002	0.007	0.835	-0.017	0.009	0.066	-0.001	0.010	0.891
Household stress	0.008	0.007	0.243	-0.015	0.009	0.098	0.006	0.008	0.514
Family health stress	0.004	0.007	0.620	-0.017	0.009	0.084	0.003	0.009	0.778
Family economic stress	0.004	0.010	0.693	-0.013	0.013	0.336	0.002	0.012	0.874
Everyday Discrimination	0.002	0.002	0.301	-0.003	0.003	0.680	0.001	0.003	0.681
Discrimination	0.005	0.005	0.354	-0.001	0.007	0.894	0.003	0.007	0.635
Resilience factors:									
Subjective social status	0.001	0.001	0.158	-0.001	0.001	0.254	0.001	0.001	0.450
Social support/social connection	0.002	0.002	0.363	0.002	0.003	0.529	-0.002	0.003	0.470
Optimism	-3.90e-4	0.001	0.478	0.010	0.001	0.182	-4.46e-4	0.001	0.547

Table is restricted to sites with an unadjusted p-value<1e-4 in adjusted models in at least one of the tests (significant associations shown in bold). Multivariable linear models adjusted for child's age, child's gender, mothers' marital status, problems paying basic bills, mothers' education, mothers' years in the U.S., mothers' legal status, mothers' smoking status, and estimated epithelial cell composition.

Supplemental Table S4.6. Associations between stress/resilience factors and change in candidate gene methylation over time.

	cg01819552: Body of *CRHR2* OpenSea			cg23273257: 3'UTR of *NR3C1* OpenSea			cg27107893 Body of *NR3C1* OpenSea			cg02716646: Body of *POMC* CpG Island			cg24183187: TSS1500 of *IGF2* N_Shelf		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Overtime															
Child variables															
Stress factors:															
Total stress score	0.007	0.012	0.561	0.006	0.004	0.118	0.022	0.022	0.330	0.038	0.011	0.003	0.021	0.012	0.094
School stress	0.021	0.010	0.050	0.004	0.003	0.265	0.009	0.019	0.652	**0.040**	**0.008**	**7.72e-5**	0.025	0.010	0.020
Immigrant-related stress	-0.009	0.008	0.269	0.004	0.002	0.099	0.020	0.013	0.128	0.013	0.008	0.122	0.001	0.008	0.887
Fear of parent deportation	0.001	0.005	0.874	0.002	0.001	0.150	0.009	0.007	0.257	0.006	0.005	0.211	0.006	0.005	0.238
Discrimination	-0.007	0.011	0.552	0.003	0.003	0.308	0.008	0.018	0.675	0.006	0.011	0.604	0.002	0.011	0.854
Biggest daily worry	-0.004	0.009	0.663	0.002	0.002	0.396	0.017	0.015	0.258	0.010	0.009	0.282	-0.014	0.009	0.132
Resilience factors:															
Subjective social status	-0.005	0.004	0.267	-5.41e-5	0.001	0.970	0.006	0.007	0.424	-3.10e-4	0.005	0.951	-0.004	0.005	0.408
Parental social support	-0.009	0.008	0.248	0.001	0.002	0.555	-0.008	0.013	0.540	0.005	0.008	0.544	-0.009	0.008	0.283
Mother's variables															
Stress factors:															
Total stress score	-0.066	0.024	0.014	0.019	0.007	0.010	0.137	0.035	0.001	-0.001	0.029	0.970	-0.053	0.027	0.060
Child's school stress	-0.015	0.015	0.329	**0.016**	**0.003**	**8.33e-5**	0.065	0.022	0.007	0.036	0.014	0.018	0.009	0.016	0.592
Legal Status	0.011	0.009	0.227	0.002	0.003	0.524	0.014	0.015	0.369	-0.004	0.009	0.686	0.004	0.009	0.646
Immigrant-related stress	**-0.048**	**0.009**	**1.19e-5**	0.006	0.003	0.090	0.028	0.021	0.199	-0.006	0.014	0.660	**-0.048**	**0.010**	**8.33e-5**
Household stress	0.002	0.021	0.916	0.000	0.006	0.942	0.035	0.033	0.304	-0.021	0.021	0.318	-0.007	0.021	0.753
Family health stress	-0.011	0.013	0.380	0.010	0.003	0.002	**0.071**	**0.016**	**8.16e-5**	0.003	0.013	0.804	-0.011	0.013	0.384
Family economic stress	-0.006	0.024	0.811	-0.002	0.007	0.773	0.022	0.039	0.574	-0.039	0.023	0.104	-0.022	0.024	0.374
Discrimination	-0.004	0.010	0.669	0.003	0.003	0.357	0.019	0.016	0.241	0.003	0.010	0.769	-0.005	0.010	0.611
Resilience factors:															
Subjective social status	0.001	0.001	0.493	-1.10e-4	3.78e-4	0.780	-2.90e-4	0.002	0.899	-0.001	0.001	0.695	0.002	0.001	0.138
Social support/connection	0.003	0.008	0.722	-0.004	0.002	0.084	-0.023	0.012	0.068	-0.005	0.008	0.516	0.003	0.008	0.716
Optimism	0.001	0.001	0.208	5.94e-5	3.06e-4	0.848	-4.60e-4	0.002	0.803	0.001	0.001	0.358	0.001	0.001	0.544

Table is restricted to sites with an unadjusted p-value<1e-4 in adjusted models in at least one of the tests (significant associations shown in bold). Multivariable linear models adjusted for child's age, child's gender, mothers' marital status, problems paying basic bills, mothers' education, mothers' years in the U.S., mothers' legal status, mothers' smoking status, and estimated epithelial cell composition.

Supplemental Table S4.7. EWAS between stress/resilience factors and genome-wide DNA methylation pre- and post-election with no cell type adjustment.

	cg01093395: Body of *ZNF205* CpG island			cg19542445: Body of *CACNA1C* CpG island shelf			cg12763164: Body of Unannotated (LOC284930) OpenSea			cg22302152: TSS1500 of *PPT1* S_Shore		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Pre-election												
Child variables												
Stress factors:												
Total stress score	-0.011	0.005	0.036	-0.013	0.20	0.487	0.002	0.017	0.889	0.003	0.005	0.541
School stress	-0.004	0.005	0.356	-0.004	0.017	0.815	0.001	0.015	0.929	0.003	0.004	0.511
Immigrant-related stress	-0.003	0.004	0.410	-0.003	0.133	0.816	0.015	0.011	0.162	0.004	0.003	0.169
Fear of parent's deportation	-0.001	0.002	0.615	-0.003	0.007	0.664	0.007	0.006	0.201	0.001	0.002	0.732
Discrimination	-0.008	0.004	0.078	-0.010	0.016	0.500	-0.001	0.014	0.912	0.001	0.004	0.839
Biggest daily worry	-0.008	0.004	0.037	-0.009	0.014	0.481	0.002	0.012	0.847	0.005	0.003	0.129
Resilience factors:												
Subjective social status	-0.002	0.003	0.451	-0.001	0.10	0.929	0.008	0.009	0.294	-0.002	0.002	0.290
Parental social support	-0.002	0.004	0.534	0.012	0.013	0.338	0.014	0.012	0.194	0.006	0.003	0.040
Maternal variables												
Stress factors:												
Total stress score	1.79e-4	0.011	0.987	-0.033	0.041	0.361	-0.031	0.035	-0.981	-0.001	0.010	-0.152
Child's school stress	0.005	0.007	0.517	-0.030	0.027	0.215	-0.027	0.024	0.231	0.002	0.006	0.334
Legal Status	**0.025**	**0.004**	**2.09e-8**	-0.001	0.014	0.920	0.004	0.012	0.760	-0.003	0.003	0.400
Immigrant-related stress	-0.005	0.007	0.447	0.004	0.025	0.861	0.009	0.022	0.652	-0.003	0.006	-0.458
Household stress	0.006	0.008	0.481	-0.029	0.030	0.283	-0.025	0.026	0.315	-0.004	0.006	0.648
Family health stress	4.14e-4	0.006	0.945	-0.023	0.022	0.236	-0.029	0.019	0.098	0.001	0.005	0.769
Family economic stress	-0.002	0.007	0.795	-0.012	0.28	0.642	0.001	0.025	0.037	-0.006	0.006	0.343
Discrimination	0.001	0.006	0.916	0.015	0.021	0.409	0.013	0.018	0.441	0.004	0.005	0.350
Resilience factors:												
Subjective social status	-1.21e-4	0.001	0.872	0.002	0.003	0.391	-0.001	0.002	0.812	-2.85e-4	0.001	-0.455
Social support/connection	-0.003	0.004	0.534	0.004	0.014	0.750	0.014	0.012	0.211	0.001	0.003	0.809
Optimism	-3.50e-4	4.91e-4	0.483	-0.001	0.002	0.581	0.002	0.002	0.242	2.84e-4	4.10e-4	0.495
Post-election												
Child's variables												
Stress factors:												
Total stress score	-0.003	0.012	0.781	-0.060	0.043	0.081	-0.019	0.026	0.280	0.007	0.006	0.295
School stress	0.014	0.011	0.236	0.035	0.040	0.263	0.007	0.024	0.686	0.009	0.005	0.109
Immigrant-related stress	0.001	0.007	0.905	-0.007	0.026	0.730	0.015	0.011	0.162	0.001	0.003	0.801
Fear of parent's deportation	1.32e-4	0.004	0.976	-0.011	0.015	0.355	-0.006	0.009	0.317	-0.002	0.002	0.492
Everyday Discrimination	-0.005	0.003	0.859	0.009	0.010	0.195	-0.001	0.007	0.786	0.001	0.002	0.492
Discrimination	0.010	0.010	0.323	0.007	0.035	0.815	0.009	0.021	0.524	-0.002	0.005	0.758
Biggest daily worry	-0.012	0.006	0.063	**-0.076**	**0.018**	**5.48e-8**	-0.010	0.013	0.265	-0.004	0.003	0.188
Resilience factors:												
Subjective social status	-0.004	0.005	0.448	-0.018	0.018	0.191	0.003	0.012	0.705	-0.001	0.004	0.729
Parental social support	0.003	0.008	0.714	-0.033	0.027	0.125	-0.015	0.016	0.174	3.68e-4	0.004	0.927
Optimism	5.34e-5	3.94e-4	0.895	-2.10e-4	0.001	0.855	0.001	0.001	0.317	-5.47e-5	1.97e-4	0.787

Supplemental Table S4.7. EWAS between stress/resilience factors and genome-wide DNA methylation pre- and post-election with no cell type adjustment, continued.

	cg01093395: Body of *ZNF205* CpG island			cg19542445: Body of *CACNA1C* CpG island shelf			cg12763164: Body of Unannotated (LOC284930) OpenSea			cg22302152: TSS1500 of *PPT1* S_Shore		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Maternal variables												
Stress factors:												
Total stress score	-0.018	0.025	0.481	0.050	0.100	0.516	0.032	0.063	0.433	-0.009	0.014	0.533
Child's school stress	-0.0122	0.015	0.422	0.028	0.053	0.514	0.027	0.031	0.198	-1.40e-4	0.007	0.986
Legal Status	-0.001	0.088	0.930	0.053	0.031	0.044	**0.100**	**0.015**	**1.37e-8**	**0.033**	**0.004**	**5.10e-8**
Immigrant-related stress	-0.013	0.014	0.389	0.019	0.051	0.648	0.016	0.030	0.444	-0.013	0.007	0.059
Household stress	0.005	0.014	0.715	0.029	0.049	0.455	0.016	0.030	0.438	-0.002	0.007	0.813
Family health stress	-0.012	0.013	0.391	0.054	0.053	0.198	0.023	0.033	0.282	-0.008	0.007	0.311
Family economic stress	0.005	0.020	0.828	-0.009	0.073	0.868	-0.030	0.045	0.301	0.009	0.010	0.397
Everyday Discrimination	0.003	0.005	0.533	-0.010	0.016	0.458	-0.005	0.010	0.430	-0.001	0.002	0.551
Discrimination	0.001	0.010	0.959	0.011	0.037	0.702	0.008	0.022	0.572	0.001	0.005	0.855
Resilience factors:												
Subjective social status	1.58e-4	0.002	0.938	0.008	0.007	0.136	0.003	0.004	0.215	0.001	0.001	0.425
Social support/connection	-0.005	0.005	0.291	-0.008	0.017	0.562	0.004	0.010	0.513	-0.004	0.002	0.101
Optimism	2.59e-4	0.001	0.820	-0.004	0.004	0.178	3.29e-4	0.012	0.705	-4.70e-4	0.001	0.407

The table reports all sites with an unadjusted p-value<1e-7 in adjusted models in at least one of the tests (significant associations shown in bold). Multivariable linear models adjusted for child's age, child's gender, Maternal marital status, problems paying basic bills, Maternal education, Maternal years in the U.S., Maternal legal status, and Maternal smoking status.

Supplemental Table S4.8. EWAS between stress/resilience factors and genome-wide rate of change in DNA methylation over time with no cell type adjustment.

	cg03423870: Body of *AGBL1* OpenSea			cg07725183: Body of *NOTCH4* OpenSea			cg26613628: Body of *RELN* OpenSea		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Overtime									
Child's variables									
Stress factors:									
Total stress score	0.005	0.036	0.880	0.013	0.025	0.603	0.014	0.030	0.635
School stress	0.028	0.030	0.361	-0.002	0.022	0.945	-0.007	0.026	0.780
Immigrant-related stress	-0.016	0.020	0.450	0.011	0.014	0.484	0.021	0.017	0.225
Fear of parent's deportation	-0.008	0.011	0.472	0.001	0.001	0.120	0.011	0.009	0.240
Discrimination	0.001	0.028	0.962	0.003	0.020	0.896	0.006	0.023	0.793
Biggest daily worry	-0.031	0.023	0.182	0.030	0.016	0.067	0.017	0.020	0.404
Resilience factors:									
Subjective social status	0.005	0.014	0.717	0.009	0.009	0.378	-0.002	0.012	0.845
Parental social support	-0.016	0.020	0.425	0.010	0.014	0.484	0.014	0.017	0.415
Maternal variables									
Stress factors:									
Total stress score	**-0.265**	**0.032**	**4.54e-8**	**0.178**	**0.023**	**6.61e-8**	**0.222**	**0.028**	**7.19e-8**
Child's school stress	-0.050	0.037	0.190	0.024	0.027	0.377	0.026	0.032	0.412
Legal Status	-0.004	0.024	0.860	-0.014	0.017	0.421	0.019	0.020	0.349
Immigrant-related stress	-0.095	0.025	0.001	0.076	0.017	1.35e-4	0.091	0.019	9.97e-5
Household stress	-0.009	0.050	0.855	-0.011	0.035	0.751	0.033	0.041	0.431
Family health stress	-0.110	0.024	1.12e-4	0.063	0.019	0.004	0.085	0.021	9.97e-5
Family economic stress	-0.104	0.047	0.039	0.083	0.031	0.013	0.099	0.039	0.019
Discrimination	-0.066	0.022	0.006	0.048	0.015	0.005	0.060	0.018	0.002
Resilience factors:									
Subjective social status	0.004	0.003	0.306	-0.002	0.002	0.382	-0.005	0.003	0.074
Social support/social connection	0.041	0.020	0.047	-0.022	0.015	0.145	-0.025	0.017	0.164
Optimism	1.45e-4	2.41e-4	0.961	-2.18e-5	0.002	0.992	0.002	0.002	0.456

The table reports all sites with an unadjusted p-value<1e-7 in adjusted models in at least one of the tests (significant associations shown in bold). Multivariable linear models of rate of change over time (in years) adjusted for child's age, child's gender, Maternal marital status, problems paying basic bills, Maternal education, Maternal years in the U.S., Maternal legal status, and Maternal smoking status.

Supplemental Table S4.9. Associations between stress/resilience factors and DNA methylation in proximity to candidate genes pre- and post-election with no cell type adjustment.

	cg23753947: 5'UTR of LEP Open sea			cg19920989: TSS1500 CRHR2 Open sea		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Pre-election						
Child variables						
Stress factors:						
Total stress score	0.004	0.005	0.458	-0.035	0.013	0.007
School stress	0.001	0.004	0.897	-0.023	0.013	0.095
Immigrant-related stress	0.006	0.003	0.056	**-0.039**	**0.009**	**8.21e-5**
Fear of parent's deportation	0.002	0.002	0.293	-0.014	0.005	0.006
Discrimination	-0.001	0.004	0.808	-0.018	0.012	0.144
Biggest daily worry	-0.001	0.004	0.755	1.54e-4	0.011	0.989
Resilience factors:						
Subjective social status	-0.004	0.003	0.110	-3.83e-4	0.007	0.955
Parental social support	**0.015**	**0.003**	**1.86e-6**	-0.016	0.011	0.125
Maternal variables						
Stress factors:						
Total stress score	0.002	0.011	0.870	0.005	0.033	0.878
Child's school stress	-0.006	0.007	0.429	4.18e-4	0.022	0.985
Legal Status	0.003	0.004	0.367	0.014	0.011	0.208
Immigrant-related stress	0.006	0.006	0.325	-0.003	0.020	0.862
Household stress	-0.016	0.008	0.041	0.024	0.024	0.317
Family health stress	-0.001	0.006	0.927	-0.002	0.017	0.920
Family economic stress	-0.001	0.007	0.854	0.012	0.023	0.588
Discrimination	0.007	0.005	0.167	-0.003	0.017	0.850
Resilience factors:						
Subjective social status	-0.001	0.001	0.152	0.003	0.002	0.203
Social support/social connection	0.001	0.004	0.872	-0.001	0.011	0.901
Optimism	0.001	4.40e-4	0.107	-0.001	0.001	0.721
Post-election						
Child variables						
Stress factors:						
Total stress score	-0.010	0.008	0.262	0.034	0.029	0.261
School stress	0.001	0.008	0.891	0.008	0.026	0.760
Immigrant-related stress	0.001	0.005	0.780	-7.22e-5	0.018	0.997
Fear of parent's deportation	0.002	0.003	0.460	-0.006	0.010	0.587
Everyday Discrimination	-0.002	0.002	0.263	0.006	0.007	0.392
Discrimination	0.003	0.007	0.651	0.039	0.023	0.100
Biggest daily worry	-0.004	0.004	0.430	0.016	0.015	0.303
Resilience factors:						
Subjective social status	-0.006	0.004	0.097	0.005	0.013	0.707
Parental social support	-0.006	0.005	0.271	0.015	0.019	0.445
Optimism	1.92e-4	2.73e-4	0.489	-0.002	0.001	0.041
Maternal variables						
Stress factors:						
Total stress score	-0.023	0.019	0.246	-0.044	0.071	0.544
Child's school stress	0.003	0.010	0.755	-0.027	0.036	0.461
Legal Status	0.009	0.006	0.150	-0.001	0.022	0.979
Immigrant-related stress	-0.010	0.010	0.294	-0.012	0.035	0.727
Household stress	-0.019	0.009	0.040	0.023	0.035	0.523
Family health stress	-0.014	0.010	0.199	-0.029	0.037	0.437
Family economic stress	-0.012	0.014	0.399	0.006	0.051	0.900
Everyday Discrimination	-0.004	0.003	0.275	0.019	0.011	0.089
Discrimination	-0.001	0.007	0.919	0.005	0.025	0.840
Resilience factors:						
Subjective social status	-0.001	0.001	0.290	-0.004	0.005	0.423
Social support/social connection	0.001	0.003	0.839	0.005	0.011	0.662
Optimism	0.001	0.001	0.448	0.002	0.003	0.563

Table is restricted to sites with an unadjusted p-value<1e-4 in adjusted models in at least one of the tests (significant associations shown in bold). Multivariable linear models adjusted for child's age, child's gender, Maternal marital status, problems paying basic bills, Maternal education, Maternal years in the U.S., Maternal legal status, and Maternal smoking status.

Supplemental Table S4.10. Association between stress/resilience factors and epigenetic clocks pre- and post-election and change over time with no cell type adjustment.

	DNAmAge			DNAmAgeHannum			DNAmAgeSkinBloodClock			PedBE_age		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Pre-election												
Child Variables												
Stress Factors:												
Total stress score	-1.242	0.974	0.207	3.484	2.113	0.105	-0.424	0.441	0.341	0.497	0.469	0.293
School stress	-0.932	0.807	0.253	1.358	1.840	0.463	-0.470	0.362	0.200	0.293	0.401	0.467
Immigrant-related stress	-0.768	0.644	0.238	**4.125**	**1.327**	**0.003**	-0.076	0.287	0.793	0.470	0.306	0.130
Fear of parent's deportation	-0.291	0.322	0.369	**1.784**	**0.672**	**0.010**	0.049	0.142	0.734	0.295	0.150	0.054
Discrimination	-0.773	0.779	0.325	1.379	1.710	0.423	-0.216	0.344	0.533	0.377	0.372	0.314
Biggest daily worry	-1.277	0.666	0.060	1.263	1.493	0.401	0.003	0.302	0.991	0.061	0.328	0.852
Resilience factors:												
Subjective social status	-0.027	0.496	0.957	-0.780	1.081	0.474	-0.206	0.219	0.351	0.211	0.239	0.382
Parental social support	0.335	0.661	0.614	2.778	1.406	0.053	0.164	0.291	0.575	**0.806**	**0.299**	**0.009**
Maternal variables												
Stress Factors:												
Total stress score	-1.659	2.006	0.412	-0.749	4.404	0.866	1.011	0.874	0.253	-0.943	0.953	0.327
Child's school stress	1.251	1.338	0.353	-1.931	2.942	0.514	0.423	0.590	0.477	-0.550	0.640	0.394
Legal Status	0.357	0.693	0.608	-0.565	1.519	0.711	-0.403	0.305	0.191	0.201	0.331	0.546
Immigrant-related stress	-1.320	1.22	0.284	2.920	2.672	0.279	0.469	0.539	0.387	0.270	0.588	0.648
Household stress	-2.134	1.464	0.150	-5.849	3.174	0.070	0.549	0.651	0.402	**-1.441**	**0.687**	**0.040**
Family health stress	-0.012	1.073	0.991	1.025	2.347	0.664	1.038	0.453	0.025	-0.129	0.513	0.802
Family economic stress	-1.647	1.365	0.232	-2.344	3.032	0.443	0.757	0.601	0.213	-0.327	0.663	0.624
Discrimination	-0.691	1.020	0.500	2.303	2.223	0.304	-0.083	0.450	0.854	-0.541	0.484	0.268
Resilience factors:												
Subjective social status	-0.124	0.133	0.354	**-0.755**	**0.277**	**0.008**	-0.084	0.058	0.152	-0.068	0.063	0.287
Social support/social connection	0.279	0.694	0.689	-1.843	1.505	0.225	-0.163	0.305	0.594	0.235	0.331	0.481
Optimism	0.030	0.076	0.695	-0.062	0.193	0.748	-0.029	0.036	0.430	-0.004	0.042	0.918
Post-Election												
Child Variables												
Stress Factors:												
Total stress score	2.801	1.813	0.135	-6.392	3.755	0.102	-0.290	0.960	0.765	-0.912	0.970	0.356
School stress	1.731	1.698	0.318	-1.106	3.547	0.758	0.159	0.877	0.858	-0.321	0.879	0.718
Immigrant-related stress	-0.108	1.125	0.924	-1.131	2.315	0.630	0.162	0.569	0.778	0.366	0.574	0.529
Fear of parent's deportation	0.034	0.658	0.959	-0.991	1.346	0.468	0.022	0.333	0.949	0.487	0.324	0.145
Everyday Discrimination	-0.290	0.440	0.518	-0.020	0.938	0.983	-0.121	0.196	0.546	0.153	0.235	0.525
Discrimination	1.759	1.472	0.243	-2.493	3.089	0.427	0.304	0.764	0.694	-0.223	0.776	0.777
Biggest daily worry	**1.938**	**0.910**	**0.043**	-2.135	2.000	0.296	0.412	0.494	0.412	-0.172	0.507	0.738
Resilience factors:												
Subjective social status	0.255	0.822	0.759	0.091	1.742	0.959	-0.276	0.409	0.506	-0.405	0.397	0.318
Parental social support	1.871	1.150	0.116	-2.183	2.461	0.384	-0.319	0.609	0.605	-0.735	0.604	0.235
Optimism	0.007	0.061	0.910	0.114	0.123	0.364	0.008	0.031	0.808	0.033	0.031	0.290
Maternal variables												
Stress Factors:												
Total stress score	-5.608	4.116	0.187	0.220	8.814	0.980	**-3.968**	**1.909**	**0.049**	1.260	2.265	0.584
Child's school stress	-3.421	2.190	0.131	-0.343	4.744	0.943	-1.517	1.121	0.188	-0.287	1.178	0.809
Legal Status	-0.715	1.357	0.603	**6.131**	**2.806**	**0.038**	0.174	0.687	0.802	0.993	0.697	0.166
Immigrant-related stress	-0.647	2.198	0.771	1.778	4.538	0.698	-1.096	1.093	0.325	1.349	1.099	0.231
Household stress	-1.174	2.118	0.584	-6.495	4.194	0.135	-1.685	1.060	0.125	-1.034	1.110	0.361
Family health stress	-2.165	2.328	0.362	0.083	4.907	0.987	-1.610	1.097	0.155	1.089	1.189	0.369

Supplemental Table S4.10. Association between stress/resilience factors and epigenetic clocks pre- and post-election and change over time with no cell type adjustment, continued.

	DNAmAge			DNAmAgeHannum			DNAmAgeSkinBloodClock			PedBE_age		
	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)	Estimate	SE	Pr(>|t|)
Family economic stress	-2.462	3.026	0.424	1.134	6.301	0.859	-0.993	1.554	0.529	-0.130	1.644	0.938
Everyday Discrimination	-0.231	0.706	0.746	-2.112	1.391	0.142	-0.620	0.326	0.069	-0.653	0.342	0.068
Discrimination	-0.752	1.579	0.638	-2.399	3.245	0.467	**-1.663**	**0.731**	**0.032**	-0.380	0.812	0.643
Resilience factors:												
Subjective social status	-0.143	0.301	0.640	0.749	0.607	0.229	0.074	0.152	0.631	0.040	0.155	0.800
Social support/social connection	1.219	0.684	0.087	-0.684	1.495	0.651	0.019	0.367	0.959	-0.089	0.373	0.812
Optimism	0.252	0.162	0.134	-0.047	0.352	0.895	0.127	0.082	0.135	-0.069	0.086	0.432
Change over time												
Child Variables												
Stress Factors:												
Total stress score	-0.241	0.939	0.800	-2.647	1.913	0.180	-0.610	0.577	0.303	-0.357	0.393	0.374
School stress	0.019	0.805	0.981	-1.936	1.656	0.255	-0.480	0.496	0.344	-0.351	0.334	0.306
Immigrant-related stress	-0.045	0.542	0.934	-1.448	1.105	0.203	-0.140	0.339	0.682	-0.083	0.228	0.721
Fear of parent's deportation	-0.095	0.305	0.758	**-1.411**	**0.575**	**0.022**	-0.181	0.188	0.346	**-0.298**	**0.113**	**0.015**
Discrimination	-0.306	0.735	0.681	-1.043	1.545	0.507	-0.803	0.432	0.076	-0.255	0.307	0.416
Biggest daily worry	0.919	0.597	0.137	-1.788	1.271	0.173	-0.068	0.393	0.865	-0.110	0.264	0.680
Resilience factors:												
Subjective social status	0.130	0.328	0.697	0.657	0.756	0.395	0.267	0.218	0.236	0.199	0.148	0.195
Parental social support	0.860	0.500	0.099	-1.583	1.074	0.154	-0.316	0.327	0.344	-0.376	0.210	0.087
Maternal variables												
Stress Factors:												
Total stress score	0.199	1.762	0.911	**-11.316**	**2.678**	**<0.001**	-1.499	1.058	0.171	-0.967	0.715	0.191
Child's school stress	-1.581	0.956	0.112	0.739	2.132	0.732	-0.721	0.617	0.254	0.921	0.382	0.024
Legal Status	0.052	0.633	0.936	-0.421	1.337	0.756	0.030	0.397	0.940	0.038	0.267	0.887
Immigrant-related stress	1.447	0.788	0.079	-4.376	1.532	0.009	-0.050	0.529	0.925	-0.276	0.352	0.441
Household stress	-1.356	1.289	0.304	0.319	2.789	0.910	-0.531	0.821	0.524	-0.344	0.553	0.540
Family health stress	-0.549	0.853	0.526	**-4.362**	**1.575**	**0.011**	-0.701	0.520	0.191	-0.292	0.358	0.423
Family economic stress	0.254	1.420	0.860	**-5.830**	**2.648**	**0.039**	-0.470	0.887	0.602	**-1.451**	**0.511**	**0.010**
Discrimination	0.590	0.664	0.383	**-3.881**	**1.177**	**0.003**	-0.422	0.415	0.319	-0.279	0.279	0.328
Resilience factors:												
Subjective social status	-0.035	0.090	0.700	0.107	0.190	0.578	-0.026	0.057	0.651	-0.007	0.038	0.850
Social support/ connection	0.970	0.530	0.080	1.388	1.163	0.245	0.577	0.335	0.098	0.074	0.239	0.760
Optimism	0.089	0.073	0.234	-0.166	0.157	0.304	0.024	0.046	0.612	-0.028	0.032	0.397

Table is restricted to sites with an unadjusted p-value≤0.05 in adjusted models in at least one of the tests (significant associations shown in bold). Multivariable linear models adjusted for child's age, child's gender, Maternal marital status, problems paying basic bills, Maternal education, Maternal years in the U.S., Maternal legal status, and Maternal smoking status.

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Chapter 5

CONCLUSION

This dissertation contributed to the broad overarching question of how the social and political environment may become embodied and ultimately affect health. Societal exposures that become embodied can induce pathogenic outcomes that are mediated by physiology, behavior, and gene expression (i.e., ecosocial theory; Krieger 2012). This in turn affects development, growth, regulation, and death of our body's biological systems, organs, and cells, which ultimately culminates in disease, disability, and/or death. This dissertation explored how the life circumstances and experiences of Latinx immigrant mothers and their children may alter their stress physiology over time, potentially setting them up for higher risk for stress-related diseases in adulthood and later life. This study focuses specifically on stress experiences of Latinx immigrant mother-child dyads living in Nashville, Tennessee, and how these experiences affected their health. This is a pressing and timely question given the rapidly changing pace of current national policies of the former administration toward immigrants which could significantly alter the lives of immigrant mothers and their children in the US, creating an environment of uncertainty for current immigrant families, regardless of documentation status.

Throughout my dissertation, I have integrated data, analytical techniques, and perspectives from diverse disciplines both within and outside of anthropology, including biological and medical anthropology, genetics, public health, social epidemiology, and psychology. Integrative and collaborative analyses are critical to resolve the persisting problem of social and racial health disparities. Including and integrating multiple levels of analyses, including individual (e.g., genetic, biological, psychological), interpersonal (relationships, social support), community (resources, neighborhoods, structural violence), societal (social policies,

institutional racism), and national level (laws and policies) is necessary to fully understand the different factors that work together to affect health (Sallis et al. 2008).

Ultimately it will take a great collaborative effort, in which anthropology is well positioned to play a key central role to understand all of the interconnected components of health disparities. By having the opportunity to bridge disciplines, methods, and perspectives from multiple disciplines, I was able to make new connections (e.g., recognizing the multilevel and dynamic nature of human adaption), which facilitated a comprehensive exploration of the embodiment of sociopolitical environment. The exploration of anthropological questions can greatly benefit from the use of a more integrative research environment in order to resolve complex research questions. For example, in each of my projects, I specifically examined data through a multidisciplinary perspective. The results of these studies have sparked new hypotheses for future avenues of research, and contribute to advance our understanding of the ultimate causal factors and proximate pathways leading to social and racial health disparities.

A central focus of ecosocial theory is how we literally biologically embody various exposures from societal and ecological contexts to address health disparities (Krieger 2012).

SUMMARY OF KEY FINDINGS

Immigrant-related stressors and mental health:

This study explored how a shift in political leadership might affect the mental health of a vulnerable population in the US. We found that immigrant-related stress, everyday discrimination, and school stress in children were all positively associated with anxiety and depressive symptoms, including separation anxiety. In mothers, we found discrimination stress, family economic stress, and household stress were positively associated with anxiety, depression, and perceived stress, respectively. Subjective social status and optimism were negatively

associated with perceived stress and depression, respectively. Given decreasing protective factors over time in the mothers, targeted interventions to increase these factors and increase screenings for children and mothers could offset declines in mental health. Access to mental (or any medical) health care has historically been limited for immigrant communities, and further inhibited by stressful events such as the COVID-19 pandemic, and changes to the "public charge" rule, which penalizes immigrants for using Medicaid (Duncan and Horton 2020). Continued research on increasing access to healthcare, particularly for children, and best practices for enhancing protective factors for minority health is warranted.

Epigenetics as a mechanism of embodiment:

This study was an investigation of how immigration-related stress may impact the cardiometabolic health and epigenetic markers of Latinx immigrant mothers and children in Nashville, TN, considering recent increases in divisive rhetoric and anti-immigrant policies in the U.S. We compared stress and resilience factors reported by Latina immigrant mothers and their children (aged 5-13) from two time points spanning the 2016 presidential election with cardiometabolic health markers (BMI, waist circumference, and blood pressure). We also analyzed these factors in relation to DNA methylation in saliva of stress-related candidate genes (SLC6A4 and FKBP5), generated via bisulfite pyrosequencing. In general, we found some cardiometabolic markers to be associated with both stress and resilience factors in both mothers and children (e.g., social support and acculturation were associated with lower BMI in mothers, and discrimination with greater waist circumference in children). We also found some of these same stress and resilience factors to associate with methylation at various CpG sites in both tested stress-related genes. At both time points, mothers had significantly higher mean

methylation at SLC6A4 than children ($p<0.001$). More research is needed to determine the role of these epigenetic differences for understanding embodiment of stress across generations.

Epigenetic aging/epigenome-wide association study

We presented the first longitudinal study of epigenetic age and epigenomes in relation to psychosocial stress or resilience factors in children of immigrants. While findings were not always consistent across time points, overall, the bulk of the epigenetic age findings may indicate slower child development with more stress exposures, particularly at the later time point. Children aging more slowly may reach developmental milestones more slowly, which could be harmful for later life health. This is a relatively new hypothesis, as most adult research indicates faster aging with stress exposures, and very little has investigated epigenetic aging in children. We also identified some limited evidence for associations with stress or resilience factors genome-wide (e.g., only maternal legal status associated with any sites across both time points) or with candidate genes (e.g., only two sites associated at both time points), and little evidence that these factors modified change in methylation over time. Though we did not find many differences of large magnitude, if these findings can be replicated in larger samples and across racial/ethnic groups, they may suggest both psychosocial stress and resilience factors may be relevant contributors to racial disparities in health and aging through epigenetic mechanisms. Future studies are necessary to validate our findings and ascertain if methylation in these CpGs regions relates to health outcomes and racial disparities in health.

Our analysis of change in methylation over time before and after the 2016 presidential election may represent the first natural experiment of epigenomic associations influenced by a national election, which led to dramatic increases in threats to Latinx immigrant families. This is also one of the first studies to examine changes in methylation levels over time during this

sensitive window of development in children ages 6-13. In a study by Cao-Lei et al., they found that the number of days an expectant mother was deprived of electricity during an ice storm in 1998 Quebec predicted the epigenetic profile of the child (Cao-Lei et al. 2014). Cao-Lei et al. concluded for the first time that maternal hardship could predict the degree of DNA methylation; however, they did not look at changes over time. In another study, Simpkin et al. investigated DNA methylation patterns over time in blood over a 10-year span in elementary-aged Dutch children, but the focus was only on epigenetic aging measures, drawn from a fraction of the whole genome data (Simpkin et al. 2015). No similar study has been done in minority racial/ethnic children. Though our sample size in the longitudinal analyses was limited, we did find some evidence that stressors influenced changes in methylation and epigenetic age over time (e.g., greater maternal social status pre-election and fear of parent deportation post-election both associated with decreased Hannum age, p's$\leq$0.01).

STRENGTHS AND LIMITATIONS

Across all three studies, the participants lived only in Nashville, TN, and thus findings are not widely generalizable to other national or global regions. However, this study site represents an important site for US immigration studies, particularly because interior US cities have been newly targeted by the anti-immigrant policies of the current administration (2017; Farzan 2019). Like many studies of vulnerable populations, our sample size was unavoidably limited by inherent difficulties in recruiting a largely undocumented immigrant population (Hacker et al. 2015), and the difficulties in re-contacting participants who were reluctant to be found post-election. During my fieldwork, several factors influenced conducting interviews in Nashville, TN (Davidson County). For example, in April of 2018, just a week after our post-election study collection began, the largest ICE raid of the state took place, arresting 97 workers

at a meat processing plant in Morristown, TN, a city just 3 hours from Nashville and well known to many of our study participants. The governor of Tennessee, Bill Haslam, allowed a banning of "sanctuary cities" bill to become law, which requires local law enforcement officials to comply with ICE (Immigration and Customs Enforcement) requests to hold immigrants for purposes of deportation (Sher 2018). In several interviews, some women explained their neighbors and friends (many of whom were also participants in our first study) moved either back to their home country or towards more rural parts of Nashville directly because of this bill.

Despite the small sample size, however, we generated rich and detailed data on both positive and negative experiences in the lives across two generations of immigrants, and generated data from multiple biological systems and pathways that could be influenced by these experiences. Our survey data were obtained through extensive 2–3-hour interviews with the mothers and an hour with the children. Another strength of this study lies in the depth of data from two perspectives – mothers and children. This is especially important as children's perspectives on stress are very underrepresented in the literature, and provides insights on different epigenomic dynamics in different life stages. In addition to the longitudinal and cross-generational aspects, these papers are unique in integrating these types of rigorously collected data together within one study. Further, the timing of this study before and after a national political transition created an important contribution to the literature on immigrant health, and the biology of embodiment of stress.

FUTURE DIRECTIONS

The findings from this dissertation provide fundamental information for understanding how alterations in our social environment affect our bodies, and the mechanism that may link stressors with health outcomes. Like the majority of scientific research, my work has generated

more questions than answers. Despite the limitation of small sample sizes, we were able to identify some interesting suggestive trends to pursue in future studies, including reductions in mental health and resilience factors over time, warranting the need for further study and support of immigrant populations. Larger studies could examine interactions between immigrant status and sociocultural stressors on mental health outcomes, methylation of candidate genes, and epigenomic-wide association studies. More research in larger samples is also needed to validate the trends we identified. Functional studies in animal models and in vitro will be necessary to confirm if any gene-specific findings we report contribute to racial health disparities. In particular, gene editing technologies could be used to potentially alter methylation states in cell lines and across tissue types, to validate effects of any findings on cortisol response or other cellular phenotypes (Kang et al. 2019).

More longitudinal research is especially important to understand how the social environment impacts on epigenetic aging across childhood, and if faster or slower aging in children predisposes them to heightened chronic disease risk (like cardiometabolic diseases and mental health disorders). Future studies could also examine epigenetic aging across generations (in both mothers and children). Studies may also compare immigrant families to non-immigrant but underserved communities, to tease apart the burden of immigrant-relevant stressors specifically, and to learn more about processes that lead to embodiment of stress. However, in addition to focusing on epigenetic mechanisms of embodiment, it is also important not to lose sight of the structural forces that shape stressful environments and access to resilience resources for immigrant families in the first place, and to address policies to reduce inequalities in stress exposures before they impact future generations of children.

All research with vulnerable populations has an obligation to provide feedback and benefit to the participating community. In order to fulfill our original intentions to the community, I would like to have a follow-up workshop in Nashville to return overall results of the project to the participants, in an accessible and digestible manner. During this workshop, I would also like to discuss possible health interventions targeting mental health, cardiometabolic health, and epigenetics that may benefit the community, and connect participants with current mental health and clinical resources. We provided a flyer on community resources in 2018 which could be updated with newer relevant information for the participating families.

Approaching my research topic from various perspectives has led me to new research questions relating to health disparities. It would be interesting to explore how the sociopolitical environment in cities with higher immigrant populations, like San Diego, compares with a more interior city like Nashville. While one of our studies has directly compared discrimination, acculturation, and mental health outcomes between the cities, we have yet to compare epigenetic findings across sites. In the next stage of my research, I have developed an interest in the biological consequences of different social environments, such as socioeconomic status (SES) and social stress across the life course affecting health. Specifically, I am interested to explore the independent and cumulative role of childhood and adult SES and social stress (e.g., job stress, caregiving stress, adverse experiences, and discrimination) on genome-wide methylation, methylation age, changes in cardiometabolic health, and telomere length in adulthood with a much larger sample size.

Continued research on increasing access to healthcare, and best practices for enhancing protective factors for Latinx health is warranted. Additionally, access to mental (or medical) health care has historically been limited for immigrant Latinx communities, and has been further

inhibited by stressful events such as the COVID-19 pandemic, and changes to the “public charge” rule, which penalizes immigrants for using Medicaid (Duncan and Horton 2020).

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