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In Older Adults, Intervention Impacts the Association Between the Cortisol Awakening Response and Three Measures of Wellbeing: Meaningful Activities, Life Satisfaction and Perceived Control

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Abstract

Studies report associations between the cortisol awakening response (CAR) and measures of psychological stress and well-being suggesting the possibility that individual differences in the CAR might influence which individuals respond to intervention programs aimed at promoting healthier lifestyle. This issue is studied in a randomized control trial in a large (N =460) ethnically diverse community sample of elder adults (M age 74.9; 66% female) using a cross-over design. Three key measures of wellbeing (i.e., meaningful activity, perceived control, and life satisfaction) were taken before and six months later. Some participants (N = 232) did not receive intervention the first six months, they acted as a control group, but after six months they received intervention and were measured again six months later. The intervention was a lifestyle-oriented occupational therapy program. Results revealed that prior to intervention, no associations were found between the CAR and the wellbeing measures. However, after intervention, associations between the CAR and wellbeing were pronounced. After intervention, as CAR increases, typical MAPA, PC and LSIZ scores tend to decrease. For PC and LSIZ, this is particularly true for positive CAR values; for negative CAR values there is a relatively small change in PC and LSIZ scores. The CAR, measured after intervention, is also associated with the extent MAPA and PC scores improve compared to baseline measures. Findings are among the first to document the nature of the effects of intervention on the association between activity of the hypothalamic-pituitary-adrenal axis and key measures of wellbeing. Implications for future investigations are discussed.

Keywords: Cortisol; Meaningful Activity; Perceived Control; Life Satisfaction; Well Elderly 2 Study

Introduction

As the elderly population expands, there will be a corresponding downward change in some measures of wellbeing and functional ability [1-3]. Fortunately, age-related declines can be delayed by engagement in a healthier lifestyle (e.g., [1, 3-11]), a result that highlights the need to develop interventions that promote modifiable healthy behaviors in older people. Extant results indicate that the lifestyle intervention program used in the Well Elderly 2 study tends to improve measures of wellbeing among ethnically diverse elders in community-based settings, the majority of whom are from populations at risk for health disparities [12]. Measures were taken both before intervention and six months later. Some participants did not receive intervention the first six months, they acted as a control group, but after six months they received intervention and were measured again six months later. (A cross-over design was used.) Currently, however, little is known regarding what role, if any, cortisol plays in the effectiveness of this particular intervention strategy in terms of improving psychosocial measures of wellbeing. Cortisol, the primary hormone product secreted by the hypothalamus-pituitary-adrenal (HPA) axis, is considered to be a biomarker of HPA axis activity (e.g., [6]). Dysfunction in the HPA axis is implicated in the development of a variety of sub-clinical and clinical conditions (e.g., [1,13-18]).

The change in cortisol upon awakening, and when measured 32-60 min later, is known as the cortisol awakening response (CAR). One appeal of the CAR is that it is an easy parameter of HPA axis function to measure because it does not require laboratory conditions or administration of exogenous agents; rather awakening itself is a consistent, recurring, and strong stimulus for HPA activity [22]. The CAR was first established by Pruessner [17] as a useful index and has since attracted growing attention. Both enhanced and reduced CARs are associated with various psychosocial factors including measures of wellbeing, depression and anxiety disorders (e.g., [17,21-27]). These results suggest that intervention might impact the association between the CAR and the psychosocial measures used in the Well Elderly 2 study. They also suggest that the CAR might play a role in terms of the extent individuals respond to intervention.

Material and Methods

The data stem from the Well Elderly 2 study [12], which was generally aimed at assessing whether a six-month lifestyle, activity-based intervention leads to reduced decline in physical health, mental wellbeing and cognitive functioning among ethnically diverse older people. Jackson et al. [12] provide a detailed description of methodological and logistical issues. The participants were 460 men and women aged 60 to 95 years (mean age 74.9). All participants were residents of, users of, or visitors to the study recruitment sites, demonstrated no overt signs of psychosis or dementia, and were able to complete the study assessment battery (with assistance, if necessary). All prospective participants completed the informed consent process prior to study entry. Participants were recruited from 21 sites in the greater Los Angeles area, including nine senior activity centers, eleven senior housing residences, and one graduated care retirement community. The study was approved by the USC IRB.

Intervention in the Well Elderly 2 study consisted of small group and individual sessions led by a licensed occupational therapist. (For a more detailed description, see [4].) Typically, each group had six to eight members, all recruited from the same site and treated by the same intervener. Monthly community outings were scheduled to facilitate direct experience with intervention content such as the use of public transportation. Due to the overt nature of lifestyle programs, neither the therapists nor the treated participants were blind to the intervention. However, the interveners and participants were blind to the study design and hypotheses. Key elements of intervention were: Identification and implementation of feasible and sustainable activity-relevant changes, development of plans to overcome mundane obstacles to enacting activity-relevant changes (e.g., bodily aches or transportation limitations), and participation in selected activities; rehearsal and repetition of changes to everyday routine. Therapists completed 40 hours of training to standardize provision of the Lifestyle Redesign protocol in accord with manualized specifications. Therapists participated in weekly or bi-weekly meetings with the on-site project director and manager to ensure intervention fidelity and quality control. Weekly two hour small group sessions were used, led by a licensed occupational therapist. Included were didactic presentations, peer exchange, direct experience (participation in activities) and personal exploration (application of content to self). There were up to 10 individual one hour sessions with an occupational therapist in homes or community settings.

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Behavioral and Biological Assessments

Testing sessions typically occurred in groups of four to 19 elders and took place in recreation or meeting rooms at the study sites. The frequency of meaningful activities was measured with the Meaningful Activity Participation Assessment (MAPA) instrument, which was studied by Eakman et al. [28] and found to be a reliable and valid measure of meaningful activity, incorporating both subjective and objective indicators of activity engagement. It consists of the sum of 19 seven-point Likert scales. The maximum observed MAPA score before intervention was 140 and the maximum after intervention was 143. For the adults studied here, the reliability of MAPA, based on coefficient alpha, was estimated to be .79 prior to intervention and .81 after intervention. (A robust analog of coefficient alpha [19] gives the same estimate.)

Perceived Control (PC) was measured with an instrument studied by Eizenman et al. [30]. It consists of the sum of 8 four-point Likert scales. So the possible PC scores range between 8 and 32. Higher PC scores reflect greater perceived control. For the data at hand, coefficient alpha was estimated to be .66 before intervention and .67 after intervention. (An estimate of a robust analog of coefficient alpha was .75 both before and after intervention.)

Life satisfaction was assessed by the Life Satisfaction Index-Z (LSIZ) [31], which has established psychometric properties for use in older adults. The LSIZ consists of 13 items, with responses indicating satisfaction, dissatisfaction, and unsure scored as two, zero, and one, respectively. Values on the 13 items are then summed to give a score range of 26 (zero to 26). Coefficient alpha was reported as .79 and the LSIZ has previously been found to have correlation .57 with a life satisfaction rating. Here, coefficient alpha was estimated to be .75 before intervention and .77 after. (The robust estimates were .81 both before and after intervention.)

All participants received in-person instruction about the self-performance of saliva collection, and were left color-coded written instructions to follow on the day of sample collection. Saliva samples were taken at four times: upon awakening, typically 32 minutes later prior to eating breakfast, typically five hours later before eating lunch, and generally about five hours after eating lunch but before eating dinner. After each sample was collected, the specimen was stored frozen in the participant's residence. Once all sampling was completed, a study team member transported the samples on ice to a laboratory freezer at USC. Following Granger et al. (2007), samples were assayed for cortisol using either kinetic or enzyme immunoassays without modifications to the manufacturer's recommended protocols (Salimetrics LLC, State College, PA). The assays had average intra- and inter-assay coefficients of variation of less than 5 and 10%, respectively.

Study Design

Participants were randomly assigned to the intervention or no-treatment control condition for their first six months of study involvement. All participants were baseline-tested before starting and post-tested after completing their respective conditions. Reflecting a crossover design component, control group participants undertook the intervention during the six months period immediately following the trial's main experimental phase. This strategy enabled secondary analyses of pre-post intervention-based change involving control participants, and was consistent with ethical treatment of human participants.

Adherence

Past studies indicate that when dealing with cortisol, adherence can be important. When morning samples are inaccurately timed in relation to either awakening time, or in relation to each other, this can have a significant (negative) impact on estimates of the cortisol awakening response [34]. Consequently, participants were instructed to record the times they awoke and took the saliva sample, as well as when subsequent samples were taken. Evidence suggests that participants do collect morning samples accurately in relation to objectively determined wake times [33, 34]. Here, there were 19 instances where the time between awakening and the second sample exceeded 60 minutes. These cases were considered to be erroneous and were eliminated.

Assessment

Testing sessions typically occurred in groups of four to 19 elders and took place in recreation or meeting rooms at the study sites. Assessment of health-related quality-of-life, life satisfaction and depression was based on self-rated questionnaires, and was overseen by trained testers who were blind to the participant's condition assignments. Spanish versions of the questionnaires were provided for individuals in a Spanish study segment (n=67). The cognitive tests were conducted individually, in a private area adjacent to the main testing room, at varying points during the testing session

Statistical Methods

All analyses were performed using the software R [20] in conjunction with the R functions in [19]. Generally, modern robust methods for dealing with outliers, skewed distributions and curvature were used. It is well known in the statistics literature that classic least squares techniques and Pearson's correlation are not robust under general conditions (e.g., [19, 35-39]). Methods for comparing means can have relatively poor power due to non-normality, particularly when there are outliers. Also, the mean can poorly characterize the typical value when distributions are skewed.

When studying associations, outliers among the independent variable were identified and eliminated using the MAD-median rule (e.g., [19] section 3.13.4]). Outlier detection methods based on means and variances are known to be highly unsatisfactory, because the very presence of outliers can cause them to be missed; see for example [19, 38].

(Roughly, outliers inflate the sample variance, which in turns results in outliers being missed.) It is noted that eliminating outliers among a dependent variable and estimating the standard error in the usual way can result poor control over the Type I error probability regardless of how large the same size might be. (This approach leads to a theoretically unsound estimate of the standard error.) The methods used here are designed to deal with this issue in a technically correct manner.

Standard hypothesis testing methods, when dealing with regression, assume that the variance of the dependent variable does not depend on the value of any independent variable (homoscedasticity). Violating this assumption (heteroscedasticity) can result in poor control over the Type I error probability and poor power. The hypothesis testing methods used here allow heteroscedasticity. Testing the usual homoscedasticity assumption, with the goal of salvaging methods that assume homoscedasticity, is known to be rather ineffective (e.g., [19, 40]). Simple transformations are sometimes suggested for dealing with heteroscedasticity, but they are not as effective as heteroscedastic methods derived more recently.

The least squares regression estimator was replaced by a variation of the regression estimator derived by Theil [32] that is designed to deal effectively with both tied values and outliers among the dependent variable. This regression estimator is designed to predict the median value of the dependent variable, rather than the mean. Curvature was addressed using the locally weighted scatterplot smoother (LOESS) [19]. The strength of the association between two variables was based on a robust analog of Pearson's correlation (e.g., [19, section 11.9]). This approach to measuring the strength of an association reduces to Pearson's correlation when using least squares regression. Inferences about the median of difference scores were based on the method in [19, section 5.4] (via the R function hdpb in the R package WRS).

Results

About 1% of the pre-intervention MAPA scores were flagged as outliers, and 5% were flagged as outliers after intervention. For perceived control these proportions were approximately 8% and 7%, respectively, and for life satisfaction they were 3% both before and after intervention. Approximately 10% of the CAR values were flagged as outliers.

First we consider MAPA. Prior to intervention, no association with the CAR was found (p=.65). When the control group was measured again after six months, again no association was found (p=.21). For the group receiving intervention, there is a negative association between the CAR and MAPA (p=.04). Figure 1 shows a plot of the regression lines, where the solid line is the regression line before intervention. (No indication of curvature was found.) The correlation between CAR and MAPA before intervention was .1 and after intervention it was −.14.

Note that the regression lines in Figure 1 cross at a point close to where CAR is equal to zero. For CAR less than or equal to −.1 ug/dL (cortisol increases by .1 ug/dL or more after awakening), predicted MAPA scores are significantly larger after intervention. Otherwise, no significant difference in predicted MAPA scores is found over the range of CAR values that were observed. (Approximately 37% of the CAR values are less than −.1 ug/dL after intervention.)

For perceived control, again no significant association with the CAR was found prior to intervention (p=.18). For the control group, no association is found after six months (p=.33). After intervention, there is an indication of curvature as indicated in the left panel of Figure 2, which shows a plot of the regression line. (The dashed lines indicate .95 confidence intervals.) Figure 2 indicates that typical PC scores are highest for CAR less than −.1 ug/dL with little or no change in predicted PC scores when cortisol increases after awakening. Fitting a straight line to only those points for which CAR is less than −.1, ug/dL a formal test that the slope is zero failed to reject (p=.48). But for CAR greater than −.1 ug/dL, the plot indicates a negative association, which is significant (p<.001); the correlation is −.24. Moreover, the slope corresponding to CAR less than −.1 ug/dL differs significantly from the slope when the CAR is greater than −.1 ug/dL (p=.02). That is, after intervention, the hypothesis that the regression line is straight is rejected: the nature of the association depends on whether CAR is relatively high or low. As was the case for MAPA, predicted PC scores are significantly higher after intervention, compared to predicted scores before intervention, when CAR is less than −.1 ug/dL. For CAR greater than −.1 ug/dL, no significant difference is found when using the CAR as a covariate.

As for lifestyle satisfaction, no association with the CAR is found both before intervention (p=.71) and six months later with no intervention (p=.12). For the group receiving intervention, there is an indication of curvature as indicated in the right panel of Figure 2. Again there appears to be a distinct bend approximately where the CAR is equal −.1 ug/dL. For CAR less than −.1, ug/dL the slope does not differ significantly from zero (p=.13). For CAR greater than −.1 ug/dL, a significant result is obtained (p=.003) and the correlation is estimated to be −.18. If the apparent curvature is ignored, the estimated slope is negative and differs significantly from zero (p=.023). However, the slope when CAR is less than −.1 ug/dL differs significantly from the slope when CAR is greater than −.1 ug/dL (p=.007). So as was the case for perceived control, the hypothesis that the regression line is straight is rejected. In contrast to MAPA and PC, a significant increase in the predicted LSIZ scores (based on the estimated regression lines) was not found over the range of the observed CAR values. But if the hypothesis of no change in LSIZ is tested using all individuals whose CAR is less than −.1 after intervention, ignoring the CAR, the median increase is significant (p=.004). And for a CAR greater than −.1, again a significant increase in LSIZ is found (p=.04). That is, predicted increases based on the CAR are not significant, but all indications are that intervention improves LSIZ scores.

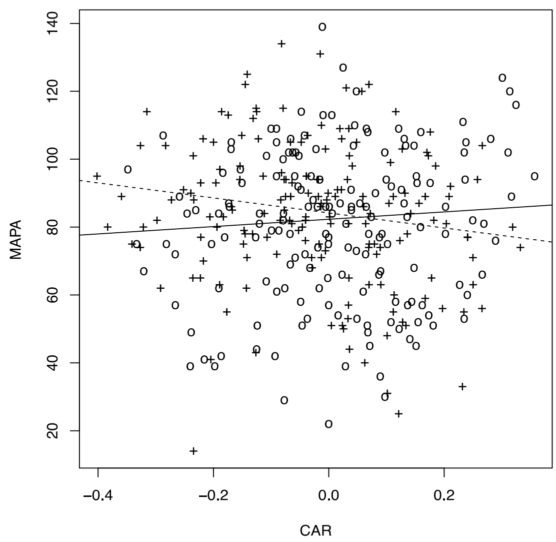

Figure1. Regression lines for predicting MAPA based on the CAR before and after intervention. (The solid line is the regression line before intervention.)

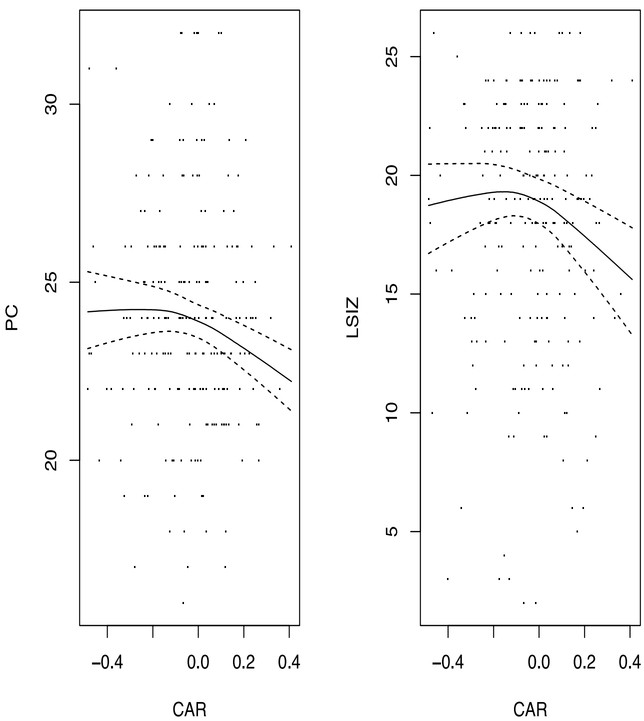

Figure 2. Regression lines (and .95 confidence intervals) for predicting perceived control (left panel) and life satisfaction based on the CAR after intervention.

Discussion

In summary, prior to intervention, no association was found between the cortisol awakening response and three measures of well being: meaningful activities, perceived control and lifestyle satisfaction. The same result was obtained for a control group that was measured again six months later with no intervention. After intervention an association with all three psychological measures was found. For meaningful activities (MAPA), there was a negative association with the CAR. That is, the more cortisol increases soon after awakening, the higher the typical level of meaningful activities.

After intervention, the participants with a significantly higher increase in meaningful activities, compared to pre-intervention levels, were those whose cortisol levels increased after awakening by a sufficient amount (.1 ug/dL or more). With a small increase or a decline in cortisol after awakening, measured after intervention, no significant benefit was found. The crossing regression lines in Figure 1 suggest that intervention has a negative impact on attempts to increase meaningful activities when cortisol declines sufficiently after awakening, but no significant result was found.

For both perceived control and lifestyle satisfaction, after intervention, the nature of the association with the CAR depends on whether the CAR is sufficiently negative. It was found that when CAR is less than −.1 ug/dL (cortisol increases by a reasonable amount), no association is found. That is, predicted PC and LSIZ scores are relatively high in this range of CAR values with little or no variation in the predicted values. But otherwise there is a negative association. After the intervention, those whose perceived control and lifestyle satisfaction decreased, the typical cortisol awakening response was decreased as well. For lifestyle satisfaction, no significant improvement was found after intervention based on predicted LSIZ scores, even when cortisol increases. The similarity of the results for perceived control and lifestyle satisfaction is, perhaps, not too surprising because they have a fairly strong correlation, namely .42. Yet, in terms of the typical benefit after intervention, only perceived control showed a significant improvement when using CAR as the covariate. However, this does not necessarily mean that intervention has no practical value in terms of increasing LSIZ scores among individuals for whom cortisol stays about the same or decreases. Based on the median increase in LSIZ scores, ignoring the CAR, a significant increase was found.

A point worth stressing is that although intervention was found to impact the associations among the measures considered, no association between the CAR, measured prior to intervention, was found with any of the pre-post changes in the psychosocial measures. Testing the hypothesis of a zero slope, the p-values were .59, .15 and .71 for MAPA, PC and LSIZ, respectively. In practical terms, there is no indication that CAR, measured before intervention, provides a reasonably good way of predicting who will benefit. It is the CAR measured after intervention that has an association with improved psychosocial measures.

On a broader level, the results in this paper have implications about future investigations: methods that deal effectively with outliers and curvature might be of crucial importance. Here, using least squares regression in the usual manner leads to substantially different conclusions. For example, after intervention, no association between the CAR and the three dependent variables is found; the p-values are .85, .23 and .19, for MAPA, PC and LSIZ, respectively. Very similar results are obtained after taking logs. This reflects the well-known fact (in the statistics literature) that violating assumptions can seriously impact the power and validity of standard least squares techniques. This suggests that more modern methods for dealing with violations of assumptions might make a practical difference in future studies aimed at understanding the association between cortisol and any psychosocial measures of interest.

Conflict of interests

In the interest of full disclosure, we note that DAG is the founder and Chief Scientific and Strategy Advisor at Salimetrics LLC (State College, PA) and this relationship is managed by the policies of the conflict of interest committee at the Johns Hopkins University School of Medicine and Office of Research Integrity and Adherence at Arizona State Universtiy. No other authors declare conflicts of interest.

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