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Diurnal salivary cortisol and nativity/duration of residence in Latinos: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Latino immigrants have lower prevalence of depression, obesity and cardiovascular disease than US-born Latinos when they are recently arrived in the US, but this health advantage erodes with increasing duration of US residence. Cumulative exposure to psychosocial stress and its physiological sequelae may mediate the relationship between nativity and duration of US residence and poor health. We used data from Latino cohort study participants ages 45–84 to examine cross-sectional (n=558) and longitudinal (n=248) associations between nativity and duration of US residence and features of the diurnal cortisol curve including: wake-up cortisol, cortisol awakening response (CAR, wake-up to 30 min post-awakening), early decline (30 min to 2 h post-awakening) and late decline (2 h post-awakening to bed time), wake-to-bed slope, and area under the curve (AUC). In cross-sectional analyses, US-born Latinos had higher wake-up cortisol than immigrants with fewer than 30 years of US residence. In the full sample, over 5 years the CAR and early decline became flatter and AUC became larger. Over 5 years, US-born Latinos had greater increases in wake-up cortisol and less pronounced flattening of the early diurnal cortisol decline than immigrants with fewer than 30 years of US residence. Immigrants with 30 or more years of US residence also had less pronounced flattening of the early decline relative to more recent immigrants, and also had a less pronounced increase in AUC. In sum, we saw limited cross-sectional evidence that US-born Latinos have more dysregulated cortisol than recently-arrived Latino immigrants, but over time US-born Latinos had slower progression of cortisol dysregulation.

Keywords

Latinos/Hispanics; Nativity; Immigrant duration of residence; Cortisol; Stress; Hypothalamic-pituitary-adrenal axis

1. Introduction

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

of Mexican origin and in middle age (approximately ages 45–65) (Alegria et al., 2007; Sánchez-Vaznaugh et al., 2008).

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

1.1 Nativity/duration of residence and Latino health: stress as a theoretical pathway

Numerous studies have found that newly arrived Latino immigrants have good health despite facing a number of stressors, sometimes terming this the "immigrant paradox" (Salazar et al., 2016; Rubalcava et al., 2008). Some portion of the immigrant mortality advantage may be an artifact of selective migration of healthy immigrants (Rubalcava et al., 2008), undercount of Latino immigrant deaths, or selective out-migration of ailing immigrants ("salmon" bias) (Palloni and Arias, 2004; Patel et al., 2004), but these biases and selection effects do not fully explain the Latino/Hispanic immigrant mortality advantage (Turra and Elo, 2008; Markides and Eschbach, 2005). Another body of scholarship attributes these patterns to the deleterious health effects of "acculturation" or "negative assimilation", including the decline of protective cultural resources (Gallo et al., 2009; Almeida et al. 2009) and the adoption of unhealthful behaviors over time and generations of US residence (Abraido-Lanza et al 2005).

However, a number of scholars have argued that a decline in health across time and generations in the United States not "paradoxical" at all in light of the social and structural obstacles faced by many Latinos in the United States (Acevedo-Garcia et al. 2012; Viruell-Fuentes et al. 2012). The cumulative burden of navigating the challenging context for employment, housing, legal status and political resources as an immigrant to the United States (Hall and Greenman, 2014, 2013; Laird, 2015; Torres and Young, 2016) could contribute to the observed declines in health with additional years in the US. Although some immigrants experience improvements in income as they spend more time in the US, these improvements in material circumstances may come at the cost of high-effort striving in adverse circumstances (Viruell-Fuentes, 2007). Furthermore, there is evidence that immigrants may become more attuned to experiences of discrimination and their constructed position within the US ethnoracial hierarchy as they spend more time in the US environment (Viruell-Fuentes, 2011).

While US-born Latinos have the advantage of citizenship and tend to have higher education and income than Latino immigrants, they still experience higher rates of poverty than the general US population, which affects their ability to live in healthy environments and access health-promoting resources (Acevedo-Garcia and Bates, 2008). Many US-born Latinos have

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

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

1.2 Diurnal cortisol

The release of cortisol throughout the day (diurnal cortisol) represents a biological marker of the functioning of the HPA axis (Adam and Kumari, 2009; Miller et al., 2007). A typical diurnal cortisol curve consists of a relatively steep increase in salivary cortisol during the first half-hour after waking, followed by a gradual decline over the rest of the day (with some fluctuations after eating and in response to stressors throughout the day), reaching the lowest level in the evening. Diurnal variations in cortisol, particularly the steep increase in cortisol upon wake-up, are essential for healthy functioning, cueing cascades of neuroendocrine signals that mobilize multiple bodily systems (Clow, Hucklebridge & Torn, 2010). However, long-term neuroendocrine arousal in response to psychosocial stress may result in chronic, potentially maladaptive alterations of the HPA axis (Sapolsky et al. 1986). These alterations can vary according to the type and chronicity of stress exposure, but generally individuals facing stressors related to social position and social evaluation tend to have higher morning cortisol and flatter declines in cortisol over the course of the day (Miller et al., 2007). The diurnal curve also changes in response to aging, with higher wake-up cortisol, a flatter decline throughout the day, and higher total cortisol output as individuals age (Wang et al., 2014). These aging- and stress-mediated dysregulations in the cortisol curve have been linked in turn to health and mortality risk; for example, a flatter decline in cortisol throughout the day has been associated with higher risk for obesity, diabetes, and cardiovascular disease and higher all-cause mortality (Champaneri et al., 2012; Hackett et al., 2014; Kumari et al., 2011, 2010).

There is a small literature on variation in diurnal cortisol according to scale measures of acculturation or cultural orientation—which are distinct from but tend to be correlated with nativity/duration (Thomson and Hoffman-Goetz, 2009)—in Latino samples. A study of 100 Mexican-American adolescents identified a positive correlation between acculturation and the cortisol awakening response (Zeiders et al., 2012), but a study of 59 Mexican-American adults ages 18–38 found the opposite: that more acculturated individuals had blunted cortisol awakening responses (Mangold et al., 2010). The dynamics of diurnal cortisol vary by age (Karlamangla et al., 2013), as does association between social exposures and diurnal cortisol (Heaney et al., 2010), which may explain the contrasting findings in these studies of two different age groups. However, these studies use relatively small samples and are cross-sectional. Examining dynamics of diurnal cortisol, including longitudinal dynamics, in a large, late-middle-age Latino sample may offer additional insight into HPA function across time and generations.

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

2. Methods

2.1 Data

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

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

Of MESA's 6814 original participants, 1002 (528 Latino) participated in MESA Stress I and 1082 (438 Latino) participated in MESA Stress II, including many follow-up participants from Stress I. Latino participants in MESA Stress were from a range of Latino/Hispanic subgroups including Mexican (47%), Dominican (17%), Puerto Rican (13%), Cuban (4%) and Other Hispanic (16%), with 4% of Latino participants missing data on specific Hispanic subgroup. There are 499 Latino participants with valid diurnal cortisol samples from MESA Stress I and 424 participants with valid diurnal cortisol samples from MESA Stress II, for a total of 613 unique individuals with valid cortisol samples at one or both wave. There were 309 Latino participants with valid diurnal cortisol samples from both waves of the study. The MESA Stress Study was approved by institutional review boards at each study site and written informed consent was obtained from participants.

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

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

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

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

2.1.3 Covariates—We used a directed acyclic graph (DAG) to identify potential confounders of the association between nativity/duration of residence and diurnal cortisol (Figure S1).

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

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

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

were mean-centered for ease of interpretation. Wake-up time was centered at 7:00 AM, also for ease of interpretation.

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

2.2 Statistical Analysis

2.2.1 Statistical model—We use a piecewise linear mixed effects model to examine associations between our exposure of interest (nativity and duration of US residence) and features of the diurnal cortisol curve. Instead of calculating cortisol features and running separate models for each one (a less efficient two-step approach to calculating cortisol features), we include all cortisol samples (log-transformed to account for the skewed distribution of salivary cortisol (Wang et al., 2014)) in a single model. Each cortisol sample is modeled according to its actual time of collection (recorded by tracking caps in Stress I, and self-reported in Stress II), not according to the prescribed collection time. Piecewise splines capture the non-linearity of the cortisol curve across the day, with two knots fixed at 0.5 hours and 2 hours after wake-up (Hajat et al., 2010; Sánchez et al., 2012). Parameter estimates from the model are used to estimate the association of the exposure (nativity/duration) with the following cortisol features: wake-up cortisol level, cortisol awakening response (CAR, the rise in cortisol in the first 30 minutes after waking), early decline slope (the average hourly rate of decline in cortisol from 30 minutes to 2 hours after waking), late decline slope (the average hourly rate of decline in cortisol from 2 hours after waking to bedtime), wake-to-bed slope (the average hourly rate of decline in cortisol from waking to bedtime, excluding the peak after awakening), and standardized total area under the curve (AUC or total cortisol: the area under the linear spline, standardized to 16 hours of waking time, calculated by the trapezoid rule (Yeh and Kwan, 1978)). See Figure S2 for a visual representation of features of the cortisol curve.

For each hypothesis, we used a staged modeling approach, adding more variables to each subsequent model. Immigrants with fewer than 30 years of US residence were the reference group as we hypothesized they would have the least-dysregulated cortisol. Model 1 adjusted for basic potential confounders of the relationship between nativity/duration and cortisol levels: age, sex, and time of wake-up. Model 2 adjusted for years of education, which we theorized was a confounder. Model 3 further adjusted for income-wealth index, which we theorized to be either a confounder or a mediator. Lastly, Model 4 was further adjusted for potential behavioral or health-status mediators of the nativity/duration-cortisol association: smoking status, BMI, depressive symptoms and reported physical activity. All covariates were included as main effects and as interactions with each spline term, the latter to enable estimation of the association of nativity/duration of US residence with each feature of the cortisol curve. We also ran models stratified on the four largest Hispanic subgroups (Mexican, Dominican, Puerto Rican, and Other Hispanic) to evaluate heterogeneity of results by Hispanic origin.

2.2.2 Descriptive analysis—We visually examined differences between cortisol curves across study wave and nativity/duration of residence using locally estimated scatterplot

smoothing (LOESS) curves. We also use unadjusted piecewise models to estimate features of the cortisol curve at each level of nativity/duration and to estimate p-values for unadjusted differences in cortisol features by nativity/duration.

2.2.3 Cross-sectional analysis—To increase power, data from Stress Studies I and II (n=1458) were combined for cross-sectional analyses. After combining the two studies, we had 613 unique Latino individuals, 2292 days and 14,546 samples. We excluded samples that had missing or incomplete cortisol data (including time since wake-up), samples with cortisol values equal to 0 nmol/L or >100 nmol/L (generally considered to be outliers (Wang et al., 2014)), persons on steroids or hormone replacement therapy, and those who had missing covariates and were left with 558 persons, 1983 days and 12,724 samples. Individuals excluded from the cross-sectional analysis were more likely to be immigrants, were more likely to be from the New York study site, had higher average CES-D scores and had lower average income-wealth indices. There were no differences between included and excluded participants in age, sex, education, BMI, smoking, or physical activity.

The main effects of covariates and interactions of covariates with each spline term were included to adjust the associations of nativity/duration for these possible confounders. Within-person correlations and between-person variation in slopes were modeled as individual-level random components for the intercept and slopes of the cortisol curve for the first and third splines. In addition, a study-level random effect for Stress Study indicator was included in the intercept to account for within study correlation. Day-level variability was accounted for using fixed effects for day of sample.

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

between-person variation in cortisol curves. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

3. Results

3.1 Cross-sectional results

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

We present results of regression models adjusting for all confounders (age, sex, wake-up time and education) in Table 3 and include results of other staged models in Table S1. US-born individuals had slightly higher wake-up cortisol (12.6% higher, 95% CI −1.7%, 28.9%) than immigrants with fewer than 30 years of US residence. Further adjustment for income-wealth attenuated the association much further, to 8.7% (95% CI −6.1%, 25.7%), but this was because income was acting as a mediator of the association between nativity/duration and wake-up cortisol (Table S1). Further adjustment for health behaviors that may mediate the association between nativity/duration and diurnal cortisol did not alter our estimates (Table S1). The finding of higher wake-up cortisol in US-born individuals compared to immigrants with fewer than 30 years of US residence was consistent across Hispanic subgroups, although difference was not large enough to reach statistical significance in any of the subgroup-stratified analyses.

3.2 Longitudinal results

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

For the sample overall, the AUC became larger (1.45 to 1.67 log nmol/L/hr) and the wake-to-bed slope became flatter (−0.98 to −0.86 log nmol/L/8hr) over time (Table 4). Participants at Stress II tended to have flatter curves with higher cortisol at every time point (See Figure S3 for Stress I and Stress II LOESS curves).

Descriptive statistics (Table 4) and visual examination of LOESS curves by study wave and nativity/duration category (Figure 2) indicate that, between Stress I and Stress II, the cortisol awakening response flattened over time but the flattening was smaller for US-born participants (−31.1% change) than for immigrants with fewer than 30 years of US residence (−132.1% change) (Table 4). The early decline steepened slightly for US-born participants

(−3.9% change) while it became substantially flatter for immigrants with fewer than 30 years of US residence (34.7% change). Similarly, the wake-to-bed slope flattened only slightly for US-born participants (6.3% change) while new immigrants had a more pronounced flattening (17.2%).

Table 5 presents the estimates for the mean 5-year change and the mean differences in 5-year change by nativity/duration for each feature of the log cortisol curve, adjusted for age, sex, wake-up time and education. Other staged models are listed in Table S2. The mean differences in 5-year change reflect the deviation from the average 5-year change associated with each nativity/duration category (relative to immigrants with fewer than 30 years of US residence). Overall, the cortisol awakening response flattened between Stress Studies I and II (mean 5-year change: −0.55 log nmol/L/hr, 95% CI −0.95, −0.16), the early decline became flatter (0.23 log nmol/L/8hr, 0.11, 0.35) and total AUC increased (0.20 log nmol/L/8hr, 0.08, 0.32). US-born participants had a greater increase in wake-up cortisol than immigrants with fewer than 30 years of US residence (0.23 nmo/L, −0.03, 0.49). Immigrants with 30 or more years of US tenure and US-born participants had far less flattening of the early decline slope than new immigrants (mean difference in 5-year change: (−0.20 log nmol/L/8hr (95% CI −0.35, −0.05) and −0.24 log nmol/L/8hr (95% CI −0.42, −0.06), respectively). Immigrants with 30 or more years of US residence had a less pronounced increase in the AUC than new immigrants (mean difference in 5-year change: −0.15 log nmol/L/hr cortisol, (95% CI −0.31, 0.01)). Some longitudinal results differed by Hispanic subgroup: the association between US nativity and a greater increase in wake-up cortisol was strongest (and statistically significant) in the Puerto Rican and “Other Hispanic” subgroups but not in the Mexican or Dominican subgroups., The direction of the association of US nativity or 30+ years of US residence with less change in the early decline was consistent (but not statistically significant) across all Hispanic subgroups. The direction of the association of a smaller increase in the AUC for immigrants with 30+ years of US residence relative to new immigrants was consistent (but not significant) for all Hispanic subgroups except “Other Hispanic”, where the direction of the association was the opposite.

Adjusting for income-wealth (a mediator) attenuated the increase in wake-up cortisol among the US-born but did not affect any other estimates (Table S2). Adjusting for behavioral and health-status mediators slightly attenuated the association between US nativity and change in the early decline slope (Table S2).

4. Discussion

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

4.1 Cross-sectional findings

In cross-sectional analysis adjusted for confounders we found that US-born participants and immigrants with a longer duration of US residence had higher wake-up cortisol than more

recently-arrived immigrants. We did not observe significant nativity/duration differences in the cortisol awakening response, the early or late decline, the wake-to-bed slope or the AUC.

Our finding of higher wake-up cortisol among US-born participants was consistent with our hypothesis that we would observe more dysregulated cortisol in this group. Higher wake-up cortisol is consistently associated with an dysregulated HPA axis and higher risk of poor health: for example, it is generally associated with older age (Karlamangla et al., 2013; Wang et al., 2014) and higher cortisol output throughout the day (Golden et al., 2013), and is also associated with higher risk of depression (Bhagwagar et al., 2005), a condition that affects US-born Latinos at higher rates than immigrant Latinos (Alegria et al., 2007). The finding of higher wake-up cortisol among US-born Latinos may indicate that this group experiences greater HPA dysregulation than recently arrived Latino immigrants, which may contribute to higher risk of poor health.

However, it is notable that we did not observe any nativity/duration differences in the early or late diurnal decline in cortisol; a flatter decline in cortisol throughout the day has consistently been observed among groups at high risk of psychosocial stress, including racial/ethnic minorities (Hajat et al., 2010), individuals with low socioeconomic status (Karlamangla et al., 2013), and individuals residing in a stressful neighborhood environment (Do et al., 2011).

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

4.2 Longitudinal findings

In our longitudinal analysis we found that participants generally tended to exhibit a decrease in the cortisol awakening response, a flattening of the diurnal decline, and an increase in the AUC, which is consistent with longitudinal patterns observed in the full MESA sample (Wang et al., 2014), although a longitudinal study in a different sample observed no consistent pattern of change in diurnal cortisol curves (DeSantis et al., 2015). Our hypothesis of greater progression in dysregulation of diurnal cortisol among participants with US nativity or longer duration in the US was confirmed for one cortisol feature: US-born participants had a greater increase in wake-up cortisol than immigrants with fewer than 30 years of US residence (although immigrants with more than 30 years of residence did not have different change in wake-up cortisol than their more recently-arrived counterparts). The finding of greater increases in wake-up cortisol in the group hypothesized to be least healthy

(US-born Latinos) aligns with previous longitudinal findings whereby Latino adults in MESA had a greater increase in wake-up cortisol relative to non-Latino White participants (Wang et al., 2014). This would imply that US-born Latinos experience a more accelerated aging of wake-up cortisol dynamics relative to recently arrived immigrants.

Contrary to our hypotheses, we generally found that change in diurnal cortisol was less exaggerated among US-born participants and immigrants with longer tenure in the US. US-born participants had a smaller flattening of the early decline relative to more recently-arrived immigrants. Immigrants with longer US residence also had a smaller flattening of the early decline and a smaller increase in the AUC relative to more recent immigrants. Adjustment for the income-wealth index did not affect either nativity/duration group's estimates for change in the early decline or the AUC. This finding would imply that the group experiencing the fastest dysregulation of the diurnal cortisol curve is the group typically found to be healthiest, that is, the more recently arrived immigrants.

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

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

Some previous studies have found that the association between nativity/duration and health outcomes is strongest among Latinos of Mexican origin and that the nativity/duration gradient is less pronounced in other Hispanic subgroups (Acevedo-Garcia et al., 2007;

Borrell and Crawford, 2008). In subgroup-stratified analyses we generally found that diurnal cortisol was associated with nativity and duration of US residence in similar ways across Hispanic subgroups. This is consistent with a recent study of allostatic load in a large Latino sample, which found that nativity and duration of residence had similar associations with allostatic load across Hispanic subgroups (Salazar et al., 2016).

4.3 Limitations

Our sample had very few recently arrived immigrants, which led us to dichotomize duration of residence at 30 years, a higher cutoff than most studies of duration of US residence, many of which have multiple categories of duration of residence and use 10 or 15 years as the highest cutoff (Albrecht et al., 2013; Creighton et al., 2012). We would have chosen a duration-of-residence cutoff more comparable to other studies of nativity/duration and health if we had a larger sample of recently arrived immigrants. Some studies that examine health gradients at longer durations of US residence continue to observe associations with duration of residence and health outcomes even after 25 (Park et al., 2008) or 30 years of US residence (Moran et al., 2007). Our use of such a high cutoff to dichotomize duration of residence may have obscured important differences in HPA dynamics among immigrants with shorter tenure in the United States. Future research on HPA dynamics and nativity/duration of residence should examine samples with more recently-arrived immigrants.

Recent studies indicate that measurement of wake-up cortisol and the CAR can be sensitive to errors in reporting wake-up time and excess time elapsed between wake-up and taking the wake-up sample (Smyth et al., 2013). Although the Stress I study used track-caps to monitor the sample time, wake-up was self-reported and errors in reporting wake-up time may affect measurement of wake-up cortisol and the CAR. If error in reporting wake-up time varied by nativity and duration of residence this could have induced a spurious correlation between nativity/duration and wake-up cortisol. It is also possible that errors in measurement of the CAR could contribute to our lack of finding an association between nativity/duration and the CAR. To allow for comparability with other studies of the CAR that do not use piecewise linear mixed models, we also estimated cross-sectional and longitudinal mixed effects models comparing a calculated CAR (calculated by subtracting the second sample from the first sample), by nativity and duration of US residence, for individuals with samples collected within ten minutes of the sampling times prescribed in the protocol. The findings from these models were also null (Tables S3 and S4).

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

4.4 Strengths

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

5. Conclusions

Ours is the first study to examine cross-sectional or longitudinal variation in diurnal cortisol according to nativity and duration of US residence in a sample US Latinos in late-middle-age. We found limited cross-sectional evidence that US-born Latinos have more dysregulated cortisol than recently-arrived Latino immigrants, but over time US-born Latinos had slower progression of cortisol dysregulation. As a growing literature explores the role of social and structural stressors in persistent Latino health disparities (Viruell-Fuentes et al., 2012), evidence about the biological pathways by which these stressors operate will become increasingly important. Future studies should examine more recently-arrived Latino immigrants and examine nativity/duration disparities in diurnal cortisol dynamics throughout the life course. We hope to contribute to the growing literature that evaluates the role of chronic stress and its physiological sequelae for US-born and immigrant Latinos.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- For Latinos, US nativity and longer US residence is associated with poor health.
- Psychosocial stress and its physiological effects may mediate this association.
- We examine associations of nativity/duration and diurnal cortisol, a stress biomarker.
- US nativity is cross-sectionally associated with higher wake-up cortisol.
- Over time, US nativity was associated with slower progression of cortisol dysregulation.

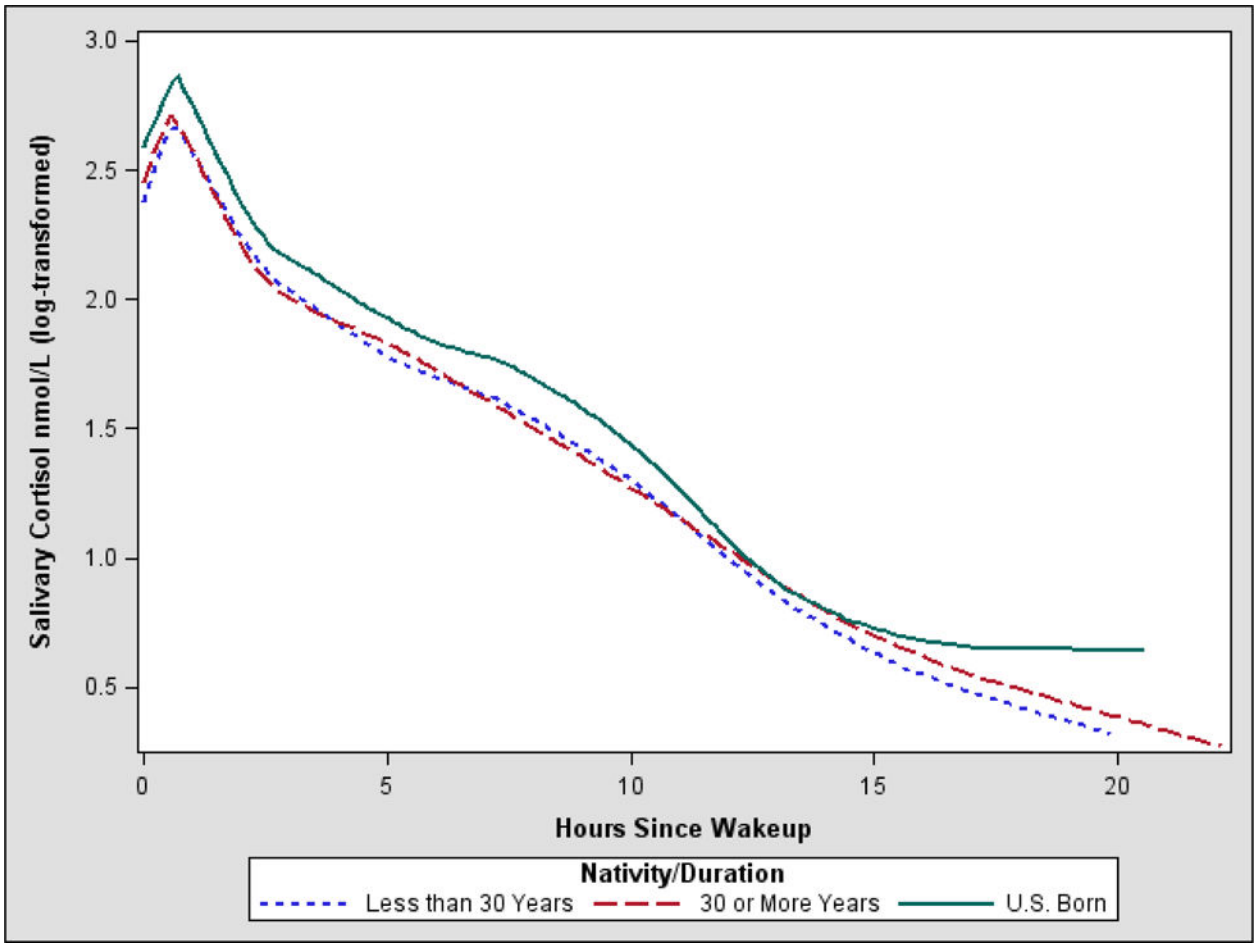

Figure 1.

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

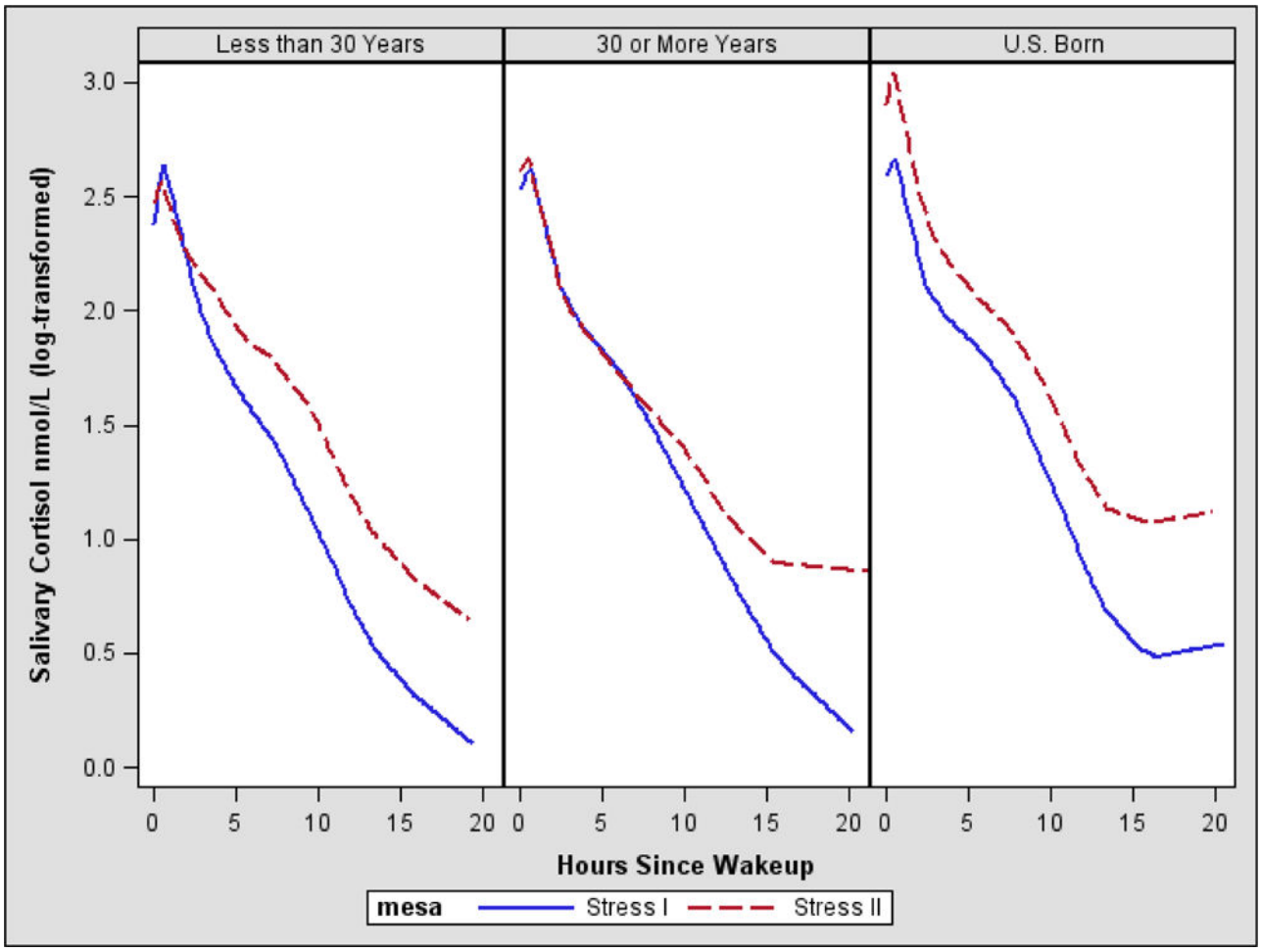

Figure 2.

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

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Table 1

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

	Stress study I	**Stress study II**	**Sample in pooled cross-section**	**Sample in longitudinal analysis**	
				At Stress I	**At Stress II**
N Persons	446	360	558	248	248
N Days	1280	703	1983	707	488
N Samples	7391	5333	12724	3867	3980
Age (mean (SD))	65.2 (9.5)	69.4 (9.3)	67.1 (9.6)	63.9 (9.5)	69.6 (9.4)
Male (%)	49.8	48.6	49.3	52.0	52.0
Income/wealth index (mean (SD))	3.2 (2.2)	3.5 (2.1)	3.3 (2.2)	3.5 (2.2)	3.7 (2.1)
Education (%)					
Less than high school	44.0	39.7	42.1	38.7	38.7
Completed high school	46.2	49.2	47.5	50.8	50.8
Completed college	9.9	11.1	10.4	10.5	10.5
Cigarette smoking status (%)					
Never	47.5	49.4	48.4	51.4	47.6
Former	46.2	46.4	46.3	42.9	48.4
Current	6.3	4.2	5.3	5.7	4.0
Body mass index (mean (SD))	29.4 (5.3)	29.1 (5.2)	29.3 (5.3)	28.9 (4.9)	29.1 (5.2)
Center for Epidemiologic Studies Depression Scale (mean (SD))	9.1 (9.2)	9.3 (8.6)	9.2 (8.9)	8.9 (9.3)	9.1 (8.6)
Total moderate or vigorous physical activity METS/week (mean (SD))	4636.0 (4476.6)	4443.4 (5149.2)	4550.0 (4786.6)	5059.1 (4893.7)	4370.1 (5391.2)
Study Site (%)					
New York, NY	40.1	45.8	42.7	40.3	40.3
Los Angeles, CA	59.9	54.2	57.3	59.7	59.7
Nativity/duration					
Foreign-born <30 years	23.5	24.4	24.0	22.6	22.6
Foreign-born 30+ years	50.9	51.7	51.2	53.6	53.6
US-born	25.6	23.9	24.8	23.8	23.8
Outcomes					

	Stress study I	Stress study II	Sample in pooled cross-section	Sample in longitudinal analysis	
				At Stress I	At Stress II
Cortisol nmol/L (mean(SD))	8.75 (8.82)	10.63 (10.50)	9.54 (9.61)	8.39 (8.61)	11.12 (10.74)
Log cortisol (mean (SD))	1.69 (1.07)	1.87 (1.14)	1.76 (1.10)	1.63 (1.09)	1.93 (1.12)
Wake-to-bed slope (mean (SE))	−0.96 (0.02)	−0.82 (0.02)	−0.90 (0.02)	−0.98 (0.02)	−0.86 (0.03)
Area under the curve (mean (SE))	1.47 (0.02)	1.65 (0.03)	1.53 (0.02)	1.45 (0.03)	1.67 (0.04)

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

Table 2

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

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

* s indicate significant difference from foreign-born with <30 years of US residence.

*** p<0.01,

** p<0.05,

* p<0.10

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

Table 3

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

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

** p<0.05,

* p<0.10

Percent differences were calculated from regression coefficients using the conversion (1-1/e^β)*100 where β<0, and (e^β-1)*100 where β>0.

Table 4

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

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

Estimates of cortisol features and p-values comparing cortisol features were calculated from unadjusted piecewise models. Percent change in cortisol features are the relative difference of log-cortisol unit features between the two waves of the Stress study.

Table 5

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

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

** p<0.05,

* p<0.10