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Nativity, Immigration, and Cardiovascular Health in Older Mexican-origin Adults

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Nativity, Immigration, and Cardiovascular Health in Older Mexican-origin Adults

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Nativity, Immigration, and Cardiovascular Health in Older Mexican-origin Adults

Tu My To

Abstract

Immigrants in the United States make up 13% of the total population and have been a critical component in the country's population growth. Previous studies have shown that immigrants tend to perform better in overall mortality and other health conditions, a phenomenon commonly known as the healthy immigrant effect. However, the growing literature on immigrant health has been primarily cross-sectional. A longitudinal perspective is needed, particularly since age of immigration or duration of stay in the receiving country can influence risk factors for adverse health conditions. Mexico is the most common country of origin for immigrants, and Hispanic adults carry significant cardiovascular burden due to their high levels of cardiovascular risk factors.

This dissertation focuses on two particular risk factors: low density lipoprotein cholesterol (LDL-C) and blood pressure, which are both strongly associated with myocardial infarction (MI) and stroke. In the first two chapters, a variable for immigration history is used and incorporates both nativity and age of immigration. The first chapter examines the role of immigration history on longitudinal changes in elevated LDL-C. The second chapter evaluates how immigration history affects trajectories of systolic blood pressure over time. Analyses also examine the associations between immigration history, LDL-C, and systolic blood pressure with MI/stroke. Chapter 3 extends the work of Chapter 2 by assessing the differences by nativity status in systolic and diastolic blood pressure trajectories before and after MI/stroke.

Analyses used data from the Sacramento Area Latino Study on Aging, a cohort study of community-dwelling older adults of Mexican-origin. Mixed effects and Cox proportional hazards models were used to address the research questions. Results indicate that participants born outside the United States and immigrated in later adulthood (i.e. after age 20) had poorer cardiovascular risk factors over time: they were more likely to have elevated LDL-C and had a faster rate of increase in systolic blood pressure. While risk of incident MI/stroke did not differ between each group of immigration history, there were nativity-related differences in blood pressure trajectories before and after MI/stroke. These results provide evidence to reevaluate previous perspectives on immigrant health and the healthy immigrant effect.

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Chapter 1

Longitudinal changes in low density lipoprotein cholesterol and risk of cardiovascular disease: the influence of immigration history in a cohort of Mexican-origin older adults

Introduction

An estimated 40 million immigrants live in the United States (US) and make up almost 13% of the total population.[1] The rapidly growing immigrant population in the US may influence population health. In 2015, almost half of all immigrants were Hispanic; in fact, Mexico is the most common sending country for immigrants living in the US, though that is expected to change with recent shifts in immigration patterns.[1,2] Prior studies, which have mainly focused on the Hispanic population, have reported a protective advantage against overall mortality and other health conditions among Hispanic immigrants when compared to US-born individuals.[3–7] Explanations for this healthy immigrant effect include, among other factors, 1) health selection: people who immigrate may often be wealthier, younger and healthier than those who choose to stay behind and 2) reverse migration: immigrants may return to their country of origin as they become ill, and are not counted in health estimates based in the receiving country.[8–10]

In addition to the place of birth, age at migration and the duration spent in the receiving country are also critical components of immigrant history. Social, economic, and behavioral factors influence health of immigrants. Individuals who migrate in early life (i.e. before age 20) to a wealthier country may have greater opportunities for more education and employment and may better assimilate to the country compared to older migrants.[11,12] As they continue to live in the receiving country, immigrants may adopt lifestyle behaviors that lead to changes in risk factors.[9] In a population-based study of older Mexican-origin adults, those who immigrated to the US in early life experienced higher risk of cardiovascular mortality than those who migrated later in life.[13] In another cohort study of older Mexican-origin immigrants, those who migrated to the US in mature adulthood (age 50 or older) had notably lower mortality risk compared to those who arrived in childhood (before age 18) or midlife (age 19-49).[10] However, few studies have

simultaneously examined nativity and age at migration and their roles in cardiovascular disease (CVD) within the immigrant population.

Heart disease is a leading cause of death for the Hispanic population. Previous studies on cardiovascular health among Hispanics have noted a cardiovascular-related mortality advantage that favors those of Hispanic origin compared to non-Hispanic whites (NHW).[7,14–16] However, some findings challenge this view, showing that some Hispanics may have similar or worse mortality risk compared to NHW.[16,17] Many of these studies tend to compare all Hispanics with to NHW, which may mask differences due to foreign nativity within the Hispanic population. There are profound differences between US- and foreign-born Hispanics, with self-reported prevalence of heart disease being 89% higher for US-born Hispanics.[14] Few studies have examined longitudinal changes in CVD risk factors within immigrant populations and in comparison to native-born counterparts. Since age and duration of exposure to the US host culture are critical components of the healthy immigrant effect, a longitudinal perspective is important to consider when assessing how CVD risk factors may differ between native and foreign born individuals.

Elevated low-density lipoprotein cholesterol (LDL-C), an important cardiovascular risk factor, has seldom been explored within this population.[18–20] A large population-based study of Hispanic/Latino adults indicated that prevalence of elevated LDL-C was 36.0%.[21] Notable differences have also been reported in mean LDL-C levels between Hispanics and non-Hispanic whites (around 7 mg/dL higher for Hispanic men but 2 mg/dL lower for Hispanic women compared to their non-Hispanic white counterparts).[22] However, differences in LDL-C levels have not been well documented between immigrant and native born Hispanic populations. Our study aims to bridge this gap by integrating nativity and age of immigration in order to examine

their associations with elevated LDL-C levels and CVD within a longitudinal context. First, we will test whether immigration history (nativity and age of immigration) influences the risk of elevated LDL-C level over ten years of study follow-up. Second, we will assess whether immigration history and elevated LDL-C are each associated with risk of myocardial infarction (MI)/stroke. Finally, we will also determine if the risk of incident MI/stroke by immigration history is modified by time under follow-up. We hypothesize that participants who immigrated to the US at an older age will be at lower risk of both elevated LDL-C and MI/stroke compared to those who are US-born or immigrated at a younger age.

Methods

Study Population

This analysis includes participants from the Sacramento Area Latino Study on Aging (SALSA). Details for SALSA have been published previously.[23] Briefly, SALSA is a longitudinal cohort study of 1,789 Mexican-Americans living in California's Sacramento Valley who were aged 58-101 years at baseline.[23] Study recruitment began in 1998-1999. Participants were followed every 12–15 months until 2008 with home visits that included clinical, cognitive, and functional assessments. Participants were briefly interviewed by telephone every six months between annual home visits to report changes in medications, update marital and vital status, and confirm contact information. Fasting blood samples were collected at baseline and at follow-up visit 3-6.

Only participants with information on nativity, age at immigration to the US, and at least one LDL-C measurement were included in the analyses. There were 10 people who did not report place of birth, 138 who were born outside the US but did not provide age at immigration or length of time in the US, 161 without baseline LDL-C measures and 117 lacking LDL-C

measures at any visit. Participants with baseline prevalent MI or stroke (n=291) or censored at baseline (n=51) were also excluded from analyses assessing risk of incident events. Total unique exclusions were 203 for analysis on odds of high LDL-C and 492 for analysis of incident MI/stroke. SALSA has been approved by the Institutional Review Boards at the University of Michigan, the Universities of California at San Francisco and Davis, and the University of North Carolina at Chapel Hill.

Measurements

Low-density lipoprotein cholesterol

Fasting blood samples for LDL-C ascertainment were collected at baseline, follow-up visit (FV) 3, FV4, FV5, and FV6. These samples were assayed using the LDL Direct Liquid Select from Equal diagnostics (No.7120), a homogeneous method used for directly measuring LDL-C in serum or plasma. Elevated LDL-C level was defined as a laboratory measurement of 130 mg/dL or above. The LDL-C level was dichotomized at 130 mg/dL according to standard guidelines, which define LDL-C ≥130 mg/dL as borderline high risk for adverse cardiovascular health.[24,25]

Myocardial infarction and stroke

Incident MI or stroke during the study was either fatal or non-fatal. Non-fatal events were determined by asking participants if a physician ever informed them that they had an MI or stroke. Fatal events were deaths where MI or stroke was listed anywhere in the death certificate. Mortality was ascertained using online obituary surveillance, the National Death Index, the Social Security Death Index, California vital statistics data, and interviews with family members of the deceased. Approximately 83% of deaths were reviewed using death certificates. For participants with both incident MI and stroke, only the earliest event was included in analyses.

Those who were alive at the end of the study without incident MI or stroke were censored at the date of last contact.

Immigration history

Participants were categorized as being born in the US or in Mexico/Latin America. Age at immigration was defined as immigration to the US before or at/after age 20 to distinguish those who immigrated in early life.[26,27] These were integrated into an immigration history variable with three categories: US-born, born in Mexico/Latin America and immigrated before age 20 (MLA<20), and born in Mexico/Latin America and immigrated at or after age 20 (MLA20+). All foreign-born individuals were categorized into one group as Mexico/Latin American as very few (i.e. less than 10%) were born outside Mexico.

Other covariates

Remaining covariates included baseline measurements of age in years, sex, body mass index (BMI, kg/m^2), presence of type 2 diabetes (yes/no) and hypertension (yes/no), smoking status (non-, former, or current smoker), acculturation score, and years of education. Diabetes was defined as a self-report of physician-diagnosed diabetes, the use of insulin or oral hypoglycemic agents, or a fasting glucose ≥126 mg/dL. Hypertension was defined as a self-report of physician-diagnosed hypertension, the use of antihypertensive medications, or a sitting systolic/diastolic blood pressure of ≥140/90 mmHg. Acculturation was quantified using the Acculturation Rating Scale for Mexican Americans Version II, a widely used measure of cultural orientation that assesses multiple dimensions of the acculturative process, including ethnic identity and co-ethnic social ties. In this scale, higher scores indicated greater Anglo orientation.[28] Statin use (yes/no) was time-updated to indicate current use; this allows for report of statin use to change at each visit time. Time (in years) was measured as the interval between baseline enrollment and the date

in which the LDL-C sample was collected. Baseline physical activity was measured by asking participants how many hours per week they spent on 17 different kinds of activities; a summary score was composed by summing up these individual item scores, resulting in a possible range of 0-51. Other covariates included baseline indicators for having access to a doctor (yes/no) and having health insurance (yes/no).

Statistical Analyses

ANOVA, Kruskal-Wallis, and chi-square tests were used to assess bivariate associations between participant characteristics and immigration history. To examine the association between immigration history and odds of elevated LDL-C, we used mixed effects logistic models with random intercepts in order to account for repeated measurements of LDL-C for each participant. Predictors in the base model (Model 1) consisted of immigration history, time, and the interaction term as a product of immigration history and time. We included the time interaction to determine if the association between immigration history and elevated LDL-C varied with time. Baseline age and sex were added in Model 2 as potential confounders. Remaining covariates were added in Model 3. Using this full model, we calculated the predicted probabilities of elevated LDL-C across the study period for each immigration history group and graphically displayed the results. We also conducted sensitivity analyses with the addition of physical activity level, access to a regular doctor, and having health insurance in the final model.

For analyses evaluating the association between immigration history, high LDL-C, and risk of incident MI/stroke, we used an extension of the Cox proportional hazards model that allowed for time-dependent effects. The extended Cox model was used in order to allow for time-dependent effects of immigration history (i.e. interaction between immigration history and

time), which would violate the proportional hazards assumption of the standard Cox model. Participants were observed from study enrollment to occurrence of an incident event (MI/stroke) or being censored (last date of contact or death). The base model (Model A) consisted of immigration history and time interaction with immigration history (the main effect of time is excluded in extended Cox models). Model B included baseline age and sex as potential confounders. Elevated baseline LDL-C and all other remaining covariates were added in the final model (Model C). Statin use was time-updated, allowing for survival time to depend on changing exposure values. All covariates were interacted with time in order to test for violation of proportional hazards assumption.We conducted sensitivity analyses with the addition of physical activity level, access to a regular doctor, having health insurance, and interaction between immigration history and elevated LDL-C in the final model, as well as the use of time-updated LDL-C (rather than using baseline LDL-C), which would assume a cross-sectional association between LDL-C and incident MI/stroke. To account for competing risk due to non MI/stroke-related deaths, we also ran sensitivity analyses using Fine-Gray models to examine association between immigration history and incident MI/stroke while accounting for non MI/stroke-related deaths as a competing event. All analyses were conducted using Stata 13 (StataCorp, College Station, TX).

Results

Table 1 shows the baseline characteristics of the sample by immigration history. In total, there were 1,586 participants and almost half of these individuals were born outside the US (47.7%). Immigration as a young adult or an older adult were nearly equal in the Mexican/Latin American-born group. Mean age at enrollment did not differ by immigration history as all three

groups were on average 70 years old, but there were statistically significantly more females in the MLA20+ group compared to the MLA<20 and US-born groups. Years of education were highest in the US-born group, followed by the MLA<20 group. People who immigrated after age 20 had the lowest amount of education with an average of 4.7 years. The average length of stay in the US was about as long for the MLA<20 group compared to the MLA20+ group.

All three groups had high BMI ($\geq$29 kg/m^2) but the US-born were highest at mean of 30.1 (p-value across the three groups=0.04). Most participants (70.5%) were hypertensive at baseline but there was no statistically significant difference across groups. Prevalent diabetes was highest in the US-born group (37.5%). Medical insurance coverage and access to a regular doctors or health professional was lowest for the MLA20+ group. Smoking status were significantly different across the groups; however, percentages of current smokers were very low (<12% for all three groups). Baseline LDL-C was highest and baseline HDL-C lowest in the MLA20+ group, and the percentage of those with borderline high LDL-C was also largest in this group (45.3%). By the end of the study, of those who remained and had an LDL measurement (n=719), elevated LDL-C was highest in the US-born group (14.3%). The number of incident MI/stroke cases was not significantly different across the three groups.

Table 2 presents results from the mixed logistic models examining within subject changes in immigration history and risk of elevated LDL-C over time. However, since immigration history is a predictor that does not vary within subjects, we focus on the predictors that do change over the course of the study – time. There is evidence that the subject-specific odds of the elevated LDL-C decreased over the study period (OR=0.79, 95% CI: 0.76, 0.83). Though the MLA<20 group appeared to be similar to the US-born group at baseline while the MLA20+ group was significantly different, the subject-specific changes in the odds of elevated LDL-C did

not depend on their immigration history (p-value for interaction>0.05 for both groups). This lack of statistically significant time by group interaction indicates that the trajectories of elevated LDL-C were not different across the groups of immigration history, though the magnitude of the interaction term suggests that these trajectories among the two foreign-born groups were protective over time. In Model 2, adjustment for covariates did not affect the associations found in Model 1, and neither age nor sex was significant. In the fully adjusted Model 3, the effect estimates remain nearly unchanged, though the association for the MLA20+ increased in magnitude. Other significant covariates in this model included diabetes status at baseline and current statin use; both covariates were associated with lower odds of elevated LDL-C. Sensitivity analyses with physical activity level, access to a regular doctor, and having health insurance showed no statistical significance for these covariates.

We used the final model in Table 2 to calculate odds of elevated LDL-C for each group of immigration history after one, five, and ten years compared to the odds at baseline. As shown in Table 3, the odds of elevated LDL-C decreased similarly all three groups. Figure 1 depicts the predicted probabilities of high LDL-C over the study period for each group, calculated from the fully adjusted model (Model 3) in Table 2. In this figure, those who were born outside the US and immigrated after age 20 started with a higher probability of high LDL-C; US-born participants had the lowest probability. However, as time progressed, the predicted probabilities for all three groups converged to a similar (and lower) value as they decreased at a similar rate over time. Notably, the MLA<20 appeared to be most similar to the US-born group.

Results from the extended Cox models for risk of incident MI/stroke in each of the immigration history groups are shown in Table 4. The magnitude of the interaction between immigration history and time was null and not statistically significant, indicating that time effects

were not different between these groups. Both foreign-born groups exhibited higher but non-significant risk of an incident event at baseline (Model A). In Model B, the addition of baseline age and sex to the model did not affect the associations found in Model A. Older age was a significant predictor of incident MI/stroke (HR=1.05, 95% CI: 1.03, 1.07) while being female was protective (HR=0.70, 95% CI: 0.53, 0.91). Inclusion of the remaining covariates (Model C) also did not change the statistical associations found in the previous two models (though the direction of the effect estimate for MLA20+ changed, the association was still not statistically significant). Baseline LDL-C was not associated with MI/stroke. Having diabetes at baseline was a significant predictor for incident MI/stroke (HR=1.86, 95% CI: 1.40, 2.46) as was baseline hypertension (HR=1.52, 95% CI: 1.09, 2.12). The remaining covariates were not statistically associated with MI/stroke. Since the interaction between immigration history and time was not significant in all three models, the proportional hazards (PH) assumption was held for this predictor and the extended Cox model was not needed. PH assumption also held for other covariates in the model as well. In our sensitivity analyses, the addition of physical activity, access to a regular doctor, having health insurance, and interaction between immigration history and LDL-C were not significant in the final model. Results using time-updated LDL-C in the Cox models were also not significant and near null, suggesting no cross-sectional association between current LDL-C status and incident MI/stroke. Results from sensitivity analyses using Fine-Gray models were not different from the Cox models.

Discussion

In this population-based study of older Mexican Americans, our results show that the early life migrants were most similar to the US-born individuals and that odds of elevated LDL-C were

highest for those who immigrated after age 20. Over the course of the study period, odds of elevated LDL-C decreased as an effect of time. However, there was no significant evidence that the trajectory of elevated LDL-C was different across the groups of immigration history nor that foreign nativity was protective against elevated LDL-C. Statins use among participants increased by the end of the study (highest for MLA<20 group at 44.4%) but was not significantly different between the three groups. The extended Cox models indicate that neither immigration history nor elevated LDL were associated with greater risk of incident MI/stroke. Furthermore, these models also suggested that there were no time-dependent associations between immigration history and MI/stroke. Our study adds to the literature as it is the first, to our knowledge, to examine longitudinal changes in elevated LDL-C within the context of nativity and age of immigration. It is also unique in examining how these immigration measures relate to cardiovascular outcomes.

The direction of the association between immigration history and elevated LDL-C in our results are noteworthy in that they appear to conflict with the healthy immigrant effect and reaffirm the need to further examine the relationship between immigration and health. There are several reasons that may explain the study results. According to Spallek *et al*., the migration experience should be approached through a life-course perspective, with the understanding that exposures occur before, during, and after migrating into the host country.[29] For example, the migration process itself can be a stressful experience that has lasting impacts on various conditions, including cardiovascular risk factors. The negative effects of stress due to migration can permeate long after the immigrants have settled into the host country. While immigrant populations are characterized by factors that are protective against adverse health outcomes, such as having better health behaviors, they are prone to risk accumulation as a result of the poorer conditions they may face.[30,31] A critical component of this risk accumulation includes

acculturative stress, where immigrants (particularly those who immigrated at an older age) often face difficulties in gaining employment, accessing resources such as housing or healthcare, adapting to a new culture, and learning a new language.[32] The stress that results from this, along with the poorer socioeconomic conditions in which they live, can have notable impacts on their risk factors for chronic conditions. Therefore, our results highlight the need to reexamine the healthy immigrant effect, particularly among older immigrants, and how it may pertain to CVD. Mechanisms that characterize the healthy immigrant effect may not fully explain the patterns in risk factors and health outcomes among immigrant and non-immigrant populations, and our findings suggest that this phenomenon may not always be consistently present in all immigrant populations.

The odds of elevated LDL-C declined over time, which is similar to declines in LDL-C levels associated with aging.[33,34] Interestingly, the decrease led to a convergence in all three groups. Similar convergence patterns are found in the literature, although they are typically in the context of immigrants having worse risk factor profiles over the course of their residence in the host country.[8,9] The characteristics of factors typically associated with elevated LDL-C are notable: prevalent obesity was similar in across the three groups, though presence of type 2 diabetes was lowest in the MLA<20 group. The decline of the immigrant health advantage over time can result from assimilation to the culture of the host country and adoption of less healthy lifestyles, leading immigrants to become more similar to their US-born counterparts and non-Hispanic whites.[32] While our study shows a convergence in the positive direction, it is nonetheless important to understand the varying influences on immigrant health that result in individuals becoming more similar to non-immigrants in the host country. These results

underline the age-related patterns of LDL-C decline among older populations that are not accounted for by differences in immigration history.

Previous literature on the association between nativity and cardiovascular health has been varied. Studies show that various immigrant groups have lower rates of cardiovascular events compared to native-born or long-term residents of the receiving country, or have lower incidence of coronary heart disease (CHD) compared to NHWs.[31,35] However, there is evidence that immigration and time spent in the host country are both associated with greater risk of subclinical atherosclerosis.[36] The lack of an association between immigration and MI/stroke in our study can be explained by a multitude of factors, including the race/ethnic makeup of the population studied, the health, social, and cultural behaviors of the participants, and the exposures they may face in the host country. While we see that the lipid risk profile of our participants changed over time according to their nativity and immigration history, this did not translate into higher risk for CVD. Sensitivity analyses indicate that LDL-C levels did not modify the association between immigration history and MI/stroke. In fact, elevated LDL-C itself was not associated with greater MI/stroke risk. This is consistent with evidence that finds the association between serum lipids (including LDL-C) and CVD to remain inconclusive, particularly for older adults, despite trials showing that reduction in LDL-C levels can be protective against cardiovascular outcomes.[37–39] Indeed, emerging data suggest that lipid particle sizes are likely more important in ascribing CVD risk, though little data are available in Mexican-origin populations.[40]

There are several limitations to our study. First, as we only examined adults of Mexican-origin, our study does not capture heterogeneity in CVD risk based on race/ethnicity of various immigrant populations. A previous systematic review found that Chinese immigrants had

differing patterns of CHD incidence and short term mortality after MI compared to NHWs and adults of South Asian origin. Host countries can differ by the social, cultural, and economic barriers immigrants may face, with critical implications for health outcomes. People immigrating from different countries may vary widely in terms of health status and behaviors, social and economic characteristics, and cultural factors, resulting in important differences that affect their interactions and exposures within the host country. Future studies can help determine if CVD risks vary across all US immigrant populations.

Second, our study population consisted of older adults, including many immigrants who have lived in the US for several decades. This would mean that any acculturative processes would have been in place, resulting in the groups being more similar to one another and to their US-born peers. Because our study captures the population long after they have arrived into the US, we are unable to accurately assess the differences in risk factors and health outcomes between recent immigrants, long-term immigrants, and native-born residents. Third, participants self-reported CVD risk factors and outcomes which might be subject to reporting bias, albeit validation of self-report in this cohort suggests moderate to high correlation with medical record review. Additionally, we did not include coronary revascularizations as part of our definition of incident CVD outcomes because this information was not collected.

Our study contributes to the existing literature in a number of ways. First, the longitudinal nature of the study population allows us to examine changes in elevated LDL-C over time and determine incident cases of cardiovascular events. Our population-based cohort has been followed over ten years and social, biological, and health changes were captured over the course of the study period. Furthermore, studies on immigrant health often compare foreign-born populations to NHWs, which can conflate differences due to both nativity and race/ethnicity. Our

study population consisted of only older Hispanic adults, which allowed us to capture any heterogeneity in health that may be primarily due to nativity within a particular ethnic group. Our findings also add to the growing literature on immigrant health, which is critical as rising trends in immigration pose to significantly shift US population dynamics. Immigration, in particular from Latin America, accounts for much of the population growth in the US in the past few decades. The foreign-born population living in the US increased from 9.6 million in 1970 to nearly 45 million in 2015 and is predicted to compose 18% of the total population by 2065.[2] In conclusion, our results highlight the heterogeneity of LDL-C changes by immigration history in a population of older adults primarily of Mexican-origin. Moreover, we observed no relationship between LDL-C and incident MI/stroke, highlighting the need to re-evaluate LDL-C as a singular risk factor for CVD. Overall, these findings underscore the need to better understand the role of CVD risk factors and health outcomes within the rapidly growing US immigrant populations, especially within the contexts of other social determinants of health.

References

1. U.S. Census Bureau. *The Foreign-Born Population in the United States: 2010*. *American Community Survey Reports*. Washington, D.C.; 2012.
2. Pew Research Center. *Modern Immigration Wave Brings 59 Million to U.S., Driving Population Growth and Change Through 2065: Views of Immigration's Impact on U.S. Society Mixed*. Washington, D.C.; 2015. doi:10.1017/CBO9781107415324.004.
3. Markides KS, Eschbach K. Aging, Migration, and Mortality: Current Status of Research on the Hispanic Paradox. *Journals Gerontol Ser B Psychol Sci Soc Sci*. 2005;60(Special Issue 2):S68-S75. doi:10.1093/geronb/60.Special_Issue_2.S68.
4. Singh GK, Hiatt RA. Trends and disparities in socioeconomic and behavioural characteristics, life expectancy, and cause-specific mortality of native-born and foreign-born populations in the United States, 1979-2003. *Int J Epidemiol*. 2006;35(4):903-919. doi:10.1093/ije/dyl089.
5. Abraído-Lanza AF, Dohrenwend BP, Ng-Mak DS, Turner JB. The Latino mortality paradox: A test of the "salmon bias" and healthy migrant hypotheses. *Am J Public Health*. 1999;89(10):1543-1548. doi:10.2105/AJPH.89.10.1543.
6. Argeseanu Cunningham S, Ruben JD, Venkat Narayan KM. Health of foreign-born people in the United States: A review. *Heal Place*. 2008;14(4):623-635. doi:10.1016/j.healthplace.2007.12.002.
7. Willey JZ, Rodriguez CJ, Moon YP, et al. Coronary Death and Myocardial Infarction among Hispanics in the Northern Manhattan Study: Exploring the Hispanic Paradox. *Ann Epidemiol*. 2012;22(5):303-309. doi:10.1016/j.annepidem.2012.02.014.
8. Antecol H, Bedard K. Unhealthy Assimilation: Why Do Immigrants Converge to

American Health Status Levels? *Demography*. 2006;43(2):337-360. doi:10.1353/dem.2006.0011.

9. McDonald JT, Kennedy S. Insights into the "healthy immigrant effect": health status and health service use of immigrants to Canada. *Soc Sci Med*. 2004;59(8):1613-1627. doi:10.1016/j.socscimed.2004.02.004.

10. Angel RJ, Angel JL, Díaz Venegas C, Bonazzo C. Shorter Stay, Longer Life: Age at Migration and Mortality Among the Older Mexican-Origin Population. *J Aging Health*. 2010;22(7):914-931. doi:10.1177/0898264310376540.

11. Leu J, Yen IH, Gansky SA, Walton E, Adler NE, Takeuchi DT. The association between subjective social status and mental health among Asian immigrants: Investigating the influence of age at immigration. *Soc Sci Med*. 2008;66(5):1152-1164. doi:10.1016/j.socscimed.2007.11.028.

12. Hermansen AS. Age at Arrival and Life Chances Among Childhood Immigrants. *Demography*. 2017;54:201-229. doi:10.1007/s13524-016-0535-1.

13. Colón-López V, Haan MN, Aiello AE, Ghosh D. The effect of age at migration on cardiovascular mortality among elderly Mexican immigrants. *Ann Epidemiol*. 2009;19(1):8-14. doi:10.1016/j.annepidem.2008.08.010.

14. Dominguez K, Penman-Aguilar A, Chang M-H, et al. Leading Causes of Death, Prevalence of Diseases and Risk Factors, and Use of Health Services Among Hispanics in the United States — 2009–2013. *Morb Mortal Wkly Rep*. 2015;64(17):469-478. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6417a5.htm.

15. Liao Y, Cooper RS, Cao G, Kaufman JS, Long AE, McGee DL. Mortality from coronary heart disease and cardiovascular disease among adult U.S. Hispanics: findings from the

National Health Interview Survey (1986 to 1994). *J Am Coll Cardiol*. 1997;30(5):1200-1205. http://www.ncbi.nlm.nih.gov/pubmed/9350915.

16. Swenson CJ. Cardiovascular Disease Mortality in Hispanics and Non-Hispanic Whites. *Am J Epidemiol*. 2002;156(10):919-928. doi:10.1093/aje/kwf140.

17. Hunt KJ, Williams K, Resendez RG, Hazuda HP, Haffner SM, Stern MP. All-cause and cardiovascular mortality among diabetic participants in the San Antonio Heart Study: Evidence against the "Hispanic Paradox." *Diabetes Care*. 2002;25(9):1557-1563. doi:10.2337/diacare.25.9.1557.

18. Ridker PM. LDL cholesterol: controversies and future therapeutic directions. *Lancet*. 2014;384(9943):607-617. doi:10.1016/S0140-6736(14)61009-6.

19. Parish S, Offer A, Clarke R, et al. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. *Circulation*. 2012;125(20):2469-2478. doi:10.1161/CIRCULATIONAHA.111.073684.

20. Tikhonoff V, Casiglia E, Mazza A, et al. Low-density lipoprotein cholesterol and mortality in older people. *J Am Geriatr Soc*. 2005;53(12):2159-2164. doi:10.1111/j.1532-5415.2005.00492.x.

21. Rodriguez CJ, Daviglus ML, Swett K, et al. Dyslipidemia Patterns among Hispanics/Latinos of Diverse Background in the United States. *Am J Med*. 2014;127(12):1186-1194. doi:10.1016/j.amjmed.2014.07.026.

22. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics—2016 Update. *Circulation*. 2016;133(e38):360. doi:10.1161/CIR.0000000000000350.

23. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of dementia in older latinos: the influence of type 2 diabetes mellitus, stroke and genetic

factors. *J Am Geriatr Soc*. 2003;51(2):169-177.

24. NCEP. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final. *Circulation*. 2002;106(25). doi:http://www.royalcommission.vic.gov.au/finaldocuments/summary/PF/VBRC_Summary_PF.pdf.

25. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American college of cardiology/American heart association task force on practice guidelines. *J Am Coll Cardiol*. 2014;63(25 PART B):2889-2934. doi:10.1016/j.jacc.2013.11.002.

26. Downer B, Garcia MA, Saenz J, Markides KS, Wong R. The Role of Education in the Relationship Between Age of Migration to the United States and Risk of Cognitive Impairment Among Older Mexican Americans. *Res Aging*. 2017:16402751770144. doi:10.1177/0164027517701447.

27. Hill TD, Angel JL, Balistreri KS, Herrera AP. Immigrant status and cognitive functioning in late-life: An examination of gender variations in the healthy immigrant effect. *Soc Sci Med*. 2012;75(12):2076-2084. doi:10.1016/j.socscimed.2012.04.005.

28. Cuellar I, Arnold B, Maldonado R. Acculturation Rating Scale for Mexican Americans-II: A Revision of the Original ARSMA Scale. *Hisp J Behav Sci*. 1995;17(3):275-304. doi:10.1177/07399863950173001.

29. Spallek J, Zeeb H, Razum O. What do we have to know from migrants' past exposures to understand their health status? a life course approach. *Emerg Themes Epidemiol*.

2011;8(1):6. doi:10.1186/1742-7622-8-6.

30. Fenelon A. Revisiting the Hispanic mortality advantage in the United States: The role of smoking. *Soc Sci Med*. 2013;82:1-9. doi:10.1016/j.socscimed.2012.12.028.

31. Tu J V., Chu A, Rezai MR, et al. Incidence of Major Cardiovascular Events in Immigrants to Ontario, Canada: The CANHEART Immigrant Study. *Circulation*. 2015;132(16):1549-1559. doi:10.1161/CIRCULATIONAHA.115.015345.

32. Goldman N. Will the Latino Mortality Advantage Endure? *Res Aging*. 2016;38(3):263-282. doi:10.1177/0164027515620242.

33. Ettinger E, Wahl P, Kuller L, et al. Lipoprotein lipids in older people. Results from the Cardiovascular Health Study. *Circulation*. 1992;86:858-869.

34. Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and HDL Cholesterol Decrease With Age in Older Men and Women: The Rancho Bernardo Study 1984–1994. *Circulation*. 1997;96(1):37-43. doi:10.1161/01.CIR.96.1.37.

35. Jin K, Ding D, Gullick J, Koo F, Neubeck L. A Chinese Immigrant Paradox? Low Coronary Heart Disease Incidence but Higher Short Term Mortality in Western Dwelling Chinese Immigrants: A Systematic Review and Meta-Analysis. *J Am Heart Assoc*. 2015;4(12):e002568. doi:10.1161/JAHA.115.002568.

36. Lear SA, Humphries KH, Hage-Moussa S, Chockalingam A, Mancini GBJ. Immigration presents a potential increased risk for atherosclerosis. *Atherosclerosis*. 2009;205(2):584-589. doi:10.1016/j.atherosclerosis.2008.12.037.

37. Psaty B, Anderson M, Kronmal R, et al. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. *J Am Geriatr Soc*. 2004;52(10):1639-1647. doi:10.1111/j.1532-5415.2004.52455.x.

38. Krumholz HM, Seeman TE, Merrill SS, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA*. 1994;272(17):1335-1340. doi:10.1001/jama.272.17.1335.

39. Cholesterol Treatment Trialists' Collaboration. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380(9841):581-590. doi:10.1016/S0140-6736(12)60367-5.

40. Kuller L, Arnold A, Tracy R, et al. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. *Arterioscler Thromb Vasc Biol*. 2002;22(7):1175-1180. doi:10.1161/01.ATV.0000022015.97341.3A.

Table 1.1. Baseline Characteristics of SALSA Participants by immigration history (n=1586)

	Place of Birth			
	US-born n=829 (52.3%)	**Mexico/LA, immigrated at age <20 n=177 (11.2%)**	**Mexico/LA, immigrated at age 20+ n=580 (36.6%)**	**p-value**
Age at enrollment, mean (SD)	70.0 (6.3)	71.0 (7.7)	70.7 (7.2)	0.32
Female, n (%)	468 (56.5)	91 (51.4)	366 (63.1)	0.01
Years of education, mean (SD)	9.7 (4.9)	6.5 (4.9)	4.7 (4.7)	<0.001
Years in the US, mean (SD)	*N/A*	60.1 (12.1)	31.6 (15.6)	<0.001
Acculturation score, mean (SD)	45.5 (9.6)	37.5 (11.0)	26.8 (7.0)	<0.001
Baseline BMI, kg/m2, mean (SD)	30.1 (6.1)	28.9 (4.6)	29.5 (5.9)	0.04
Hypertensive at baseline, n (%)	584 (70.5)	121 (68.4)	391 (67.4)	0.47
Type 2 diabetes at baseline, n (%)	311 (37.5)	49 (27.7)	162 (27.9)	<0.001
Has medical insurance, n (%)	805 (97.5)	161 (91.0)	477 (82.4)	<0.001
Has a regular doctor/health professional, n (%)	795 (96.3)	162 (91.5)	449 (77.6)	<0.001
Smoking status at baseline, n (%)				
Never	355 (42.9)	74 (41.8)	300 (51.8)	
Former	379 (45.8)	82 (46.3)	215 (37.1)	0.01
Current	93 (11.3)	21 (11.9)	64 (11.1)	
Taking statins at baseline, n (%)	78 (9.4)	17 (9.6)	49 (8.5)	0.80
Baseline HDL-C level, mg/dL, mean (SD)	51.9 (13.8)	54.2 (14.8)	51.4 (12.7)	0.11
Baseline HDL-C <40 mg/dL, n (%)	128 (15.7)	21 (12.0)	88 (15.6)	0.45
Baseline LDL-C level, mg/dL, mean (SD)	119.8 (35.0)	121.2 (32.6)	126.6 (33.8)	<0.01
Baseline LDL-C 130+ mg/dL, n (%)	296 (36.3)	67 (38.3)	255 (45.3)	<0.01
Had MI/stroke at any time, n (%)	281 (32.3)	54 (30.3)	165 (27.9)	0.20
Incident MI/stroke during the study, n (%)	115 (16.3)	27 (17.9)	87 (16.9)	0.88

*Mexican/LA=Mexican/Other Latin American-born, BMI=body mass index, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, CV=cardiovascular

Table 1.2. Mixed effects logit models for association between immigration history and elevated LDL-C 130+ mg/dL, SALSA (n=1586)

	Model 1				Model 2				Model 3			
	OR	**95% CI**		**p-value**	**OR**	**95% CI**		**p-value**	**OR**	**95% CI**		**p-value**
Immigration history *(ref=US-born)*	1.00				1.00				1.00			
Mexican/LA, immigrated at age <20	1.18	0.73	1.89	0.50	1.19	0.74	1.91	0.47	1.21	0.71	2.04	0.48
Mexican/LA, immigrated at age 20+	1.77	1.30	2.42	<0.001	1.76	1.29	2.41	<0.001	2.02	1.30	3.14	<0.01
Time since baseline	0.79	0.76	0.83	<0.001	0.79	0.76	0.83	<0.001	0.83	0.79	0.86	<0.001
Immigration history x Time *(ref=US-born)*	1.00				1.00				1.00			
Mexican/LA, immigrated at age <20	0.93	0.85	1.02	0.14	0.93	0.85	1.02	0.14	0.92	0.83	1.02	0.12
Mexican/LA, immigrated at age 20+	0.95	0.89	1.01	0.08	0.95	0.89	1.01	0.08	0.95	0.89	1.01	0.11
Age at baseline, *years*					0.99	0.98	1.01	0.48	0.99	0.97	1.01	0.44
Female					1.12	0.87	1.43	0.38	1.05	0.79	1.41	0.73
BMI at baseline, kg/m^2									0.98	0.96	1.00	0.08
Type 2 diabetes at baseline									0.50	0.37	0.67	<0.001
Hypertensive at baseline									0.90	0.67	1.20	0.48
Statins use, time-updated									0.16	0.11	0.23	<0.001
Smoking status at baseline *(ref=nonsmoker)*									1.00			
Former smoker									0.87	0.64	1.17	0.35
Current smoker									0.91	0.57	1.44	0.68
Acculturation score									1.01	0.99	1.03	0.18
Years of education									0.99	0.96	1.03	0.68

*Mexican/LA=Mexican/Other Latin American-born, OR = odds ratio

Table 1.3. Odds ratios of elevated LDL-C over ten years within groups of immigration history, SALSA (n=1586)

Immigration History	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
	At baseline	*After one year of follow-up*	*After five years of follow-up*	*After ten years of follow-up*
US-born	1.00	0.83 (0.79, 0.86)	0.39 (0.31, 0.48)	0.15 (0.10, 0.23)
Mexican/LA, immigrated at age <20	1.00	0.76 (0.69, 0.84)	0.26 (0.16, 0.41)	0.07 (0.03, 0.17)
Mexican/LA, immigrated at age 20+	1.00	0.78 (0.75, 0.82)	0.30 (0.23, 0.38)	0.09 (0.05, 0.15)

*p-values all <0.001
OR = odds ratio, derived from the final model. Mexican/LA = Mexican/Other Latin American-born

Figure 1.1. Predicted Probability of LDL-C 130+ mg/dL by Immigration History.

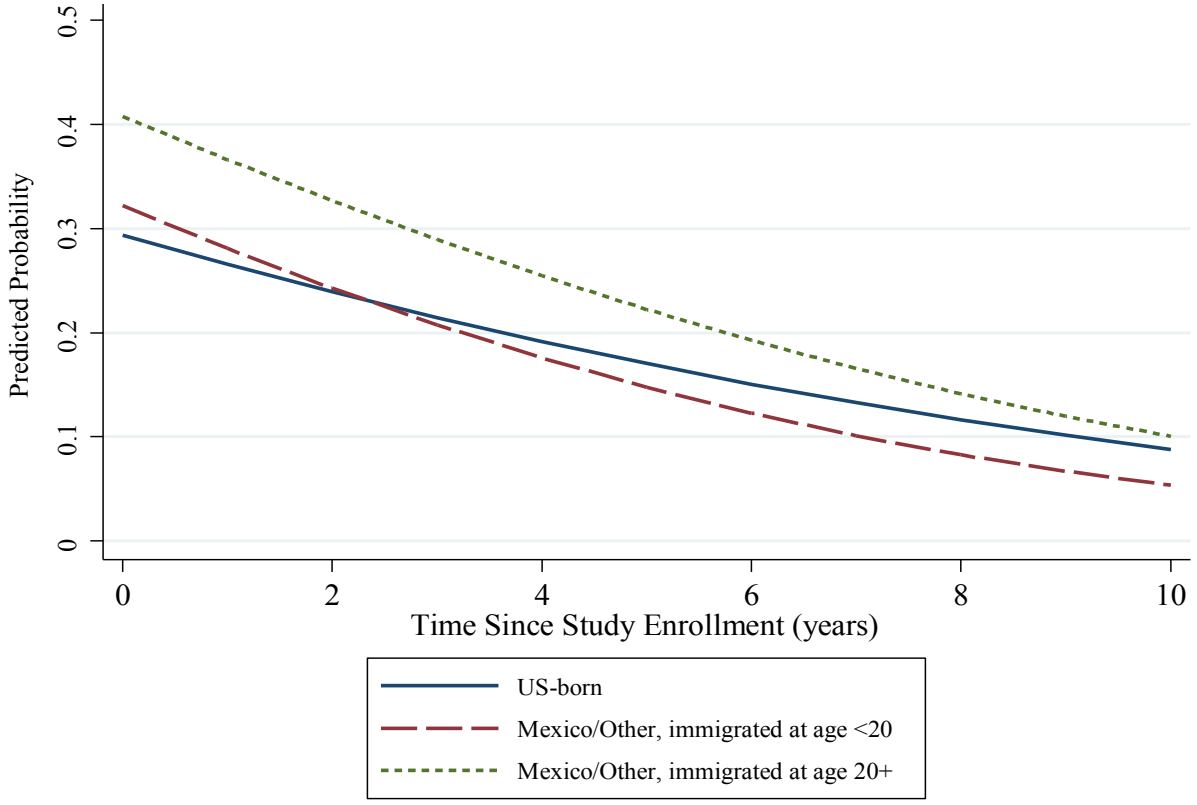


Table 1.4. Cox Model for the association between immigration history and incident myocardial infarction/stroke (n=1297)

	Model A				Model B				Model C			
	HR	**95% CI**		**p-value**	**HR**	**95% CI**		**p-value**	**HR**	**95% CI**		**p-value**
Immigration history *(ref=US-born)*	1.00				1.00				1.00			
Mexican/LA, immigrated at age <20	1.30	0.55	3.09	0.55	1.20	0.50	2.84	0.68	1.17	0.49	2.83	0.72
Mexican/LA, immigrated at age 20+	1.13	0.62	2.04	0.70	1.12	0.62	2.02	0.72	0.94	0.48	1.82	0.85
Immigration history x Time (*ref=US-born)*	1.00				1.00				1.00			
Mexican/LA, immigrated at age <20	0.96	0.80	1.16	0.68	0.96	0.80	1.15	0.66	0.96	0.80	1.16	0.70
Mexican/LA, immigrated at age 20+	0.98	0.87	1.11	0.75	0.98	0.87	1.11	0.75	0.98	0.87	1.11	0.77
Age at baseline, *years*					1.05	1.03	1.07	<0.001	1.05	1.03	1.07	<0.001
Female					0.70	0.53	0.91	0.01	0.74	0.55	0.99	0.04
LDL-C 130+ mg/dL, baseline									1.13	0.86	1.50	0.38
BMI at baseline, kg/m^2									1.01	0.99	1.04	0.27
Type 2 diabetes at baseline									1.86	1.40	2.46	<0.001
Hypertensive at baseline									1.52	1.09	2.12	0.01
Statins user, time-updated									0.83	0.58	1.19	0.31
Smoking status at baseline *(ref=non-smoker)*									1.00			
Former smoker									1.14	0.83	1.56	0.42
Current smoker									1.27	0.79	2.03	0.32
Acculturation score									0.99	0.97	1.01	0.27
Years of education									1.00	0.96	1.03	0.85

*Mexican/LA = Mexican/Other Latin American-born, LDL-C = low density lipoprotein cholesterol, BMI = body mass index

Chapter 2

Nativity and age of immigration: the association with systolic blood pressure trajectories and risk of cardiovascular disease

Introduction

High blood pressure is consistently associated with increased risk of cardiovascular disease (CVD).[1] In addition, racial, ethnic, and age differences in hypertension prevalence are also documented. For example, hypertension prevalence is nearly 30% for Hispanic men and women.[2,3] Furthermore, hypertension awareness, treatment, and control are lowest within Hispanics compared to other races/ethnicities.[4] The Hispanic population in the United States (US) has grown by 40 million between 1980 and 2014, calling for a greater need to address and understand cardiovascular risk factors among these individuals.[5] Immigrants comprised 35% of the US Hispanic population, and much evidence suggests that nativity influences health outcomes over the long term.[5]

Findings from the National Health Interview Survey indicate that the odds of hypertension is higher in US-born adults compared to foreign-born adults.[2] These findings are critical as the rapidly growing immigrant population in the US comprises almost 13% of the total US population, with Mexico as the most common country of origin.[6,7] The protective influence of foreign nativity on health has been documented in the literature, specifically among Hispanics, and is commonly known as the healthy immigrant effect. Studies have reported a protective advantage against overall mortality and other health conditions within the Hispanic immigrant population when compared to US-born individuals.[8–12] In particular, Hispanics may have a cardiovascular-related mortality advantage compared to non-Hispanic whites.[12–15] However, examinations of cardiovascular risk factors in Hispanics, both US- and foreign-born, have primarily been cross-sectional.[16–18]

Studies on immigrant health tend to compare all Hispanics to non-Hispanic whites, which may mask differences due to foreign nativity among Hispanics. Differences in health status can

exist even within the foreign-born group, resulting from factors such as age of immigration. According to the United Nations, almost 16% of all migrants are under the age of 20.[19] The age in which an individual immigrates can be critical for various social, economic, and behavioral conditions, including receiving more education or learning a new language, greater access to jobs and resources, and adoption of new lifestyle behaviors. Compared to immigration at a later age, immigration during formative years in childhood and young adulthood can influence processes that result in variations in socioeconomic opportunities and health outcomes in later life.[20] Previous studies evaluating both nativity and age of immigration simultaneously found that early-life Hispanic migrants (i.e. those who immigrated to the US before age 20) had cognitive functioning similar to their US-born counterparts and exhibit greater cardiovascular death rates than later-life migrants.[21–23]

Building on previous work in immigrant health and drawing from health patterns for US-born versus foreign-born adults, we consider how cardiovascular health in older Hispanics can vary depending on immigration history, a collective term that incorporates both nativity and age of immigration. First, we examine how immigration history may be associated with systolic blood pressure (SBP) and how this association changes longitudinally. Second, we will assess whether immigration history and SBP are associated with risk of myocardial infarction (MI)/stroke. We hypothesize that foreign-born individuals will exhibit higher SBP at baseline and have faster rates of SBP increase over time, and that they will have greater risk of MI/stroke.

Methods

Study Population

Participants come from the Sacramento Area Latino Study on Aging (SALSA). Details for SALSA have been published previously.[24] Briefly, SALSA is a longitudinal cohort study of 1,789 Mexican-Americans living in California's Sacramento Valley who were aged 58-101 years at baseline.[24] Study recruitment began in 1998-1999 and participants were followed every 12–15 months until 2008. Follow-ups consisted of annual home visits that included clinical, cognitive, and functional assessments. Participants also had telephone interviews every six months between annual home visits to report changes in medications, update marital and vital status, and confirm contact information.

Participants were included in analyses if they provided information on nativity, age at immigration to the US, and had at least one SBP measurement. There were 10 people who did not report place of birth, 138 who were born outside the US but did not provide age at immigration or length of time in the US, 143 without baseline SBP measure and 94 without SBP measures at any visit. Participants with baseline prevalent MI or stroke (n=291) or censored at baseline (n=51) were also excluded from analyses assessing risk of incident events. In total, there were 1,599 participants for analysis on average SBP and 1,352 for analysis of incident MI/stroke. SALSA has been approved by the Institutional Review Boards at the University of Michigan, the Universities of California at San Francisco and Davis, and the University of North Carolina at Chapel Hill.

Measurements

Systolic blood pressure

Sitting SBP (mmHg) was measured at baseline and at follow-up visits (FV) 1 through 6. At each visit, participants were seated for at least five minutes before having their blood pressure measured. Two measurements were taken with an Omrom automated blood pressure machine, five minutes apart, which were averaged.

Myocardial infarction and stroke

Analyses for incident MI or stroke during the study included either fatal or non-fatal events. Non-fatal events were participants' self-report of a physician informing them that they had an MI or stroke. Fatal events were deaths where MI or stroke was listed anywhere in the death certificate. Mortality was ascertained using online obituary surveillance, the National Death Index, the Social Security Death Index, California vital statistics data, and interviews with family members of the deceased. Only the first event (fatal or nonfatal) was included for participants who had either or both incident MI and stroke. Those who were alive at the end of the study without incident MI or stroke were censored at the date of last contact. During follow-up, there were 55 deaths due to MI or stroke among individuals who did not previously report having either of these conditions; these deaths were counted as a MI/stroke case in the analyses.

Immigration history

Participants reported their nativity as born in the US or in Mexico/other Latin American country. There were fewer than ten people who were born in Latin American countries outside of Mexico; therefore, all foreign-born individuals were aggregated into Mexico/Latin America. Similar to previous literature, age at immigration was defined as immigration to the US before or at/after age 20 to distinguish those who immigrated in early life.[21,22] These information were then coded

into an immigration history variable with three categories: 1) US-born, 2) born in Mexico/Latin America and immigrated before age 20 (MLA<20), and 3) born in Mexico/Latin America and immigrated at or after age 20 (MLA20+).

Other covariates

Remaining covariates included sex, years of education, and the following baseline measurements: age in years (mean-centered), body mass index (BMI, kg/m^2, mean-centered), type 2 diabetes status (yes/no), smoking status (non-, former, or current smoker), and acculturation score. Diabetes was defined as a self-report of physician-diagnosed diabetes, the use of insulin or oral hypoglycemic agents, or a fasting glucose ≥126 mg/dL. Acculturation was quantified using the Acculturation Rating Scale for Mexican Americans Version II, a measure of cultural orientation that assesses multiple dimensions of the acculturative process, including ethnic identity and co-ethnic social ties. In this scale, higher scores indicated higher Anglo orientation.[25] Other covariates included time-updated antihypertensive medication use (none, one, two or more). The time variable is the interval between baseline enrollment and the most current date when SBP was measured.

Statistical Analyses

We assessed bivariate associations between participant characteristics and immigration history using ANOVA, Kruskal-Wallis, and chi-square tests. We examined the association between immigration history and SBP over a ten-year period using linear mixed models with random intercepts in order to account for repeated measurements of SBP. Predictors in the base model (Model 1) consisted of immigration history, time, and the interaction term as a product of immigration history and time. We included a time by immigration history interaction to

determine if the association between immigration history and average SBP varied with time and tested for statistical significance using the likelihood ratio test. Remaining covariates were added in Model 2. Using this adjusted model, we calculated the predicted trajectories of SBP across the study period for each immigration history group and graphically displayed the results. We conducted sensitivity analyses to determine the influence of access to medical care on average SBP by adding in variables for having medical insurance and a regular doctor at baseline to the final model.

We used Cox proportional hazards models to evaluate the association between immigration history and risk of incident MI/stroke while adjusting for SBP and other covariates. Our Cox models consisted of two models: one using a 10mmHg difference in *baseline* SBP and one using a 10mmHg *change* in *time-updated* (or current) SBP. Use of time-updated SBP allows for hazards of MI/stroke to change depending on updated values of the exposure. Participants were observed from study enrollment to occurrence of an incident event (MI/stroke) or being censored (last date of contact or death). The base model (Model A) consisted of immigration history, age at baseline, and sex. We tested for statistical significance of immigration history in Model A using the likelihood ratio test. Baseline SBP and all remaining covariates were added to the first adjusted model (Model B). Similarly, time-updated SBP was added to base model, along with all remaining covariates, to create a second adjusted model (Model C). Antihypertensive medication use was time-updated. We also conducted sensitivity analyses by adding the following terms to the final adjusted models: interaction between immigration history and SBP (both baseline and time-updated), and interaction between immigration history and antihypertensive medication use. We checked for violations of the proportional hazards

assumption using log-log survival curves and Schoenfeld residuals. All analyses were conducted using Stata 14 (StataCorp, College Station, TX).

Results

Baseline descriptive statistics by immigration history are shown in Table 1. There were 1,599 participants in the study and over half were born outside the US (52.2%). There were more foreign-born individuals who immigrated at or after age 20 than before age 20 (36.7% versus 11.1%). Mean age at study enrollment did not differ statistically by immigration history. There were more females in the MLA20+ group compared to the US-born and MLA<20 groups. Baseline SBP was not statistically significantly different across immigration history groups. Many participants were hypertensive at baseline and prevalence was slightly higher among the US-born group (70.3%). Both foreign-born groups were more likely compared to the US-born group to not be using any antihypertensive medication at baseline. Prevalence of baseline diabetes was also higher among the US-born (37.6%) compared to either immigrant group. There was no difference in this between the two immigrant groups. All three groups had high BMI ($\geq$29 kg/m^2) but the US-born were statistically highest at mean of 30.2. Years of education were highest in the US-born group, followed by the MLA<20 group. Incident MI/stroke was not statistically different across the three groups.

Table 2 presents results for the mixed linear models examining within subject changes in immigration history and the association with average SBP. There is evidence that subject-specific changes in SBP over time varied by the immigration history of the participant (likelihood ratio test p-value<0.001). In particular, there is a significant interaction between the MLA20+ group and time (ß=0.63, 95% CI: 0.32, 0.95, p-value<0.001). For US-born participants,

SBP increased by 0.45 mmHg per year (95% CI: 0.25, 0.66, p-value<0.001). In the MLA<20 group, SBP increased by 0.48 mmHg per year (95% CI: 0.06, 0.91, p-value=0.03). In the MLA20+ group, SBP increased by 1.09 mmHg per year 95% CI: 0.84, 1.33, p-value<0.001). At baseline, immigration history was not significantly associated with SBP, even after adjustment for covariates. Adjustment for covariates did not affect the direction of change or change the magnitude of the estimates of the main predictor variables.

Baseline measures of education, age and type 2 diabetes were significantly associated with SBP. Current use of antihypertensive medication was not associated with SBP. Sensitivity analyses with indicators for access to a regular doctor and having health insurance showed no statistical significance for these covariates. We used the final model in Table 2 to calculate predicted trajectories of SBP over a ten year period for each group of immigration history, as shown in Figure 1. In this figure, those who were born outside the US had lower SBP values at baseline, though this was not significant. However, as time progressed, average SBP increased at a faster rate for the MLA20+ compared to the US-born group and the MLA<20 group. The SBP trajectory of US-born and MLA<20 individuals maintained a slower and parallel increase in SBP over the study period.

Results from the Cox models for risk of incident MI/stroke are shown in Table 3. The risk of incident MI/stroke was not associated with immigration history even after adjusting for baseline age and sex (Model A, likelihood ratio test p-value=0.98). In Model A, older age was a statistically significant predictor of higher risk of incident MI/stroke (HR=1.05, 95% CI: 1.04, 1.07) while being female was protective (HR=0.74, 95% CI: 0.57, 0.96). A 10 mmHg increase in both baseline and time-updated SBP led to a 6-12% increase in MI/stroke risk, though this was only significant in Model B after adjusting for baseline SBP (HR=1.12, 95% CI: 1.04, 1.19).

Having diabetes at baseline was also a significant predictor for incident MI/stroke in both Models B (HR=1.79, 95% CI: 1.35, 2.37) and C (HR=1.79, 95% CI: 1.35, 2.38). The remaining covariates were not statistically associated with MI/stroke, except for time-updated values of using only one anti-hypertensive medication. In our sensitivity analyses, we included an interaction term between immigration history and SBP (both baseline and time-updated), and interaction between immigration history and antihypertensive medication use. These terms were not statistically significant. We confirmed that the proportional hazards assumption was held.

Discussion

In this cohort of US- and foreign-born older Mexican Americans, foreign nativity was associated with a faster increase in SBP over time compared to the US-born group. Specifically, within the foreign-born groups, we found that age of immigration resulted in differences in the rate of increase. Those who immigrated into the US in later adulthood exhibited the most rapid SBP increase out of all three groups of immigration history. Those who immigrated in childhood or young adulthood (i.e. before age 20) were very similar to the US-born group and did not differ from the US-born in SBP change over time. Despite being associated with faster change in SBP, immigration history was not significantly associated with incident MI/stroke risk. A ten-mmHg increase in SBP alone resulted in higher risk of MI/stroke, though this was only statistically significant for baseline values of SBP. The association between SBP and MI/stroke risk did not differ across the groups of immigration history.

We observed a general increase in SBP during the study, which is consistent with studies in the literature that suggest SBP tends to increase with time, particularly among older adults.[26–28] With advancing age in older adults, blood pressure shifts to predominately systolic blood

pressure, leading to higher prevalence of systolic hypertension in this population.[29] While various age-related processes affect systolic changes in blood pressure, it is commonly due to loss of elasticity in the arterial walls and thickening and stiffening of the arteries that lead to higher hypertension prevalence.[30,31] Our study population exhibited the same pattern of increasing SBP over the ten years of study follow-up, though this trend differed by their nativity and age of immigration.

Our findings that show lack of statistically significant differences in baseline SBP between the three groups of immigration history, a more rapid increase in SBP for the late-migrant group compared to the US-born, and no association between immigration history and MI/stroke are unexpected and conflict with the healthy immigrant effect, which would suggest more favorable cardiovascular health among those of foreign nativity. Though the healthy immigrant effect can be explained by many factors, common explanations include selection of healthy migrants into the receiving country, reverse migration of unhealthy individuals to the sending country, and more favorable health behaviors among immigrants.[32,33] However, the healthy immigrant effect may not be consistently true for all immigrant groups. A study on Canadian immigrants found that the health advantage against cardiovascular events and mortality was not present among recent migrants or those with no previous education.[34] A meta-analysis, also on Canadian immigrants, showed that the healthy immigrant effect for health status and morbidity can vary across groups of immigrants, particularly across the different stages in the life-course.[35] In Europe, comparisons of health status between native- and foreign-born individuals can depend on the country in which immigrants settle, with the healthy immigrant effect being present in only some countries.[36] It is worth noting that this effect can vary widely due to a multitude of factors, and our results adds to current findings that the healthy immigrant

effect may not always be consistently present in immigrant populations.

The role of stress can also explain the differences in SBP change between native- and foreign-born individuals in our results. Immigration to a host country can be a stressful experience with lasting impacts on physical and mental health. The negative effects of stress due to migration can permeate long after the immigrants have settled into the host country, and immigrants are prone to risk accumulation as a result of the poorer socioeconomic conditions they may face.[37] One of these components include acculturative stress, where immigrants often face difficulties in gaining employment, accessing resources such as housing or healthcare, adapting to a new culture, and learning a new language.[33] Chronic stress can have negative impacts on health outcomes, including higher blood pressure.[38] Pathways involving chronic stress can also include age of immigration, as migrating during formative years (such as in childhood) can affect language acquisition and socioeconomic attainment.[20] Early migration can lead to better opportunities that mitigate the effects of stress, leading to better health outcomes. Conversely, immigrating in later life can worsen existing disparities that lead to poorer health. Our results show that the US-born and MLA<20 groups were more similar to each other than to the MLA20+ group, underlining that immigrating early in life can result in greater similarities to US-born counterparts.

The statistically significant association between baseline SBP and MI/stroke suggests that SBP history may be a stronger predictor of cardiovascular outcomes than current SBP. Few studies have compared current versus prior measures of blood pressure as predictors for CVD or for other health outcomes, particularly among Hispanics. For example, a previous study comparing the association for current versus remote (i.e. previous) blood pressure with cognitive decline, found that only blood pressure measured nine years prior was significantly associated

with errors on a mental status test.[39] A large Finnish study using history of hypertension status ascertained twenty years prior found it to be strong predictors of stroke and stroke mortality.[40] Our results provide insight on the use of either past SBP or current SBP as a predictor of cardiovascular events.

Our study has several limitations. First, we were not able to assess heterogeneity in CVD risk for foreign-born populations of various races and ethnicities since our cohort consisted of only Hispanic, mostly Mexican-origin, adults. Immigrants of various races and ethnicities vary widely in health status and behaviors, social and economic characteristics, and cultural factors, resulting in important differences that affect their interactions and exposures within the host country. Future studies can help determine if CVD risks vary across all US immigrant populations. Second, our study population consisted of only older adults, including foreign-born individuals who have lived in the US for several decades. It is possible that these individuals are very similar to their US-born peers due to their long residence in the US. Because our study captures the population long after they have arrived, we are unable to accurately assess the differences in risk factors and health outcomes between recent immigrants, long-term immigrants, and native-born residents.

A major strength of this study is the large sample size and population-based longitudinal design, which allowed us to study the changes in SBP over ten years and discern the differences between the groups of immigration history. Few studies, particularly those on immigrant health, have been able to assess longitudinal changes in cardiovascular risk factors. Furthermore, studies often compare foreign-born populations to non-Hispanic whites, which can conflate differences due to both nativity and race/ethnicity. Our study population consisted of only older Hispanic adults, which allowed us to capture any heterogeneity in health that may be primarily due to

nativity within a particular ethnic group. Our findings also add to the growing literature on immigrant health, which is critical as rising trends in immigration pose to significantly shift US population dynamics.

In conclusion, our results highlight the heterogeneity of longitudinal changes in SBP by immigration history in a population of older adults primarily of Mexican-origin. Moreover, we observed no relationship between immigration history and incident MI/stroke, and that the association between SBP and incident MI/stroke was only significant for SBP measured at the beginning of the ten-year study initiation. Overall, these findings underscore the need to better understand the role of CVD risk factors and health outcomes within the rapidly growing US immigrant populations and to reevaluate the role of the healthy immigrant effect within the contexts of different immigrant populations.

References

1. Vasan RS, Larson MG, Leip EP, et al. Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease. *N Engl J Med*. 2001;345(18):1291-1297. doi:10.1056/NEJMoa003417.
2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics—2016 Update. *Circulation*. 2016;133:e38-e360. doi:10.1161/CIR.0000000000000350.
3. Sorlie PD, Allison MA, Aviles-Santa ML, et al. Prevalence of Hypertension, Awareness, Treatment, and Control in the Hispanic Community Health Study/Study of Latinos. *Am J Hypertens*. 2014;27(6):793-800. doi:10.1093/ajh/hpu003.
4. Valderrama AL, Gillespie C, Mercado C. Racial/Ethnic Disparities in the Awareness, Treatment, and Control of Hypertension — United States, 2003–2010. *MMWR*. 2013;62(18):351-355. doi:mm6218a1 [pii].
5. Stepler R, Brown A. Statistical portrait of Hispanics in the United States, 1980 – 2013. *Pew Res Cent*. 2015:0. http://www.pewhispanic.org/2015/05/12/statistical-portrait-of-hispanics-in-the-united-states-2013-key-charts/.
6. U.S. Census Bureau. *The Foreign-Born Population in the United States: 2010*. *American Community Survey Reports*. Washington, D.C.; 2012.
7. Pew Research Center. *Modern Immigration Wave Brings 59 Million to U.S., Driving Population Growth and Change Through 2065: Views of Immigration's Impact on U.S. Society Mixed*. Washington, D.C.; 2015. doi:10.1017/CBO9781107415324.004.
8. Markides KS, Eschbach K. Aging, Migration, and Mortality: Current Status of Research on the Hispanic Paradox. *Journals Gerontol Ser B Psychol Sci Soc Sci*. 2005;60(Special Issue 2):S68-S75. doi:10.1093/geronb/60.Special_Issue_2.S68.

9. Singh GK, Hiatt RA. Trends and disparities in socioeconomic and behavioural characteristics, life expectancy, and cause-specific mortality of native-born and foreign-born populations in the United States, 1979-2003. *Int J Epidemiol*. 2006;35(4):903-919. doi:10.1093/ije/dyl089.

10. Abraído-Lanza AF, Dohrenwend BP, Ng-Mak DS, Turner JB. The Latino mortality paradox: A test of the "salmon bias" and healthy migrant hypotheses. *Am J Public Health*. 1999;89(10):1543-1548. doi:10.2105/AJPH.89.10.1543.

11. Argeseanu Cunningham S, Ruben JD, Venkat Narayan KM. Health of foreign-born people in the United States: A review. *Heal Place*. 2008;14(4):623-635. doi:10.1016/j.healthplace.2007.12.002.

12. Willey JZ, Rodriguez CJ, Moon YP, et al. Coronary Death and Myocardial Infarction among Hispanics in the Northern Manhattan Study: Exploring the Hispanic Paradox. *Ann Epidemiol*. 2012;22(5):303-309. doi:10.1016/j.annepidem.2012.02.014.

13. Dominguez K, Penman-Aguilar A, Chang M-H, et al. Leading Causes of Death, Prevalence of Diseases and Risk Factors, and Use of Health Services Among Hispanics in the United States — 2009–2013. *Morb Mortal Wkly Rep*. 2015;64(17):469-478. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6417a5.htm.

14. Liao Y, Cooper RS, Cao G, Kaufman JS, Long AE, McGee DL. Mortality from coronary heart disease and cardiovascular disease among adult U.S. Hispanics: findings from the National Health Interview Survey (1986 to 1994). *J Am Coll Cardiol*. 1997;30(5):1200-1205. http://www.ncbi.nlm.nih.gov/pubmed/9350915.

15. Swenson CJ. Cardiovascular Disease Mortality in Hispanics and Non-Hispanic Whites. *Am J Epidemiol*. 2002;156(10):919-928. doi:10.1093/aje/kwf140.

16. Daviglus ML, Talavera GA, Avilés-santa ML, Giachello AL, Gouskova N, Kaplan RC. Prevalence of Major Cardiovascular Risk Factors and Cardiovascular Diseases Among Hispanic/Latino Individuals of Diverse Backgrounds in the United States. *JAMA*. 2012;308(17):1775-1784. doi:10.1001/jama.2012.14517.Prevalence.

17. Kershaw KN, Greenlund KJ, Stamler J, Shay CM, Daviglus ML. Understanding ethnic and nativity-related differences in low cardiovascular risk status among Mexican-Americans and non-Hispanic Whites. *Prev Med (Baltim)*. 2012;55(6):597-602. doi:10.1016/j.ypmed.2012.09.019.

18. Dinwiddie GY, Zambrana RE, Garza MA. Exploring risk factors in Latino cardiovascular disease: The role of education, nativity, and gender. *Am J Public Health*. 2014;104(9):1742-1750. doi:10.2105/AJPH.2013.301280.

19. United Nations, Department of Economic and Social Affairs, Population Division (2011). The Age and Sex of Migrants 2011 Wallchart (United Nations publication, Sales No. 12.XIII.2).

20. Hermansen AS. Age at Arrival and Life Chances Among Childhood Immigrants. *Demography*. 2017;54:201-229. doi:10.1007/s13524-016-0535-1.

21. Downer B, Garcia MA, Saenz J, Markides KS, Wong R. The Role of Education in the Relationship Between Age of Migration to the United States and Risk of Cognitive Impairment Among Older Mexican Americans. *Res Aging*. 2017:16402751770144. doi:10.1177/0164027517701447.

22. Hill TD, Angel JL, Balistreri KS, Herrera AP. Immigrant status and cognitive functioning in late-life: An examination of gender variations in the healthy immigrant effect. *Soc Sci Med*. 2012;75(12):2076-2084. doi:10.1016/j.socscimed.2012.04.005.

23. Colón-López V, Haan MN, Aiello AE, Ghosh D. The effect of age at migration on cardiovascular mortality among elderly Mexican immigrants. *Ann Epidemiol*. 2009;19(1):8-14. doi:10.1016/j.annepidem.2008.08.010.

24. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of dementia in older latinos: the influence of type 2 diabetes mellitus, stroke and genetic factors. *J Am Geriatr Soc*. 2003;51(2):169-177.

25. Cuellar I, Arnold B, Maldonado R. Acculturation Rating Scale for Mexican Americans-II: A Revision of the Original ARSMA Scale. *Hisp J Behav Sci*. 1995;17(3):275-304. doi:10.1177/07399863950173001.

26. Petruski-Ivleva N, Viera AJ, Shimbo D, et al. Longitudinal Patterns of Change in Systolic Blood Pressure and Incidence of Cardiovascular Disease. *Hypertension*. 2016;67(6):1150-1156. doi:10.1161/HYPERTENSIONAHA.115.06769.

27. Portegies MLP, Mirza SS, Verlinden VJA, et al. Mid- to Late-Life Trajectories of Blood Pressure and the Risk of Stroke. *Hypertension*. 2016;67(6):HYPERTENSIONAHA.116.07098. doi:10.1161/HYPERTENSIONAHA.116.07098.

28. AlGhatrif M, Strait JB, Morrell CH, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: The Baltimore longitudinal study of aging. *Hypertension*. 2013;62(5):934-941. doi:10.1161/HYPERTENSIONAHA.113.01445.

29. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension*. 2001;37(3):869-874. doi:10.1161/01.HYP.37.3.869.

30. Chrysant SG, Chrysant GS. The Age-Related Hemodynamic Changes of Blood Pressure and Their Impact on the Incidence of Cardiovascular Disease and Stroke: New Evidence. *J Clin Hypertens*. 2014;16(2):87-90. doi:10.1111/jch.12253.

31. Fu M. Hypertension in the elderly: where are we? *Int J Cardiol*. 2012;155(1):6-8. doi:10.1016/j.ijcard.2011.01.084.

32. Antecol H, Bedard K. Unhealthy Assimilation: Why Do Immigrants Converge to American Health Status Levels? *Demography*. 2006;43(2):337-360. doi:10.1353/dem.2006.0011.

33. Goldman N. Will the Latino Mortality Advantage Endure? *Res Aging*. 2016;38(3):263-282. doi:10.1177/0164027515620242.

34. Okrainec K, Bell CM, Hollands S, Booth GL. Risk of cardiovascular events and mortality among a population-based cohort of immigrants and long-term residents with diabetes: Are all immigrants healthier and if so, for how long? *Am Heart J*. 2015;170(1):123-132. doi:10.1016/j.ahj.2015.04.009.

35. Vang ZM, Sigouin J, Flenon A, Gagnon A. Are immigrants healthier than native-born Canadians? A systematic review of the healthy immigrant effect in Canada. *Ethn Health*. 2017;22(3):209-241. doi:10.1080/13557858.2016.1246518.

36. Moullan Y, Jusot F. Why is the "healthy immigrant effect" different between European countries? *Eur J Public Health*. 2014;24(Suppl 1):80-86. doi:10.1093/eurpub/cku112.

37. Wang L, Palacios EL. The Social and Spatial Patterning of Life Stress Among Immigrants in Canada. *J Immigr Minor Heal*. 2017;epub ahead. doi:10.1007/s10903-016-0538-4.

38. Matthews KA, Katholi CR, McCreath H, et al. Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA study. *Circulation*. 2004;110(1):74-78.

doi:10.1161/01.CIR.0000133415.37578.E4.

39. Glynn RJ, Beckett L a, Hebert LE, Morris MC, Scherr P a, Evans D a. Current and remote blood pressure and cognitive decline. *JAMA*. 1999;281(5):438-445. doi:10.1001/jama.281.5.438.

40. Hu G, Sarti C, Jousilahti P, et al. The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. *Stroke*. 2005;36(12):2538-2543. doi:10.1161/01.STR.0000190894.30964.75.

Table 2.1. Baseline Characteristics of SALSA Participants by immigration history (n=1599)

	Immigration History			
	US-born n=835 (52.2%)	**Mexico/LA, immigrated age <20 n=177 (11.1%)**	**Mexico/LA, immigrated age 20+ n=587(36.7%)**	**p-value**
Age at baseline, *mean (SD)*	70.0 (6.3)	71.0 (7.7)	70.8 (7.2)	0.27
Female, *n (%)*	470 (50.3)	91 (51.4)	368 (62.7)	0.01
Baseline SBP in mmHg, *mean (SD)*	137.9 (19.5)	137.8 (17.7)	139.0 (19.2)	0.50
Hypertensive at baseline, *n (%)*	587 (70.3)	121 (68.4)	395 (67.3)	0.47
Baseline BMI, *mean (SD)*	30.2 (6.2)	28.9 (4.6)	29.5 (5.9)	0.04
Using antihypertensive medication at baseline, *n (%)*				
None	427 (51.1)	98 (55.4)	342 (58.3)	
One medication	222 (26.6)	51 (28.8)	152 (25.9)	0.02
Two or more medications	186 (22.3)	28 (15.8)	93 (15.8)	
Diabetic at baseline, *n (%)*	314 (37.6)	49 (27.7)	164 (27.9)	<0.001
Has medical insurance at baseline, *n (%)*	810 (97.4)	161 (91.0)	484 (82.6)	<0.001
Has a regular doctor at baseline, *n (%)*	800 (96.2)	162 (91.5)	456 (77.8)	<0.001
Years of education, *mean (SD)*	9.7 (4.9)	6.5 (4.9)	4.7 (4.7)	<0.001
Years in the US, *mean (SD)*	70.0 (6.3)	60.1 (12.1)	31.7 (15.6)	<0.001
Acculturation score at baseline, *mean (SD)*	45.5 (9.5)	37.5 (11.0)	26.8 (7.0)	<0.001
Smoking status at baseline, *n (%)*				
Never	356 (42.7)	74 (41.8)	303 (51.7)	
Former	382 (45.9)	82 (46.3)	218 (37.2)	0.01
Current	95 (11.4)	21 (11.9)	65 (11.1)	
Had MI/stroke at any time, *n (%)*	268 (32.1)	54 (30.5)	165 (28.1)	0.27
Incident MI/stroke, *n (%)*	111 (16.4)	27 (18.0)	87 (17.1)	0.87

US = United States, Mexico/LA = born in Mexico or other Latin American country, SBP = systolic blood pressure, BMI = body mass index, MI = myocardial infarction

Table 2.2. Mixed effects linear models for the association between immigration history and average systolic blood pressure (mmHg), SALSA (n=1599)

	Model 1				Model 2			
	beta	**95% CI**		**p-value**	**beta**	**95% CI**		**p-value**
Immigration history *(ref=US-born)*								
Mexico/LA, immigrated at age <20	-0.19	-2.94	2.56	0.89	-1.43	-4.26	1.41	0.32
Mexico/LA, immigrated at age 20+	-0.51	-2.32	1.29	0.58	-1.86	-4.25	0.53	0.13
Time since baseline, *years*	0.42	0.22	0.62	<0.001	0.45	0.25	0.66	<0.001
Immigration history x Time *(ref=US-born)*								
Mexico/LA, immigrated at age <20	0.09	-0.37	0.55	0.70	0.03	-0.44	0.49	0.91
Mexico/LA, immigrated at age 20+	0.60	0.28	0.91	<0.001	0.63	0.32	0.95	<0.001
Age at baseline, mean centered, *years*					0.33	0.22	0.45	<0.001
Female					-1.13	-2.73	0.46	0.16
BMI at baseline, mean centered, kg/m^2					0.11	-0.01	0.24	0.08
Type 2 diabetes at baseline					2.69	1.09	4.28	<0.001
Antihypertensive medication use, time-updated *(ref=none)*								
One medication					1.13	-0.10	2.35	0.07
Two or more medications					-0.69	-2.06	0.69	0.33
Smoking status at baseline *(ref=nonsmoker)*								
Former smoker					-0.87	-2.52	0.77	0.30
Current smoker					-0.14	-2.67	2.39	0.91
Acculturation score					-0.02	-0.12	0.08	0.71
Years of education					-0.23	-0.41	-0.04	0.02
Intercept	138.13	136.98	139.29	<0.001	138.03	132.10	143.95	<0.001

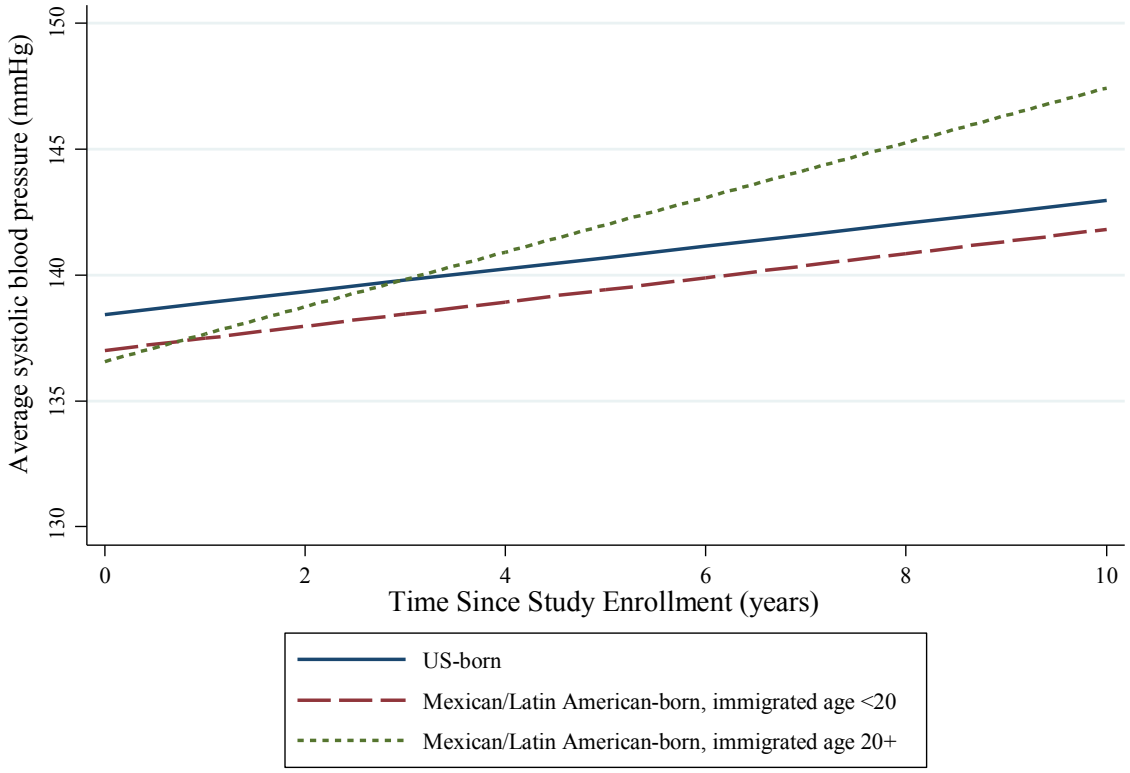
US=United States, Mexico/LA=born in Mexico or other Latin American country, BMI=body mass index
Model 1 - Likelihood ratio test for interaction term time x immigration history: p-value<0.001

Table 2.3. Relative hazards for time to incident myocardial infarction or stroke by baseline and time-updated systolic blood pressure, SALSA (n=1352)

	Baseline SBP								Time-Updated SBP			
	Model A				Model B				Model C			
	HR	**95% CI**		**p-value**	**HR**	**95% CI**		**p-value**	**HR**	**95% CI**		**p-value**
Immigration history *(ref=US-born)*	1.00				1.00				1.00			
Mexico/LA, immigrated at age <20	0.97	0.64	1.48	0.88	1.00	0.64	1.56	0.99	0.98	0.63	1.53	0.94
Mexico/LA, immigrated at age 20+	1.00	0.76	1.32	1.00	0.84	0.56	1.25	0.39	0.86	0.57	1.28	0.45
Age at baseline, mean centered, *years*	1.05	1.04	1.07	<0.001	1.04	1.02	1.07	<0.001	1.05	1.03	1.07	<0.001
Female	0.74	0.57	0.96	0.02	0.77	0.58	1.04	0.09	0.74	0.55	0.99	0.04
Systolic blood pressure, *per 10 mmHg*					1.12	1.04	1.19	0.001	1.06	0.99	1.12	0.08
BMI at baseline, mean centered, kg/m^2					1.01	0.99	1.04	0.28	1.01	0.99	1.04	0.31
Type 2 diabetes at baseline					1.79	1.35	2.37	<0.001	1.79	1.35	2.38	<0.001
Antihypertensive medication use, time-updated *(ref=none)*					1.00				1.00			
One medication					1.33	0.96	1.85	0.09	1.39	1.00	1.93	0.05
Two or more medications					1.04	0.71	1.51	0.84	1.15	0.80	1.66	0.46
Smoking status at baseline *(ref=non-smoker)*					1.00				1.00			
Former smoker					1.14	0.83	1.55	0.41	1.12	0.82	1.53	0.47
Current smoker					1.27	0.80	2.03	0.31	1.24	0.77	1.97	0.37
Acculturation score					0.99	0.97	1.01	0.26	0.99	0.97	1.01	0.25
Years of education					1.00	0.96	1.04	0.93	1.00	0.96	1.03	0.84

US = United States, Mexico/LA = born in Mexico or other Latin American country, SBP = systolic blood pressure, BMI = body mass index
Model A – Likelihood ratio test for immigration history variable: p-value=0.98

Figure 2.1. Predicted Trajectories of Systolic Blood Pressure Over Study Period by Immigration History



Chapter 3

Differences in Blood Pressure Trajectories by Nativity Status Before and After Myocardial Infarction or Stroke

Introduction

Increases over time in systolic and diastolic blood pressure (SBP and DBP) are known to be associated with greater risks of both MI and stroke.[1–4] Blood pressure may exhibit different trajectories over time that may affect the association with fatal and non-fatal MI/stroke risk.[5] For example, a study conducted on the Atherosclerosis Risk in Communities cohort found six patterns of SBP change and three patterns of DBP change over the course of the study visits.[6] The incidence rates for CVD grew larger across SBP patterns that showed an increase in SBP over time. Another study combining participants from several clinical trials showed that an increase of 20 mmHg in SBP from baseline was associated with greater risk for MI and stroke.[7] However, a 10 mmHg increase in DBP was associated with higher stroke risk and not with MI.

Few studies have examined the change in blood pressure both before and after MI/stroke, particularly among racial/ethnic minorities. Little is known about change in blood pressure over time and how this relates to MI/stroke status.[8] Understanding blood pressure patterns before and after MI/stroke can help reduce risk for a recurrent event. The Hispanic population carries significant cardiovascular burden, particularly due to high levels of cardiometabolic risk factors. Hispanic adults may have lower prevalence of hypertension compared to the general United States (US) population (~30% versus 32.6%). They also have the lowest rates of hypertension awareness, treatment, and control.[9,10] Incidence of ischemic stroke among the Hispanic population may also be higher compared to non-Hispanics whites.[9] It is critical to understand the patterns of change in blood pressure for a population that comprises 17.3% of the total US population. Prevalence of hypertension among Hispanics may continue to rise.[11,12] Thirty-five percent of the US population are foreign-born.[11] According to NHIS data, the odds of hypertension are higher among all US-born adults compared to foreign-born adults.[9] Various

studies have reported lower rates of cardiovascular events compared to US-born adults, particularly for the more recent immigrants.[13,14] Yet, it is not known whether nativity status influences how blood pressure trajectories relate to MI/stroke, particularly for Hispanics.

The objectives of this study are to: 1) assess changes in SBP and DBP trajectories due to MI/stroke and 2) Evaluate how nativity modifies these trajectories before and after MI/stroke. We hypothesize that change in both blood pressure measurements is more rapid before MI/stroke compared to after MI/stroke. We also hypothesize that nativity modifies the associations such that the change in both blood pressure measurements is more rapid in US-born before and after MI/stroke compared to the Mexican-born.

Methods

Study Population

Participants in this study come from the Sacramento Area Latino Study on Aging (SALSA). SALSA is a longitudinal cohort study of 1,789 community-dwelling Mexican origin older adults who were living in California's Sacramento Valley and were aged 58-101 years at baseline. Further details on SALSA have been published elsewhere.[15] Study recruitment began in 1998-1999 and participants were followed every 12-15 months until 2008. These annual follow-ups consisted of home visits that included clinical, cognitive, and functional assessments. Participants also received telephone interviews every six months between annual home visits to confirm contact information, report any changes in medication use, and update marital and vital status. We excluded participants who did not have at least one SBP and DBP measurement from any visit (n=79), did not provide information on place of birth (n=10), and/or had prevalent MI/stroke before study baseline (n=291). Total study population was 1,414 participants. SALSA

has been approved by the Institutional Review Boards at the University of Michigan, the Universities of California at San Francisco and Davis, and the University of North Carolina at Chapel Hill.

Measurements

Outcome: Systolic and diastolic blood pressure

Sitting systolic and diastolic blood pressure (mmHg) was measured at baseline and six follow-up visits (FV). Participants were seated for at least five minutes before having their blood pressure measured. An Omrom automated blood pressure machine was used to take two measurements, five minutes apart, which were then averaged.

Myocardial infarction and stroke status

MI/stroke status among participants was categorized as 1) no incident MI/stroke and 2) having an incident MI and/or stroke event during the study. All prevalent MI/stroke cases were excluded. Incident MI/stroke cases included either fatal or non-fatal events. Non-fatal events were participants' self-report of a physician informing them that they had an MI or stroke. Fatal events were deaths where MI or stroke was listed anywhere in the death certificate. Mortality was ascertained using online obituary surveillance, the National Death Index, the Social Security Death Index, California vital statistics data, and interviews with family members of the deceased. Only the first event (fatal or nonfatal) was included for participants who had either or both incident MI and stroke. During follow-up, there were 55 deaths due to MI or stroke among individuals who did not previously report having either of these conditions; these deaths were counted as an incident MI/stroke case in the analyses.

Other covariates

Nativity was dichotomized as US-born and Mexican-born; the majority (>90%) of the foreign-born population in our study was of Mexican origin. Remaining covariates included baseline measurements of age in years (mean-centered), sex, time-updated antihypertensive medication use (none, one, two or more), and a time variable. Time was calculated as years since time since baseline enrollment (in years).

Statistical Analyses

We compared descriptive characteristics for SALSA participants by MI/stroke status using *t*-tests and Wilcoxon rank sum tests for continuous variables and chi-square tests for categorical variables. We examined the association between MI/stroke status and blood pressure over a ten-year period using an interrupted time series approach with linear mixed effects models, with separate models for SBP and DBP[16]:

$$Y_{ij} = \beta_0 + \beta_1 X_{1ij} + \beta_2 X_{2ij} + \beta_3 X_{3ij} + \beta_4 X_{1ij} X_{2ij} + \beta_5 X_{1ij} X_{3ij} + \beta_6 X_{2ij} X_{3ij} + \beta_7 X_{1ij} X_{2ij} X_{3ij} + covariates + \mu_{0j} + \varepsilon_{ij}$$

In this model, Y_{ij} represents the outcome (either SBP or DBP) for person i at time j, X_1 is the time-dependent incident MI/stroke indicator, X_2 is the time since study baseline (in years), and X_3 indicates nativity (US- or Mexican-born). β_0 represents average SBP/DBP level at baseline, β_1 is the change associated with incident MI/stroke, β_2 is the change due to a unit increase in time, and β_3 is the difference between US- and Mexican-born individuals. β_4 indicates the slope change following the MI/stroke. We also included interactions with the nativity indicator to determine if there were differences due to place of birth. β_5 represents the fluctuation due to an incident MI/stroke among Mexican-born individuals, β_6 is the change in blood pressure over time by

nativity, and β_7 is the slope change following MI/stroke for Mexican-born individuals. Covariates in the final adjusted model included baseline age (mean-centered), sex, and time-updated use of hypertension medication (none, one, or two or more). All analyses were conducted using Stata 14 (StataCorp, College Station, TX).

Results

There were 237 (16.8%) incident cases of MI/stroke developed during the study period out of 1,414 total participants (Table 1). The MI/stroke group was statistically significantly older at baseline compared to those who do not develop MI/stroke. In both groups, over half were female. More than half of the participants were born outside the US, though this was not significantly different by MI/stroke status. At baseline, compared to those who don't develop MI/stroke, participants with incident MI/stroke had higher SBP (143.7 versus 137.1 mmHg, p-value<0.001) and higher prevalence of hypertension (77.2% versus 62.3%, p-value<0.001). Other notable differences at baseline include higher percentage of antihypertensive medication use and higher prevalence of diabetes (40.1%, p-value<0.001) in the incident MI/stroke group compared to the no MI/stroke group.

Results from the linear mixed model for SBP are presented in Table 2. In the adjusted Model 2, the pre-MI/stroke increase in SBP for the US-born group was 0.40 mmHg (95% CI: 0.17, 0.63, p-value<0.001) per year. The pre-MI/stroke SBP increase for the Mexican-born group was 1.00 mmHg (95% CI: 0.77, 1.24, p-value<0.001) per year. There was a 4.93 mmHg (95% CI: -1.72, 11.58, p-value=0.15) increase in SBP due to developing MI/stroke, though this was not statistically significant. The US-born group experienced a decline in SBP by -0.43 mmHg (95% CI: -1.51, 0.64, p-value=0.43) while the Mexican-born group increased by 0.34 mmHg

(95% CI: -0.66, 1.35, p-value=0.50) per year after MI/stroke occurred. However, these changes in SBP post-MI/stroke were not statistically significant. For the DBP linear mixed model (Table 3), there were no statistically significant trajectories before MI/stroke for both nativity groups. In the US-born, DBP declined by -0.11 mmHg (95% CI: -0.24, 0.02, p-value=0.09). After MI/stroke, however, the trajectory of DBP was statistically significant for the Mexican-born group. In this group, there was a decrease of -0.63 mmHg (95% CI: -1.18, -0.07) per year after MI/stroke.

We used results from the adjusted models for SBP and DBP to graphically display the predicted blood pressure values over the study period by MI/stroke and nativity status. Four curves for each graph were constructed to account for each combination of MI/stroke and nativity status. Each curve represents a hypothetical male individual of average age (70.2 years) who, if he had an incident MI/stroke, had the event at study year 6 (the average time to MI/stroke in the SALSA population). In the graph for SBP, there was a general increase in SBP for the no MI/stroke individuals (Figure 1). The curve representing the Mexican-born, non-MI/stroke individual had the fastest increase over time compared to any of the other three curves. In contrast, Figure 2 suggests that DBP remains largely constant over time. A key difference was the decrease in DBP among the Mexican-born individual who had MI/stroke, with the decline happening more rapidly after the event occurred.

Discussion

In this study comparing change in blood pressure before and after MI/stroke in a cohort of US- and foreign-born older Mexican Americans, we found that foreign nativity may influence blood pressure trajectories. Specifically, Mexican-born participants without incident MI/stroke had

faster rate of SBP increase over time compared to those with incident MI/stroke or those born in the US. Conversely, faster rate of DBP decline was present only for those who had MI/stroke. There were no significant differences in either measure of blood pressure levels by MI/stroke status, nor was the rate of blood pressure change different among MI/stroke participants compared to the overall effects of time. Other notable results include the constant increase in SBP over the study period while DBP generally remained consistent.

Prior work on the role of blood pressure and MI/stroke has mainly examined differences in MI/stroke risk due to changes in blood pressure. In a large meta-analysis of clinical trials for blood pressure lowering medications, reductions in SBP by 10 mmHg and DBP by 5 mmHg was associated with 25% lower risk of coronary artery disease and 36% lower risk of stroke.[17] These findings underline the importance of blood pressure management in order to prevent future cardiovascular events. However, few studies have specifically examined the changes in blood pressure that occur after an acute cardiovascular event. Individuals who have a MI or stroke are often at an increased risk of a recurrent event, even years after the first event.[18,19] Therefore, risk factor management among individuals who experienced a first event is needed in order to prevent a subsequent MI or stroke. Our findings add to the current literature on post-MI/stroke blood pressure profiles. Though we did not find significant differences between post-MI/stroke blood pressure trajectories compared to those who did not have an MI/stroke, these results can be further explored by examining the associations with recurrent MI/stroke.

A novel finding in our results is the differences in blood pressure trajectories by nativity in our study population. The faster rate of SBP increase and the faster decline in DBP among the Mexican-born population suggests a worse blood pressure profile compared to the US-born group. Though the MI/stroke status differed for the significant SBP and DBP findings in our

study, these results illustrate a possible widening of pulse pressure among those of foreign nativity. Pulse pressure, the difference between systolic and diastolic blood pressure, has been associated with increased risk of coronary heart disease and cardiovascular mortality.[20,21] Though not significantly different, the average SBP is slightly higher in the Mexican-born group compared to the US-born group (138.8 versus 13.6 mmHg). However, the decrease in DBP among Mexican-born individuals who have MI/stroke can exacerbate the effects of higher SBP as it contributes to higher pulse pressure and, subsequently, higher risk of a cardiovascular event. According to the study by Franklin *et al*., risk of CHD was greater for declines in DBP among those with SBP $\geq$ 120 mmHg.[20] In fact, there was greater increase in risk due to changes in pulse pressure as SBP stayed constant than compared to risk associated with changes in SBP where pulse pressure remained unchanged. Our results underscore the need to further understand cardiovascular health among the Mexican-born population as various risk factors may behave differently in this population.

The increase in SBP but not DBP due to time effects is consistent with other studies in the literature which suggest that SBP generally rises over time among older adults.[22,23] In addition to higher prevalence of comorbidities that may affect changes in blood pressure in older populations, age-related changes can affect the structure of blood vessels in older adults. The loss of elasticity in the arterial walls, along with thickening and stiffening of the arteries, can lead to higher rates of hypertension, primarily systolic, in older populations.[24,25] Large increases in SBP can lead to greater risk of adverse cardiovascular outcomes. For example, in the Rotterdam Study, researchers identified four different SBP trajectories in their cohort of older adults. Not surprisingly, their results suggest that the slope of SBP increase (i.e. steep rises in SBP) was associated with increasing risk of stroke and death.[22] Future studies can use a similar approach in

order to identify groups of blood pressure trajectories among those with and without MI/stroke and determine if results found in our study are reflected in these groups.

This study contains several limitations. The number of incident MI/stroke cases we have is small, leading to wider confidence intervals in our analyses. We are only able to assess changes in blood pressure over the ten-year study period, but fluctuations in blood pressure trajectories can occur beyond those ten years, both before and after MI/stroke. We are unable to examine blood pressure over the lifecourse, which may reveal patterns occurring in middle or late adulthood that may lead to increased risk of MI/stroke. This is notable considering the role of nativity in our study results. The process of immigrating can be a stressful experience as individuals settle into a new country and acclimate to new surroundings, languages, and social norms. This stress can have negative implications for the health of these immigrants, leading to adverse health conditions such as higher blood pressure that can affect their cumulative risk for MI/stroke.[26,27] Second, as our study population consists primarily of older Mexican Americans, the results found may not be generalizable to other populations. Variations in blood pressure for older adults can differ from younger populations due to the changing structure of the blood vessels and high levels of comorbidities in the older population. Future studies can examine younger cohorts to determine if similar patterns found in this study are also present in younger adults.

In spite of these limitations, a major strength of this study is the large sample size and population-based longitudinal design, which allowed us to study changes in blood pressure over ten years. Few studies on cardiovascular health, particularly those that examine the role of nativity, have been able to assess longitudinal changes in risk factors. The design of the SALSA included comprehensive at-home follow-up visits with study personnel who were able to conduct

periodic blood pressure measurements during the study period. Furthermore, though MI/stroke status in this study was based on self-report, a small validation study conducted on subset of the SALSA population confirmed these self-reports to be accurate.

To our knowledge, this is the first study to examine blood pressure patterns before and after MI/stroke in a Hispanic population. We also assessed the role of nativity in these patterns, and results offer insight into the heterogeneity of blood pressure trajectories due to foreign nativity. While we observed no association between MI/stroke status alone and changes in either SBP or DBP, results indicate that nativity may affect faster rate of change in DBP among individuals who have MI/stroke. Overall, these findings underscore the need to better understand the characteristics of blood pressure changes for individuals with and without cardiovascular disease, particularly among racial/ethnic minority populations. Results also highlight the role of nativity in influencing changes in blood pressure. This is noteworthy as the US immigrant population is rapidly growing and the racial/ethnic composition of this population is steadily changing.[28] Future studies are needed to further evaluate how blood pressure trajectories before and after a cardiovascular event may differ in other populations.

References

1. Psaty BM, Furberg CD, Kuller LH, et al. Association Between Blood Pressure Level and the Risk of Myocardial Infarction, Stroke, and Total Mortality. *Arch Intern Med*. 2001;161:1183-1192.
2. Vasan RS, Larson MG, Leip EP, et al. Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease. *N Engl J Med*. 2001;345(18):1291-1297. doi:10.1056/NEJMoa003417.
3. Lawes CMM, Bennett DA, Feigin VL, Rodgers A. Blood Pressure and Stroke: An Overview of Published Reviews. *Stroke*. 2004;35(3):776-785. doi:10.1161/01.STR.0000116869.64771.5A.
4. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet*. 2014;383(9932):1899-1911. doi:10.1016/S0140-6736(14)60685-1.
5. Smitson CC, Scherzer R, Shlipak MG, et al. Association of Blood Pressure Trajectory With Mortality, Incident Cardiovascular Disease, and Heart Failure in the Cardiovascular Health Study. *Am J Hypertens*. 2017;30(June):587-593. doi:10.1093/ajh/hpx028.
6. Petruski-Ivleva N, Viera AJ, Shimbo D, et al. Longitudinal Patterns of Change in Systolic Blood Pressure and Incidence of Cardiovascular Disease. *Hypertension*. 2016;67(6):1150-1156. doi:10.1161/HYPERTENSIONAHA.115.06769.
7. Verdecchia P, Reboldi G, Angeli F, et al. Systolic and diastolic blood pressure changes in relation with myocardial infarction and stroke in patients with coronary artery disease. *Hypertension*. 2015;65(1):108-114. doi:10.1161/HYPERTENSIONAHA.114.04310.

8. Rodriguez CJ, Allison M, Daviglus ML, et al. Status of Cardiovascular Disease and Stroke in Hispanics/Latinos in the United States: A Science Advisory From the American Heart Association. *Circulation*. 2014;130(7):593-625. doi:10.1161/CIR.0000000000000071.

9. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics—2016 Update. *Circulation*. 2016;133:e38-e360. doi:10.1161/CIR.0000000000000350.

10. Valderrama AL, Gillespie C, Mercado C. Racial/Ethnic Disparities in the Awareness, Treatment, and Control of Hypertension — United States, 2003–2010. *MMWR*. 2013;62(18):351-355. doi:mm6218a1 [pii].

11. Stepler R, Brown A. Statistical portrait of Hispanics in the United States, 1980 – 2013. *Pew Res Cent*. 2015:0. http://www.pewhispanic.org/2015/05/12/statistical-portrait-of-hispanics-in-the-united-states-2013-key-charts/.

12. Rodriguez CJ, Allison M, Daviglus ML, et al. Status of Cardiovascular Disease and Stroke in Hispanics/Latinos in the United States: A Science Advisory From the American Heart Association. *Circulation*. 2014;130(7):593-625. doi:10.1161/CIR.0000000000000071.

13. Okrainec K, Bell CM, Hollands S, Booth GL. Risk of cardiovascular events and mortality among a population-based cohort of immigrants and long-term residents with diabetes: Are all immigrants healthier and if so, for how long? *Am Heart J*. 2015;170(1):123-132. doi:10.1016/j.ahj.2015.04.009.

14. Tu J V., Chu A, Rezai MR, et al. Incidence of Major Cardiovascular Events in Immigrants to Ontario, Canada: The CANHEART Immigrant Study. *Circulation*. 2015;132(16):1549-1559. doi:10.1161/CIRCULATIONAHA.115.015345.

15. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of Dementia in Older Latinos: The Influence of Type 2 Diabetes Mellitus, Stroke and Genetic Factors. *J Am Geriatr Soc*. 2003;51(2):169-177.

16. Lopez Bernal J, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol*. 2017;46(1):348-355. doi:10.1093/ije/dyw098.

17. Law M, Morris J, Wald N. Use of blood pressure lowering drugs in the prevention of cardiovascular disease : meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ Br Med J*. 2009;338(June):1-19. doi:10.1136/bmj.b1665.

18. Jokhadar M, Jacobsen SJ, Reeder GS, Weston SA, Roger VL. Sudden death and recurrent ischemic events after myocardial infarction in the community. *Am J Epidemiol*. 2004;159(11):1040-1046. doi:10.1093/aje/kwh147.

19. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project [published erratum appears in Stroke 1994 Sep;25(9):1887]. *Stroke*. 1994;25(2):333-337. doi:10.1161/01.STR.25.2.333.

20. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart Disease? The Framingham heart study. *Circulation*. 1999;100(4):354-360. doi:10.1161/01.CIR.100.4.354.

21. Benetos A, Rudnichi A, Safar M, Guize L. Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. *Hypertension*. 1998;32(3):560-564. doi:10.1161/01.HYP.32.3.560.

22. Portegies MLP, Mirza SS, Verlinden VJA, et al. Mid- to Late-Life Trajectories of Blood Pressure and the Risk of Stroke. *Hypertension*. 2016;67(6):HYPERTENSIONAHA.116.07098. doi:10.1161/HYPERTENSIONAHA.116.07098.

23. AlGhatrif M, Strait JB, Morrell CH, et al. Longitudinal trajectories of arterial stiffness and the role of blood pressure: The Baltimore longitudinal study of aging. *Hypertension*. 2013;62(5):934-941. doi:10.1161/HYPERTENSIONAHA.113.01445.

24. Chrysant SG, Chrysant GS. The Age-Related Hemodynamic Changes of Blood Pressure and Their Impact on the Incidence of Cardiovascular Disease and Stroke: New Evidence. *J Clin Hypertens*. 2014;16(2):87-90. doi:10.1111/jch.12253.

25. Fu M. Hypertension in the elderly: where are we? *Int J Cardiol*. 2012;155(1):6-8. doi:10.1016/j.ijcard.2011.01.084.

26. Wang L, Palacios EL. The Social and Spatial Patterning of Life Stress Among Immigrants in Canada. *J Immigr Minor Heal*. 2017;epub ahead. doi:10.1007/s10903-016-0538-4.

27. Matthews KA, Katholi CR, McCreath H, et al. Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA study. *Circulation*. 2004;110(1):74-78. doi:10.1161/01.CIR.0000133415.37578.E4.

28. Pew Research Center. *Modern Immigration Wave Brings 59 Million to U.S., Driving Population Growth and Change Through 2065: Views of Immigration's Impact on U.S. Society Mixed*. Washington, D.C.; 2015. doi:10.1017/CBO9781107415324.004.

Table 3.1. Baseline Characteristics of SALSA Participants by incident MI/stroke status (*n=1414*)

	No MI/Stroke *n*=1177 (83.2%)	**MI/Stroke** *n*=237 (16.8%)	**p-value**
Age at baseline, *mean (SD)*	69.9 (6.8)	72.2 (7.6)	<0.001
Sex, *n (%)*			
Male	462 (39.3)	112 (47.3)	0.02
Female	715 (60.7)	125 (52.7)	
Nativity, *n (%)*			
US-born	567 (48.2)	111 (46.8)	0.71
Mexican-born	610 (51.8)	126 (53.2)	
Years in the US for the Mexican-born, *mean (SD)*	37.3 (18.9)	40.1 (19.7)	0.25
Years of education, *mean (SD)*	7.5 (5.4)	6.9 (5.6)	0.13
Baseline systolic blood pressure (mmHg), *mean (SD)*	137.1 (18.9)	143.7 (20.3)	<0.001
Baseline diastolic blood pressure (mmHg), *mean (SD)*	76.0 (10.5)	76.9 (9.6)	0.19
Hypertensive at baseline, *n (%)*	735 (62.4)	183 (77.2)	<0.001
Using hypertensive medications at baseline, *n (%)*			
No medication	729 (61.9)	125 (52.7)	
One medication	277 (23.5)	67 (28.3)	0.03
Two or more medications	171 (14.5)	45 (19.0)	
Baseline BMI, *mean (SD)*	29.6 (5.8)	30.1 (5.6)	0.15
Diabetic at baseline, *n (%)*	323 (27.4)	95 (40.1)	<0.001
Has medical insurance at baseline, *n (%)*	1047 (89.3)	218 (92.0)	0.21
Has a regular doctor at baseline, *n (%)*	1008 (85.9)	211 (89.0)	0.20
Smoking status at baseline, *n (%)*			
Never	568 (48.3)	101 (42.6)	
Former	472 (40.2)	109 (46.0)	0.22
Current	135 (11.5)	27 (11.4)	
Acculturation score at baseline, *mean (SD)*	37.2 (12.7)	36.2 (12.1)	0.29

US = United States, Mexican-born = born in Mexico or other Latin American country, BMI=body mass index, MI = myocardial infarction

Table 3.2. Linear mixed effects models examining association between incident MI/stroke, nativity, and changes in systolic blood pressure (mmHg), SALSA (*n=1414*)

	Model 1				Model 2			
	beta	**95% CI**		**p-value**	**beta**	**95% CI**		**p-value**
Incident MI/stroke[a]	4.73	-1.93	11.39	0.16	4.93	-1.72	11.58	0.15
Time since baseline, *years*	0.39	0.17	0.62	<0.001	0.40	0.17	0.63	<0.001
Incident MI/stroke[a] x Time	-0.82	-1.91	0.28	0.14	-0.84	-1.93	0.26	0.13
Nativity[b]	-0.10	-1.88	1.69	0.92	-0.38	-2.15	1.40	0.68
Nativity[b] x Incident MI/stroke[a]	-3.18	-12.40	6.04	0.50	-4.43	-13.64	4.78	0.35
Nativity[b] x Time	0.58	0.26	0.90	<0.001	0.60	0.28	0.92	<0.001
Nativity[b] x Incident MI/stroke[a] x Time	0.04	-1.46	1.54	0.96	0.18	-1.32	1.68	0.82
Baseline age, mean-centered, *years*					0.34	0.22	0.45	<0.001
Female					-1.43	-2.97	0.11	0.07
Current use of anti-hypertensive medication *(ref=0)*								
One medication					1.63	0.37	2.89	0.01
Two or more medications					-0.18	-1.63	1.27	0.81
Intercept	137.84	136.57	139.12	<0.001	138.59	136.96	140.21	<0.001

MI/stroke = myocardial infarction/stroke, time-dependent indicator

[a] reference group is no incident MI/stroke, [b] reference group is US-born

Table 3.3. Linear mixed effects models examining association between incident MI/stroke, nativity, and changes in diastolic blood pressure (mmHg), SALSA (*n=1414*)

	Model A				Model B			
	beta	**95% CI**		**p-value**	**beta**	**95% CI**		**p-value**
Incident MI/stroke[a]	-2.20	-5.89	1.49	0.24	-1.85	-5.52	1.81	0.32
Time since baseline, *years*	-0.13	-0.26	-0.01	0.04	-0.11	-0.24	0.02	0.09
Incident MI/stroke[a] x Time	0.12	-0.49	0.73	0.71	0.14	-0.47	0.75	0.65
Nativity[b]	-0.92	-1.86	0.03	0.06	-0.62	-1.55	0.30	0.19
Nativity[b] x Incident MI/stroke[a]	3.38	-1.72	8.48	0.19	3.25	-1.82	8.32	0.21
Nativity[b] x Time	0.16	-0.02	0.34	0.08	0.16	-0.02	0.34	0.08
Nativity[b] x Incident MI/stroke[a] x Time	-0.82	-1.65	0.02	0.06	-0.82	-1.65	0.01	0.05
Baseline age, mean-centered, *years*					-0.24	-0.29	-0.18	<0.001
Female					-1.88	-2.66	-1.10	<0.001
Current use of anti-hypertensive medication *(ref=0)*								
One medication					0.57	-0.12	1.25	0.10
Two or more medications					-1.32	-2.10	-0.54	<0.001
Intercept	76.89	76.21	77.56	<0.001	77.79	76.95	78.63	<0.001

MI/stroke = myocardial infarction/stroke, time-dependent indicator

[a] reference group is no incident MI/stroke, [b] reference group is US-born

Figure 3.1. Systolic Blood Pressure Trajectories Before and After Myocardial Infarction/ Stroke, By Nativity

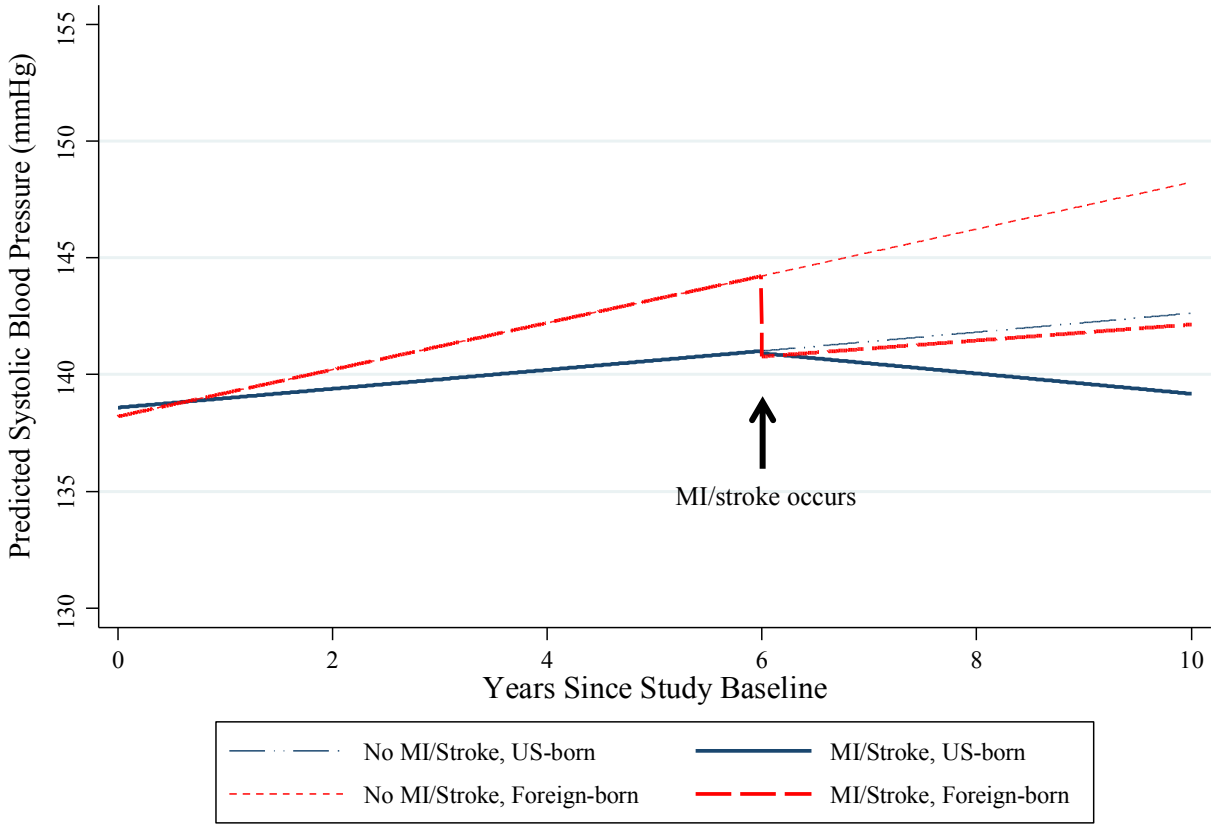
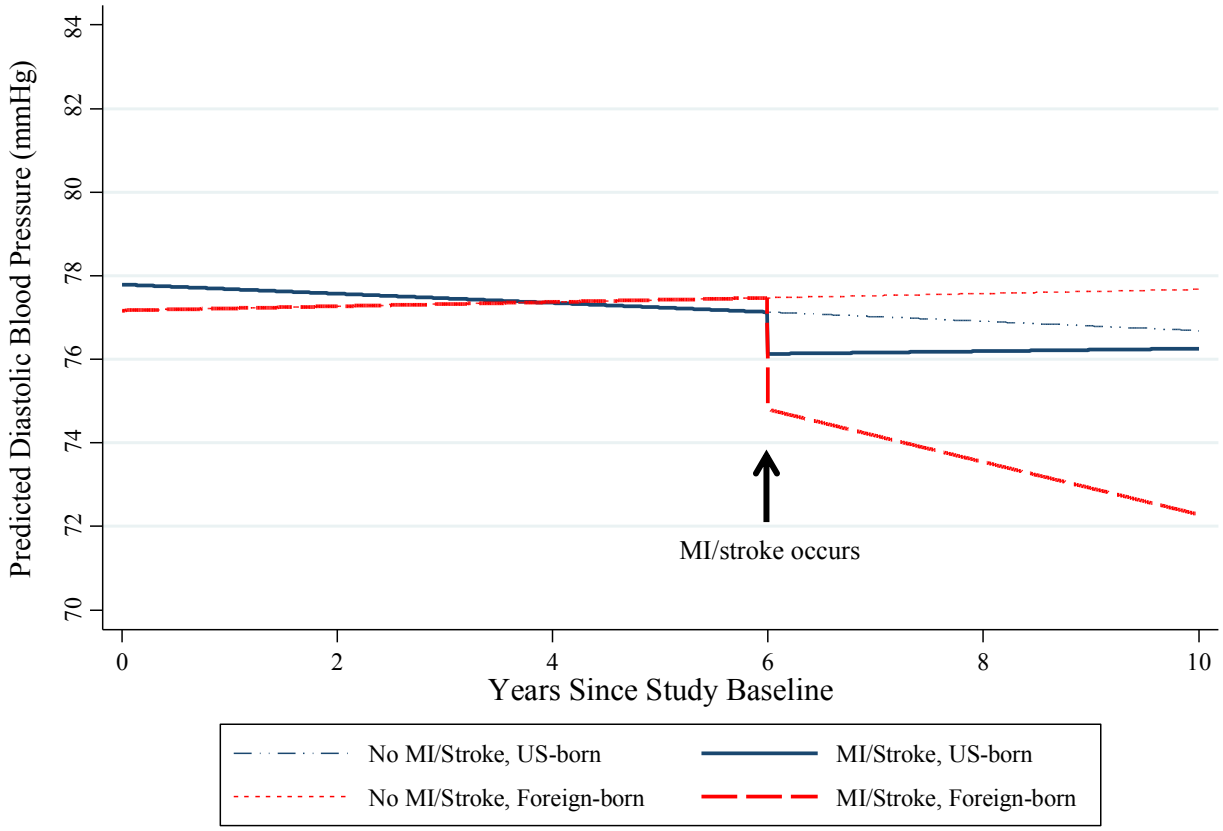


Figure 3.2. Diastolic Blood Pressure Trajectories Before and After Myocardial Infarction/ Stroke, By Nativity



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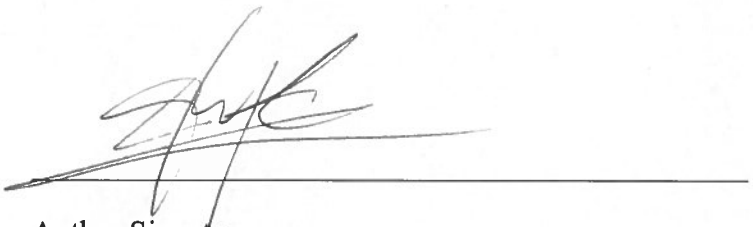

Author Signature

6/15/2017

Date