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Job Strain and the Cortisol Diurnal Cycle in MESA: Accounting for Between- and Within-Day Variability

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Evidence of the link between job strain and cortisol levels has been inconsistent. This could be due to failure to account for cortisol variability leading to underestimated standard errors. Our objective was to model the relationship between job strain and the whole cortisol curve, accounting for sources of cortisol variability. Our functional mixed-model approach incorporated all available data—18 samples over 3 days—and uncertainty in estimated relationships. We used employed participants from the Multi-Ethnic Study of Atherosclerosis Stress I Study and data collected between 2002 and 2006. We used propensity score matching on an extensive set of variables to control for sources of confounding. We found that job strain was associated with lower salivary cortisol levels and lower total area under the curve. We found no relationship between job strain and the cortisol awakening response. Our findings differed from those of several previous studies. It is plausible that our results were unique to middle- to older-aged racially, ethnically, and occupationally diverse adults and were therefore not inconsistent with previous research among younger, mostly white samples. However, it is also plausible that previous findings were influenced by residual confounding and failure to propagate uncertainty (i.e., account for the multiple sources of variability) in estimating cortisol features.

functional mixed model; job strain; salivary cortisol

Abbreviations: AUC, area under the curve; CAR, cortisol awakening response; HPA, hypothalamic–pituitary–adrenal; MESA, Multi-Ethnic Study of Atherosclerosis.

There is a rich literature on the relationship between job stress and stress biomarkers (1–4). However, findings have been inconsistent, possibly because of several common limitations of existing studies: small sample size; racially/ethnically homogeneous samples that yield results that are not generalizable; samples of workers taken from the same profession, which may result in differences in psychological characteristics driving job stress variability rather than structural job differences; residual confounding; and failure to account for measurement error and day-to-day variability of cortisol features, which result in standard errors that are too narrow.

We examined the relationship between 1 measure of job stress (job strain, defined as high job demand and low job control (5)) and 1 biomarker of hypothalamic–pituitary–adrenal (HPA) axis functioning (salivary cortisol). In previous studies, investigators found inconsistent evidence for an association between job strain and salivary cortisol levels. For example, job strain has been associated with both higher morning cortisol levels (2, 6) and lower average cortisol levels (3), although no significant association was found in other studies (7–9). Job strain and its components have also been associated with steeper cortisol awakening responses (CARs) in some studies (10), whereas no significant association was found in others (11–15). In addition, they have been associated with increased cortisol secretion over the course of the day, as measured by area under the curve (AUC), in some studies (16) but not others (17).

Our objective was to model the relationship between job strain and the cortisol diurnal cycle by modeling the whole cortisol profile, and in addition include 2 summary measures, CAR and total AUC. Our analytic approach was designed to fill the aforementioned gaps. We used a racially, ethnically, and occupationally diverse sample that provided salivary cortisol samples over the entire diurnal cycle for multiple days. In addition, we used a propensity score matching approach to create job strain groups that were comparable across an extensive set of sociodemographic and health variables coupled with flexible modeling of an individual's entire diurnal cortisol curve using functional mixed models. Because cortisol levels for an individual are highly variable within and between days, a key contribution of this approach is that it incorporates these sources of variability—in contrast to using one measurement or a simple average—resulting in more accurate inferences.

METHODS

We used data from the Multi-Ethnic Study of Atherosclerosis (MESA) Stress I Ancillary Study. MESA is a 6-site, longitudinal study designed to identify determinants of subclinical atherosclerosis (18). At baseline, there were 6,814 MESA participants who were 44–84 years of age without clinical cardiovascular disease. The Stress Ancillary Study included a subsample of 1,002 participants from the New York and Los Angeles sites and occurred from July 2004 to November 2006. The institutional review boards of all the participating institutions approved the study and consent procedures.

Because our objective was to compare those with more job strain to those with less, the present study was restricted to the 441 participants who reported being employed at visit 2 (2002–2004), when data on work-related variables were collected. There was no missingness in job strain–related variables among those who were employed. As in previous MESA Stress I analyses, we excluded participants with missing sampling times or missing cortisol samples for the entire period (11 participants) and with reported steroid use (either inhaled or oral; 11 participants). We also excluded participants whose workforce status changed between visit 2, when data on work-related variables were collected, and either visit 3 or visit 4, when data on stress biomarkers were collected (35 participants). An average of 2 years (range, 1–4 years) elapsed between visit 2 and the stress visit. As in previous MESA analyses, we also excluded those with missing data on other covariates (43 participants). After the application of these exclusion criteria, 341 participants remained in the sample.

Measures

Job strain. Job strain is defined as having a job with a high level of demands and low control (5). Participants were asked about their jobs via a self-administered Job Content Questionnaire that includes a 5-item, 4-point Likert-type job demand scale and a 9-item, 4-point Likert-type job control scale (19). Job demand and job control were defined from these scales (20) and dichotomized into high and low categories, separately for men and women, at the breakpoints in their respective distributions (see Web Figure 1, available at http://aje.oxfordjournals.org/). In the final, matched data set, 68% of men and 22% of women were classified as having high job demands. Forty-three percent of men and 48% of women were classified as having low job control. Overall, 15% (15 of 101) of men and 28% (43 of 153) of women were classified as having job strain (high job demands and low job control). The matching procedure used to obtain the final data set is described below.

Aspects of cortisol diurnal rhythm. Participants collected 6 salivary cortisol samples over the course of the day for each of 3 consecutive weekdays, resulting in a total of 18 samples per participant. The samples were collected at times designed to capture the cortisol diurnal rhythm: at wake-up, 30 minutes after wake-up, 10:00 AM, noon or before lunch (whichever was earlier), 6:00 PM or before dinner (whichever was earlier), and bedtime. Samples were collected using cotton swabs, which were removed from a container that had a time-tracking device built into the cap (Track Caps, Medication Events Monitoring System, Aprex, Union City, California). This device automatically recorded the time of each sample collection. After use, the cotton swabs were stored at −20°C. Cortisol levels were quantified using a commercially available chemiluminescence assay (IBL, Hamburg, Germany). The sensitivity of this assay is 0.16 ng/mL, and intra- and inter-assay coefficients of variation are both less than 8% (21). Participants with cortisol values of 0 nmol/L or greater than 100 nmol/L were excluded, in accordance with previous MESA Stress I analyses.

Cortisol levels increase sharply just after awakening, which is called the CAR (22), and then decline over the rest of the day. In addition to comparing the entire cortisol profiles of those in higher-strain jobs with the profiles of those with lower-strain jobs, we considered 2 cortisol features as outcomes of interest: 1) CAR, as measured by the slope in cortisol levels from wake-up to 30 minutes after wake-up, and 2) the total AUC from wake-up to 16 hours after wake-up. These 2 features were chosen because research has suggested that they represent 2 separate components of the HPA axis (23). CAR is thought to capture the ability of the HPA axis to respond to stress, and total AUC is a measure of cumulative daily cortisol exposure.

Covariates. We controlled for confounding through covariates that spanned multiple domains, including sociodemographic characteristics (age, sex, race/ethnicity, whether English or Spanish was spoken, housing (type and number in household), level of education, income-wealth index (24), and financial strain), physical health (indicators of breathlessness walking on level ground and hills and ever needing to stop walking because of breathlessness), physical activity (smoking status, metabolic equivalent minutes/week (25) of intentional and moderate to vigorous exercise), medication use (reproductive hormones, aspirin, and β-blockers), and temporality (wake-up time, whether it was a workday, and season when the cortisol sample was collected). We also controlled for MESA visit number (3 or 4) when cortisol was collected and study site.

Addressing confounding was particularly important in the present analysis because those with more job strain differed from those with less across many covariates, including sex, age, educational level, wealth, and fitness level (Figure 1). When comparing the predicted probability of more job strain given the set of covariates (i.e., the propensity score) between those who actually had more job strain versus those who had less, we found regions where there was little to no overlap (Web Figure 2A). This suggests the presence of practical positivity violations, which means that certain types of people have extremely high probabilities of more job strain, whereas

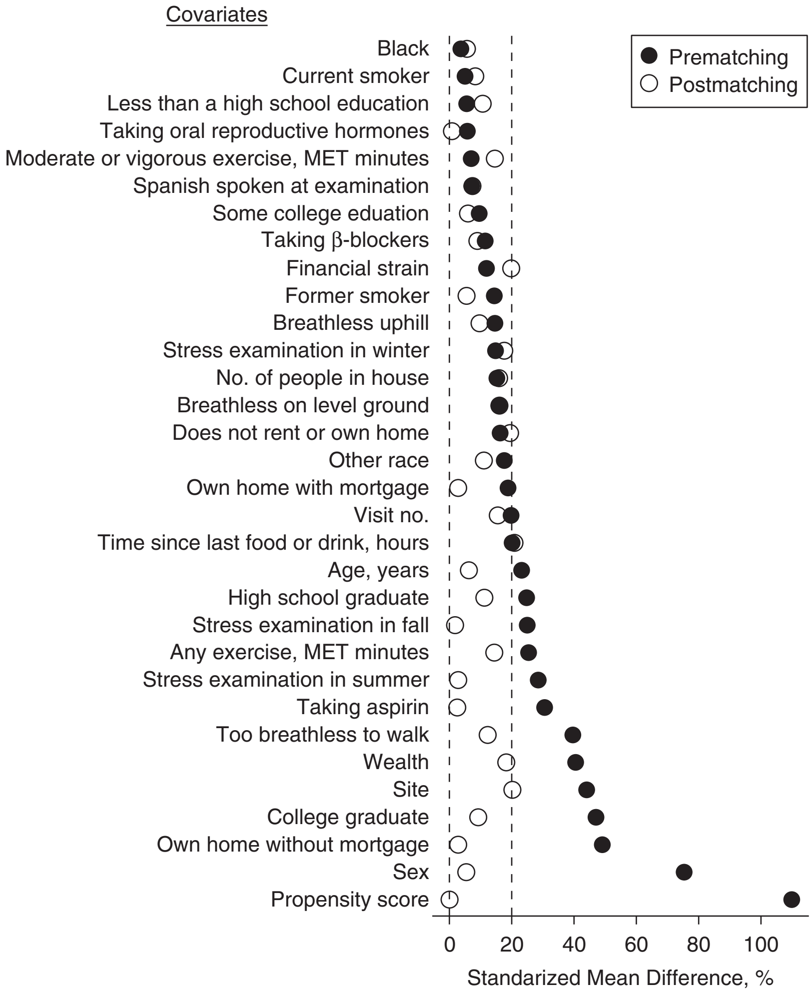

Figure 1. Covariate balance as measured using the absolute standardized mean difference (the absolute difference in means between those with more job strain and those with less job strain standardized by the standard deviation in the group with more job strain), before and after matching, Multi-Ethnic Study of Atherosclerosis, 2002–2006. Prematching standardized mean differences are represented by black circles, and postmatching standardized mean differences are represented by white circles. The vertical dashed lines represent standardized mean differences of 0% and 20%. Participants were matched on the propensity score, which is a function of the covariates shown on the left side of the figure.

others have extremely low probabilities. Including individuals with such extreme probabilities who have no similar counterparts with whom to compare them would result in having to rely heavily on extrapolation.

Propensity score matching

To address the challenges above, we used full matching on the propensity score (26), using the MatchIt package in R (27), to create groups with more and less job strain that were similar based on measured covariates (see Web Appendix 1 for propensity score model specification). Full matching provided the best balance of the various matching approaches. Using this approach, we restricted our sample to participants with more job strain who had similar counterparts with less job strain and vice versa, thereby guarding against the need for extrapolation. The weights in the propensity score–matched data set balanced the 2 groups on their propensity of job strain and related covariates, thereby addressing confounding. Figure 1 shows covariate balance before and after the matching approach. Web Figure 2B shows the distribution of propensity scores for the matched data set.

There were 254 participants in the final matched data set. Sixty percent of these participants completed all 18 samples, and 95% completed at least 13 samples. The minimum number of samples that any participant completed was 2.

Statistical analysis

For our primary analysis, we followed the approach of Sánchez et al. (28) and modeled the cortisol diurnal curve using functional mixed models with penalized thin plate splines, using the mgcv R package (29). We incorporated the propensity score weights from the full matching procedure described above.

Table 1. Matched Sample Characteristics[a] by Job Strain Status, Multi-Ethnic Study of Atherosclerosis, 2002–2006

Variable	Less Job Strain, (n = 196)		More Job Strain, (n = 58)	
	%	Mean (IQR)	%	Mean (IQR)
Sociodemographic Variables				
Educational level				
Less than high school	16		21	
High school graduate	29		24	
Some college	41		38	
College graduate	14		17	
Race				
White	14		18	
Black	27		29	
Hispanic	59		53	
Spanish language at examination	37		29	
Male	23		26	
Age, years		58.7 (53.0–61.0)		57.6 (52.5–61.5)
No. of people in household		2.1 (1–3)		2.3 (1–3)
Housing				
Rent home	56		60	
Own home, pay a mortgage	25		26	
Own home, no mortgage	5		5	
Other home type	14		9	
Job category				
Management[b]	17		3	
Professional[b]	19		17	
Service[b]	27		34	
Sales, office, or administrative support[b]	19		26	
Blue collar[b]	15		17	
Wealth index[c]		4.1 (2–5)		3.7 (2–5)

Table continues

The model can be written as $g(E(\text{cortisol}_{idt})) = f_0(t) + f_1(t)\text{job strain}_i + f_2(t)\text{workday}_{di} + f_3(t)\text{wake-up hour}_{di} + Z_{di}b_{di}(t)$, where cortisol_{idt} is the cortisol level for person i on day d at time since wake-up t. Time since wake-up was calculated using the track-cap time of the first sample. If the track-cap time was missing, the self-reported wake-up time was used. $f_1(t)$ represents the person-level fixed-effect coefficient for job strain and describes how the curve differs over the course of the day between those with more job strain and those with less. $f_2(t)$ and $f_3(t)$ represent fixed-effect day-level coefficients and describe how the average cortisol level over the course of day d differs between working and nonworking days and with a wake-up time that is 1 hour later, respectively. Coefficients were fit as previously described (28). $Z_{di}b_{di}(t)$ represents the person and day-specific intercept and slope of time since wake-up.

We modeled cortisol levels (nanomoles per milliliter) as gamma-distributed with a log link. This distribution provided the best fit and is appropriate for positive skewed data. The exponentiated coefficients have a multiplicative interpretation. Modeling log-transformed cortisol levels in a linear regression resulted in similar estimates (results not shown but available upon request). Confidence intervals were obtained using the percentile method for 1,000 bootstrapped samples.

For comparison with the functional mixed-model approach, we also present the results using a 2-step approach that is more typical in the cortisol literature. In the first step, we calculated the 2 features of the cortisol curve that are of interest (CAR and AUC) for each participant. In the second step, we regressed the feature on job strain and the other covariates described above in an outcome model in which we also used gamma regression with a log-link. As above, we calculated confidence intervals using the percentile method with 1,000 bootstrapped samples. This method treats the CAR and AUC values as known rather than estimated, ignoring a major source of variability. We used R, version 3.1.2, for all analyses (30).

RESULTS

Table 1 shows that the propensity score matching procedure resulted in similar distributions of covariates across the 2 job strain groups. The sample consisted of middle- to

Table 1. Continued

Variable	Less Job Strain, (n = 196)		More Job Strain, (n = 58)	
	%	Mean (IQR)	%	Mean (IQR)
		Health Variables		
Walking measurements				
Breathless walking on level ground	5		10	
Breathless walking up hills or steps	32		28	
Ever stop walking because of breathlessness	26		21	
Exercise				
Weekly intentional exercise, MET hours		16.1 (0.0–22.8)		20.4 (0.9–23.2)
Weekly moderate/vigorous physical activity, MET hours		98.8 (42.0–133.5)		111.7 (55.5–150.9)
Smoking status				
Never smoker	60		56	
Former smoker	32		34	
Current smoker	8		10	
Medication use				
Current aspirin use	11		12	
Taking reproductive hormones	7		7	
Taking β-blockers	11		9	
		Study Variables		
Study site				
New York	61		71	
Los Angeles	39		29	
Season				
Spring	24		19	
Summer	15		14	
Fall	44		43	
Winter	17		24	

Abbreviation: IQR, interquartile range; MET, metabolic equivalent.
[a] Propensity score weighted.
[b] Not included in the propensity score model because it was not considered as a confounder.
[c] Ordinal variable; range, 0–8.

older-aged, racially/ethnically and occupationally diverse adults with lower levels of wealth. For example, the average age in our weighted sample was 58 years. Fifteen percent of the sample participants were white, 27% were black, and 58% were Hispanic. Fourteen percent were employed in management jobs, 19% in professional jobs, 30% in service jobs, 21% in sales, office, or administrative support jobs, and 16% in blue-collar jobs. Fifty-eight percent reported renting their home.

Figure 2A shows the average estimated salivary cortisol levels over the course of the day for those with more job strain (dashed line) and for those with less (solid line). Figure 2B shows the bootstrapped average estimated log difference in cortisol levels comparing those who had more job strain over the course of the day with those who had less conditional on the other covariates (i.e., the average job strain coefficient across 1,000 bootstraps).

In contrast to a standard regression model in which the coefficient is a constant, the job strain coefficient in this functional mixed model is a function of time of day. For example, the intercept of this curve is the (log) difference in cortisol levels at wake-up when comparing persons who have more job strain with those who have less. Moving along the x-axis (time of day), the largest differences in cortisol levels associated with job strain occur just over 5 hours after wake-up and around bedtime (at the last point on the x-axis). The shaded region represents the bootstrapped 95% confidence interval.

Figure 3 shows the estimated adjusted associations of job strain with CAR and total AUC. The solid lines show the estimates from the primary analysis using functional mixed models, and the dashed lines show the estimates from the 2-step approach. In the primary analysis, those with more job strain have a total cortisol AUC that is 90% lower (for those with more job strain versus less, ratio of total AUC = 0.10, 95% CI: 0.01, 0.98) than that for those with less. There is essentially no difference in CAR when comparing those with more versus less job strain. Those with more job strain have a CAR that is 2% lower than that of those with less (or those with more job strain versus less, ratio of CAR = 0.98, 95% CI:

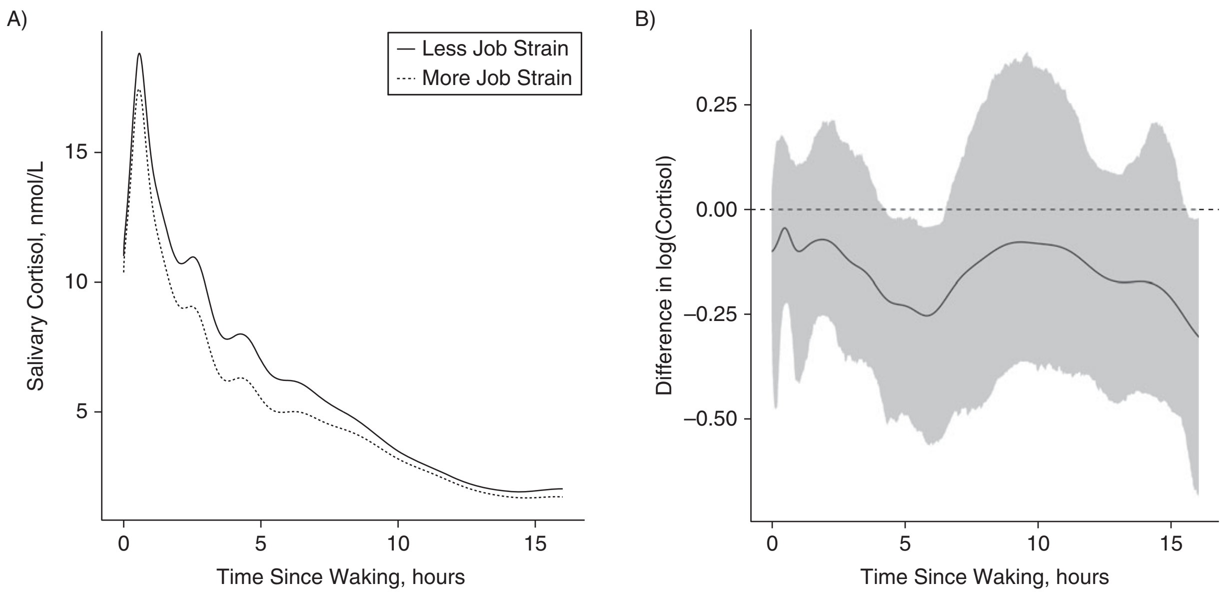

Figure 2. Average estimated salivary cortisol levels in participants with more or less job strain over the course of the day, Multi-Ethnic Study of Atherosclerosis, 2002–2006. A) Curves for the average estimated cortisol levels among those with more job strain (dashed line) versus those with less (solid line). B) Bootstrapped average expected difference in log cortisol levels between those with more versus less job strain (i.e., the job strain coefficient). The shaded region represents the bootstrapped 95% confidence interval.

0.75, 1.78). The associations estimated from the 2-step approach are slightly more conservative. The 95% confidence intervals are markedly narrower in the 2-step approach, partially because it ignores the error in estimating the features.

Sensitivity analyses

We assessed the sensitivity of our results to 3 different assumptions of our conceptual model. First, research has suggested that the combination of psychosocial stress and low social standing might be an important predictor of HPA axis dysregulation (31, 32). Although we lack a measure of social standing, the income-wealth index may serve as a proxy. We found evidence suggesting an interaction between job strain and the income-wealth index (Figure 4) in which the association between greater job strain and lower cortisol levels strengthens for participants with higher wealth and attenuates for participants with lower wealth. However, we could not estimate bootstrapped confidence intervals because of convergence problems, so this sensitivity analysis should be treated as exploratory.

Second, some have argued in favor of evaluating job demand and job control as a separate exposure variables (10, 32). Although theory and some experimental evidence have suggested that it is the combination of high job demands and low job control that is important (33, 34), we conducted a sensitivity analysis in which we used job demands and job control as separate exposures. The relationships seen between these 2 components of job strain and the cortisol diurnal cycle were similar to those presented for job strain; high job demands and low job control were associated with lower cortisol levels.

Third, evidence has suggested that job strain might only influence cortisol levels on working days (3, 35, 36). Although model fit statistics suggested that the best fitting model incorporated an indicator of workday as a confounder but not an effect modifier, we nonetheless tested the sensitivity of our results to this modeling assumption. (Participants collected cortisol samples for 3 consecutive weekdays, but not all weekdays were working days.) We reran the analysis restricted to workdays, and our results were similar.

DISCUSSION

After controlling for an extensive set of covariates and using a functional mixed-model approach that accounts for within- and between-day sources of variability in cortisol measures in a diverse sample of middle- to older-aged adults, we found that job strain was associated with lower cortisol levels throughout the day, including at bedtime, as well as a lower total AUC; however, it was not associated with CAR. CAR is thought to measure the capability of the HPA axis to respond to stress, and total AUC is thought to measure cumulative daily cortisol exposure (23).

Our finding that job strain was associated with a lower total AUC is inconsistent with findings from 2 previous studies; in one, no relationship was found (17), and in another, a weak, positive relationship was found (16). Our finding that job strain is not associated with CAR agrees those from with previous research (11–15) but is inconsistent with results from another study in which a positive association was found (10). We considered several potential explanations for these inconsistencies.

First, it is plausible that previous significant results were due to underestimated variance of regression coefficients.

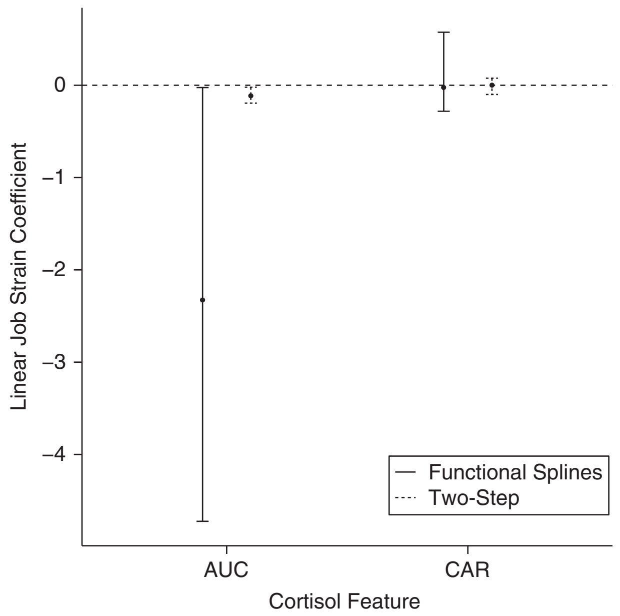

Figure 3. Linear estimates and bootstrapped 95% confidence intervals for the associations of job strain with the cortisol awakening response (CAR) and total area under the curve (AUC), Multi-Ethnic Study of Atherosclerosis, 2002–2006. These estimates are the linear (not exponentiated) job strain regression coefficients. For the CAR, the linear estimate can be interpreted as the difference between the expected initial slope of log-cortisol levels conditional on all covariates included in the propensity score and outcome models for those with more job strain and the conditional initial slope for those with less job strain. For the AUC, the linear estimate is interpreted the expected difference in area under the logged cortisol curve when comparing persons who have more job strain with those who have less, conditional on covariates. Estimates are given for the functional splines approach (which uses functional mixed models to model the association between job strain and the diurnal cortisol curve as a function of time since wake-up, incorporating within- and between-day variability in cortisol measurements) and for the 2-step approach (which calculates the CAR and AUC for each participant and then regresses those quantities on job strain and covariates, treating the CAR and AUC values as known and ignoring a major source of variability).

Cortisol is a highly variable measure that is influenced by person-level factors, such as sex and genetics (37), as well as by day- and time-specific factors, such as recent activity and diet. Fully accounting for variability requires 1) design and analysis that decomposes this variation within and between individuals and 2) propagating uncertainty (i.e., accounting for sources of variability) in estimating the cortisol feature throughout the analysis. To our knowledge, the present study is the first in which these sources of variability have been incorporated into the examination of the relationship between job strain and salivary cortisol, thereby resulting in more honest standard errors and more accurate inference. All previous studies used a 2-step approach that ignores uncertainty in estimating the cortisol feature and results in standard errors that are too narrow. We found that the conventional 2-step approach resulted in standard errors that were 5 times and 27 times smaller than our functional mixed-model approach for the associations of job strain with CAR and AUC, respectively. Although the wide confidence intervals in our primary analysis are more honest, they suggest caution—particularly in the case of the AUC—is necessary when drawing conclusions. Replication of our findings is needed.

Second, it is possible that inconsistencies could be due to residual confounding and violations of the positivity assumption (positivity violations result when individuals with certain covariate values have no similar counterparts in the comparison exposure group). In previous studies, researchers have failed to control for several potentially important confounders, such as smoking status, physical health, income, wealth, or other measures of financial strain, and have not restricted the analyses to individuals with comparable counterparts (2, 10, 16, 32, 38). We addressed these gaps by controlling for an extensive list of possible confounding variables via propensity score matching and restricting propensity score matches to the region of common support.

Third, we measured job strain in participants with diverse occupations. In contrast, in many previous studies, workers were sampled from groups with the same occupation (2, 3, 8, 9, 12, 16, 17). Assessing job strain while holding the type of job constant might tap into individual differences in psychological characteristics rather than structural job differences. Consequently, the meaning of job strain in studies in which the participants have the same occupation may be different than in studies that include participants with differing occupations.

Fourth, our results may apply only to our sample of middle- to older-aged, racially and ethnically diverse, urban-dwelling adults and therefore are not necessarily inconsistent with previous research conducted among younger, mostly European and white samples (6, 16). It is possible that among middle- to older-aged adults, job strain occurs in conjunction with fatigue or burnout. In a systematic review, Chida and Steptoe found evidence of a positive association between job stress (broadly defined rather than job strain specifically) and CAR and a negative association between fatigue/burnout and CAR (4). If job strain co-occurred with fatigue/burnout in our sample, it could explain our null findings in relation to CAR and the inverse relationship between job strain and AUC.

In accordance with previous studies, we controlled for time at wake-up in our outcome model (35). However, time at wake-up could act as a mediator as well as a confounder if job strain results in sleep disturbance that causes the participant to awake earlier (39, 40). In this case, we would estimate the association of job strain on cortisol not mediated by wake-up time.

There are several limitations related to using cortisol as an outcome. First, cortisol is only one component of a multifaceted stress response system. However, salivary cortisol has been extensively studied and demonstrated to track with adrenal cortical and HPA axis functioning (41, 42). In addition, salivary cortisol includes unbound cortisol, which is the biologically relevant form capable of stress regulation (43). Second, there is a lack of consensus about how to interpret cortisol findings. Our finding that job strain is associated with lower cortisol levels over the course of the day, including a lower AUC, initially seems to contradict traditional thinking that stressors are associated with higher cortisol levels. However, there is a growing body of literature suggesting that chronic stress and its health correlates (e.g., diabetes, obesity) lead to neuroendocrine burnout with a blunted

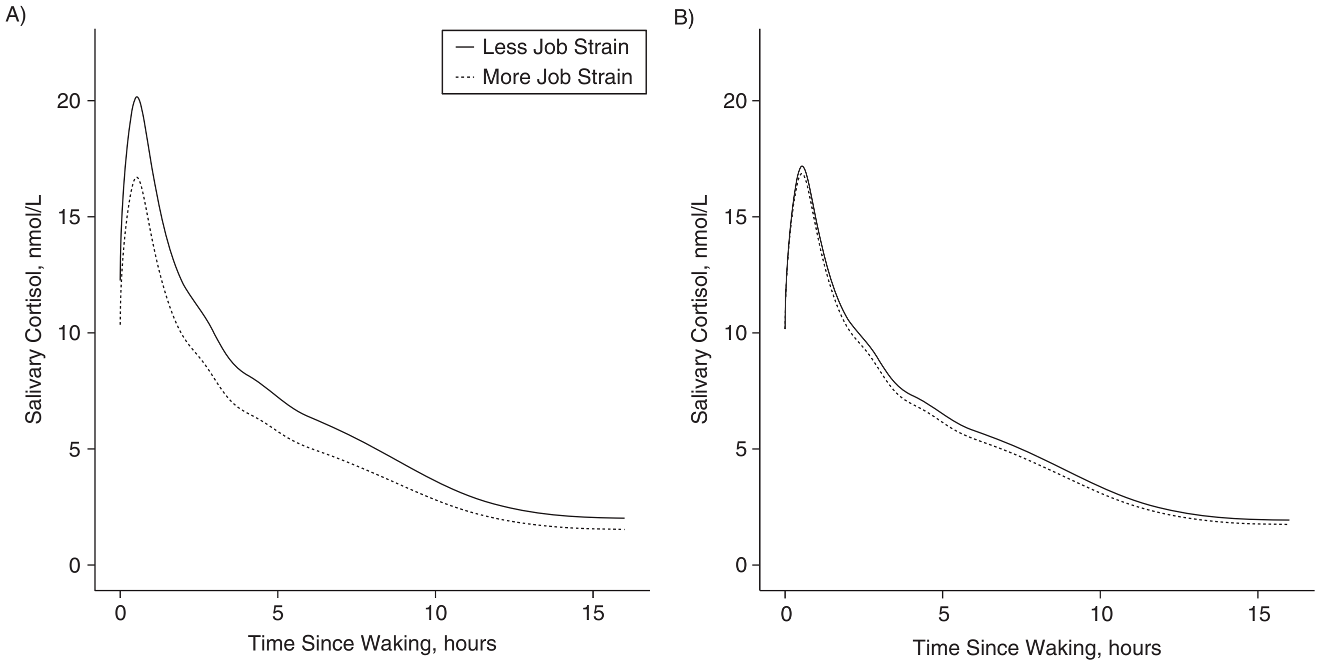

Figure 4. Interaction between job strain and income-wealth index over time, Multi-Ethnic Study of Atherosclerosis, 2002–2006. A) Comparison of the salivary cortisol profiles of those with more job strain (dashed line) with the profiles of those with less job strain (solid line) among wealthier participants (those at or above the 75th percentile for wealth). B) Comparison of the salivary cortisol profiles of those with more job strain (dashed line) with the profiles of those with less job strain (solid line) among less wealthy participants (those at or below the 25th percentile for wealth).

cortisol diurnal profile (44–46). Further understanding of how to interpret such a nuanced measure is needed.

In addition, we were unable to use multiple imputation to address missing data. Methodological development of how to integrate multiple imputation with our functional mixed-model approach that incorporates propensity score weighting and bootstrapping for inference is an area for future work.

Future studies should determine whether the relationship between job strain and HPA axis functioning varies depending on where individuals are in their work/career trajectory. There is also a need to further examine the interaction between job strain and social standing in predicting HPA axis dysregulation, including identifying which aspects of social standing are relevant (e.g., subjective vs. objective, wealth vs. occupation). Incorporation of shift work and fatigue/burnout in models used to examine the relationship between job strain and cortisol is another area for future research that could shed light on complex and inconsistent findings. Finally, our work highlights the importance of using study designs and analytic approaches that fully incorporate and propagate cortisol variability across the estimation process to obtain accurate standard errors and avoid misleading inference.

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